

Guideline endodontic diagnosis and treatment

update 2022/3

INITIATIVE

Dutch Association for Endodontology



WITH THE SUPPORT OF

J.J.A. de Beer, independent guideline methodologist

FINANCING

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Colophon

GUIDELINE ON ENDODONTIC DIAGNOSIS AND TREATMENT

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Contents

- Summary..... 5
- 1. General introduction..... 16
- 2. Methodology guideline development..... 17
 - 2.1 Validity..... 17
 - 2.2 General data..... 17
 - 2.3 Purpose and Target Group 17
 - 2.4 Declarations of Interest 17
 - 2.5 Input patient perspective 20
 - 2.6 Implementation..... 20
 - 2.7 Methodology..... 20
 - 2.8 Comment Phase..... 25
- 3. Diagnosing the condition of the pulp..... 27
- 4. Imaging diagnostics..... 41
- 5. Treatment of pulpitis 68
- 6. Regenerative endodontic treatment..... 98
- 7. Treatment of a necrotic pulp 114
- 8. Orthograde re-treatment..... 156
- 9. Acute complaints and pain management 170
- 10. Permanent and temporary restoration of elements..... 199
- 11. Association between periodontitis apicalis and systemic diseases 233
- 12. Avoiding and treating complications..... 238
- 13. Knowledge gaps 259
- 14. Implementation 260
- Appendix starting questions 261
- Appendix members sounding board group 265
- Appendix literature search patient perspective 266
- Appendix..... 273

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Summary

3. Diagnosing the condition of the pulp

To determine the sensibility and, indirectly, the vitality of the pulp, the study group suggests the use of the cold test and electrical test.

[unchanged after update 2022/3]

Rational

Of none of the tests to determine the sensibility and, indirectly, vitality of the pulp, the diagnostic value has been scientifically demonstrated with a reasonable to high degree of certainty. Of the tests based on measuring a response to sensory stimuli, the cold test and electrical test appear to be the most sensitive/specific. Moreover, they are noninvasive, inexpensive tests.

Tests based on the measurement of blood circulation to determine the vitality of the pulp have not yet been investigated in a sufficiently robust manner to be applied routinely, and are also relatively expensive. Therefore, the study group assumes that pulse oximetry and laser Doppler flowmetry, in part because of the costs associated with them, are not or rarely used by general practitioners for the time being.

At this time, one cannot rely purely on the results of sensibility tests for an accurate diagnosis of the condition of the pulp.

The working group believes that in combination with the medical and clinical history, intra-oral examination and additional X-ray diagnosis, one can ultimately arrive at a working diagnosis.

4. Imaging diagnostics

A periapical X-ray image is preferred for radiologically assessing the condition of periapical tissue. If necessary, multiple images can be taken at different angles to avoid overlap and get a better view of different structures without a 3D image.

CBCT should not be used by default as an imaging technique for identifying periapical pathology. The ALARA principle is applied here.

High-resolution CBCT with limited volume *should be considered* when

- 1) no clear diagnosis of periapical abnormalities can be made from the clinical signs and periapical radiographs because of:
 - (a) conflicting clinical symptoms, or
 - b. because of poorly localized symptoms associated with an un-treated or previously endodontically treated tooth.
- 2) *[update 2022/3] on serious suspicion of the presence of an additional channel*
- 3) *[update 2022/3] in serious suspicion of the presence of a vertical root fracture.*

Application of CBCT should only be done by a dentist or endodontist who has been trained in it. Otherwise, referral to a dentist or endodontist trained in it is necessary.

When using CBCT to image multiple teeth in one image, radiological abnormalities of other teeth should also be checked for. The entire image should be assessed, and thus all the different tissues and structures.

[modified after update 2022/3: added two indications for CBCT and formulated recommendation more strongly on this basis]

Rational

Despite the fact that the cost of CBCT versus that of a periapical X-ray image is higher, CBCT gives a higher radiation exposure than a periapical X-ray image [update 2022/3], the working group gave great weight to the evidence on presence of an extra canal and a vertical root fracture as well as the relevant opinions of European Society of Endodontology position statement on CBCT.

5. Treatment of pulpitis

Consider the use of MTA when partial or total pulpotomy is chosen.*

[update 2022/3: new recommendation]* see glossary (<https://nvve.com/wp-content/uploads/2018/03/Begrippenlijst-Endodontologie.pdf>).

Rationale

The working group placed great weight on the more favorable clinical effect of MTA compared to calcium hydroxide, the multiple uses of MTA, and little weight on the fact that MTA is more expensive than calcium hydroxide.

When irreversible pulpitis is suspected, pulpectomy is the standard treatment. [update 2022/3] However, pulpotomy may be considered, with the advantages and disadvantages of pulpectomy for irreversible pulpitis discussed with the patient and weighed in concert.

[modified after update 2022/3: the old recommendation contained a passage that could be perceived as discriminatory. The passage read, "In case of limited financial resources, pulpotomy may be considered as an alternative."]

Rational

The Working Group gave considerable weight to the fact that despite new studies published since 2016, there are still insufficient studies available comparing the long-term effects (minimum follow-up duration of 48-60 months) of pulpotomy with those of pulpectomy. On this basis, pulpectomy is considered the standard treatment for the time being.

In patients with permanent dentition, try to avoid pulpal exposure.

[Update 2022/3] *Selective removal of carious tissue is preferable to 'stepwise excavation'.*

[modified after update 2022/3: partial removal has been replaced by selective removal to put more emphasis on targeted rather than partial removal of carious tissue]

Rational

The working group placed great weight on avoiding pulpal exposure. In addition, incomplete removal of carious tissue does not reduce clinical success, provided the enamel-dentin boundary is clean. Selective removal of *central* carious tissue can be done in one sitting, as opposed to "stepwise excavation".

For patients with permanent dentition and deep caries in whom pulpal exposure occurs, MTA and [update 2022/3] Biodentine are the agents of first choice as direct overdenture materials.

[modified after update 2022/3: Biodentine has been added due to new evidence].

Rational

The working group gave great weight to the fact that MTA is likely to be less likely to cause treatment failure than calcium hydroxide and is the most researched of the hydraulic calcium silicate-based cements (HCSCs), and gave little weight to the higher cost of MTA and Biodentine.

The working group does not recommend any of the overdenture materials for indirect pulpal overdenture.

[unchanged after update 2022/3]

Rationale

The working group gave great weight on the fact that it is far from certain whether or not overdenture material is necessary at all in indirect pulpal overdenture.

Consider treating (irreversible) pulpitis in one sitting. This may be deviated from when warranted by the presence of pain (emergency), the difficulty of treatment and/or the patient's wishes.

[update 2022/3: new recommendation]

Rationale

The study group gave great weight to the fact that treating in one session is more pleasant for the patient (convenience; time savings) than treating in two sessions, costs less and the risk of leakage is reduced (since there is no temporary restoration as when a second session takes place). The study group gave little weight to the possible more frequent occurrence of post-operative pain within one week.

*For pain relief, **do not** consider occlusal reduction.*

[update 2022/3: new recommendation]

Rationale

The working group gave great weight to the view that sacrificing natural tissue by occlusal reduction for highly uncertain pain reduction is undesirable.

6. Regenerative endodontic treatment.

[new chapter added]

1. Consider preservation of an immature tooth with pulpal necrosis by regenerative therapy or apexification. The cause of pulpal necrosis (trauma, dens evaginatus or caries) *does not play a* role in choosing between the two options.
2. If regenerative therapy is chosen, consider
 - not apply EDTA irrigation, but only sodium hypochlorite,
 - avoid use of antibiotics as an intracanal medication (in favor of calcium hydroxide)
 - perform regeneration (induction of bleeding, formation of a blood clot) in a second session.
3. Consider using a non discoloring material and inform patient and/or parents or guardians of the possibility of discoloration of the element.
4. Regenerative therapy is contraindicated in case of:
 - replantation of teeth because revitalization can occur naturally,
 - Insufficient ability to isolate the dentition,
 - dentition with extensive loss of coronal tissue requiring repair with a post buildup that occupies the space required for blood clot formation.
5. The study group did not formulate a recommendation regarding regenerative therapy in the case of mature teeth. In the study group's opinion, insufficient research has been conducted to base a recommendation on this.

Rational

A clinically relevant difference in success or survival between regenerative therapy and apexification has not been demonstrated. The cause of pulpal necrosis (trauma, dens evaginatus or caries) is not an indication for one or the other treatment, the study group believes. There is evidence from the discussed literature to avoid EDTA as an irrigant and make do with sodium hypochlorite. There are also indications from the discussed literature that it is better to perform the entire regeneration procedure in two sessions *rather than* one. Regarding the avoidance of antibiotics as an intracanal medication, the study group believes that due to the risk of antibiotic resistance, it is desirable to use them as little as possible. According to Kharchi et al. (2020), their review shows that the combination of sodium hypochlorite with calcium hydroxide may provide a sufficiently disinfected environment. They acknowledge that although the evidence is weak, they note: '(...) it can be argued that when evidence is questionable but calcium hydroxide does not have the disadvantages of TAP [in addition to risk for antibiotic resistance a lesser control of discoloration], it is practical to use calcium hydroxide as a non-antibiotic intra-channel medication'. While the discussed literature provides evidence that calcium hydroxide increases the risk of calcification of the root canal compared to antibiotics, calcification should not be considered as a failure of regenerative therapy nor an obvious risk factor for root canal treatment, according to the study group.

The study group assumes that the costs for both options will be reimbursed and thus not a reason to prefer one or the other. The recommendations on contraindications were taken from European Society of Endodontists position statement (Galler et al., 2016).

7. Treatment of necrotic pulp

It is recommended to use hand irrigation with sodium hypochlorite during chemo-mechanical cleaning, preferably after each instrument.

[unchanged after update 2022/3]

Rationale The combination sodium hypochlorite + EDTA (and again sodium hypochlorite) is a simple procedure, has good dissolution capacity of organic tissue and is associated with low cost.

Do not consider adding laser techniques to chemo-mechanical cleaning.

[update 2022/3: new recommendation]

Rationale

Adding laser techniques to chemo-mechanical cleaning has no additional effect on periapical repair but requires additional costs.

Consider a reciprocating or rotary system

[update 2022/3: new recommendation]

Rationale

The two systems differ little or not at all in terms of bacterial reduction and effect on postoperative pain. Reciproke systems require a little less operating time, providing a little more comfort for the patient, and give a little less cost to the patient. Given the possibly minor or even absent differences, familiarity and experience of practitioners with these systems will play an important role.

At the end of chemo-mechanical cleaning, ultrasonic activated irrigation can be considered.

[unchanged after update 2022/3]

Rational

Ultrasonic activated cleaning seems to lead to slightly less short-term pain and slightly more healing/reduction of periodontitis apicalis. As for cost, it is variable and need not be an impediment to applying ultrasonic activated cleaning.

Removal of the resulting smear layer with EDTA may also be considered.

[unchanged after update 2022/3]

Rationale

According to the working group, removing the smear layer provides more cleaning and disinfection of the root canal walls and better adaptation of filling materials to the cavity wall.

Consider use of epoxy resin-based sealers

[update 2022/3: new recommendation]

Rational

Although "bioceramic" sealers seem to show slightly more radiographic healing in the short term than epoxy resin-based sealers, nevertheless, more studies are needed to be more certain about their long-term effect before a recommendation can be given, also considering the additional cost of "bioceramic" sealers.

Consider performing root canal treatment of a necrotic pulp in one sitting. This may be deviated from when warranted by the presence of pain (emergency), the difficulty of the treatment and/or the patient's wishes.

[unchanged after update 2022/3]

Rationale

The outcomes of treating in one or more sessions seem to differ little or not at all. Most patients prefer treatment in one session.

In root canal treatment of a necrotic pulp, consider **not using** calcium hydroxide as an intra-canal medication.

[update 2022/3: new recommendation]

Rationale

The endotoxin-reducing effect of calcium hydroxide as an intracanal medication seems to be of little importance for the final treatment outcomes. There are significant drawbacks to its use: it is difficult to remove and residual residue can cause reduced adhesion of the canal filling or composite filling used

During initial root canal treatment of a necrotic pulp or re-treatment with periodontitis apicalis, consider achieving apical clearance to prevent apical blockage.

[update 2022/3: new recommendation]

Rational

Achieving apical clearance (with a #08 or #10 K file) reduces postoperative pain and may indirectly have a beneficial effect on healing/reduction of apical periodontitis.

Antibiotics for the purpose of analgesia should not be administered.

[unchanged after update 2022/3]

Rationale

Use of an antibiotic as an ineffective form of analgesia should be avoided. Use of an antibiotic as an ineffective form of analgesia should be avoided. This also helps reduce antimicrobial resistance.

8. Orthograde re-treatment

No studies were found, insofar as they met the inclusion criteria, that examined the effect of the number of treatment sessions, instrumentation, disinfection protocol or root canal filling material in a comparative observational or experimental study. All included studies aimed to detect prognostic factors for treatment outcome.

Inform the patient in whom orthograde re-treatment is being considered, preferably also in writing, of the magnitude of the risk of inadequate healing of periodontitis apicalis.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to a well-informed patient.

9. Acute complaints and pain management

The following recommendations apply to patients in whom the symptomatic tooth has not previously been treated endodontically by a general practitioner or dental endodontist

Use of antibiotics in acute complaints related to irreversible pulpitis or symptomatic apical periodontitis and acute apical abscess is not recommended in the context of pain management.

[unchanged after update 2022/3]

Rationale

The guideline working group gave considerable weight to the finding that an antibiotic is unlikely to be effective as an analgesic and may lead to resistance and hypersensitivity.

*As part of pain management, consider **not** using an intracanal medication.*

[update 2022/3: new recommendation]

Rational

Although the use of chlorhexidine and calcium hydroxide as intracanal medicament has a beneficial effect on postoperative pain, the study group does not recommend it because of its various disadvantages. For example, calcium hydroxide is difficult to remove, dentin weakens with prolonged presence of an intracanal medication, adhesion of the filling material is impaired and an unfavorable shift in biofilm may occur.

The working group does not recommend cooling irrigants.

[update 2022/3: new recommendation]

Rational

The study group believes that additional measures to provide cooling irrigants are disproportionate to the small effect they might be expected to have on postoperative pain.

Use of premedication is not recommended.

[update 2022/3: new recommendation]

Rationale

Premedication seems to be effective only when using relatively 'heavy' analgesics, such as corticosteroids. 'Lighter' agents such as paracetamol and NSAIDs have at least the same effect when given *post-operatively*.

The working group does not provide a recommendation Regarding mepivacaine.

[update 2022/3: new recommendation]

Rationale The study group has noted the promising results of mepivacaine (i.c.w. adrenaline) but notes that this drug is not available in the Netherlands. The use of articaine and bupivacaine can be continued.

In cases of fluctuating swelling, an abscess incision is indicated.

Patients with severe swelling who also have fever and/or swallowing symptoms should be referred to an MKA surgeon immediately for treatment.

[unchanged after update 2022/3]

Rational

The proposed incision will quickly reduce pain and swelling and may allow further endodontic treatment to take place at a later stage.

As analgesia, in acute complaints associated with irreversible pulpitis or symptomatic apical periodontitis, paracetamol (whether or not in combination with an NSAID) can be given. If this medication does not provide adequate analgesia, the WHO pain ladder can be consulted (see Appendix 2 in Chapter 9 of this guideline).

Use of the combination paracetamol and codeine is not recommended.

[unchanged after update 2022/3]

Rational

Paracetamol can be used safely. *[update 2022/3]* *In severe postoperative pain, there is a reasonable degree of certainty that paracetamol is ineffective and the combination of paracetamol and NSAIDs or NSAIDs alone provide adequate analgesia.* Use of NSAIDs may be contraindicated in patients.

The efficacy of the paracetamol-codeine combination has not been demonstrated in clinical studies. The advice regarding paracetamol/NSAIDs and the WHO pain ladder is taken from the NHG standard "Pain.

If there is a previously endodontically treated element

All of the above recommendations and treatment strategies also apply to these. However, the treatment of these elements is more challenging because the old canal treatment will have to be removed first. In such cases, it is worth considering referring the patient to a dental endodontist. If the treatment is not going to be performed immediately, pain relief can also be prescribed in this case.

[unchanged after update 2022/3]

Rational

The guideline working group sees no reasons (pathophysiological or practical) why the recommendations formulated in connection with acute complaints in an element not previously endodontically treated should not be applicable for an element that has been previously endodontically treated.

10. Permanent and temporary restoration of elements

Inform the patient in whom root canal treatment is being considered that proper coronal closure will affect the outcome of treatment.

[unchanged after update 2022/3]

Rational

The guideline working group places great weight on a well-informed patient.

In a patient in whom root canal treatment is planned and in whom less than two raised walls are present, consider using a fiberglass post.

[unchanged after update 2022/3]

Rational

The working group believes that a fiberglass post can provide additional retention for coronal restoration when insufficient tooth material remains.

In a patient in whom root canal treatment is planned and in whom less than half of the coronal tooth tissue is present, consider fabricating a nodule-covering restoration.

[unchanged after update 2022/3]

Rational

The guideline working group emphasizes the importance of avoiding fracture of an element/node.

For endodontically treated molars with severe tissue loss, consider placing an endocrown or a build-up and conventional crown.

*For endodontically treated premolars with severe tissue loss, consider placing **not an** endocrown but a post buildup with conventional crown.*

[update 2022/3: new recommendation]

Rational

The survival time of an endocrown for *molars* seems similar to that of a conventional crown, The survival time of an endocrown for *premolars* seems significantly shorter than that of a conventional crown.

For a temporary restoration associated with multiple consecutive appointments, consider using Teflon instead of a cotton ball as an "endodontic spacer," if use of a "spacer" is deemed necessary.

[update 2022/3: new recommendation]

Rational

The working group attaches importance to the prevention of bacterial growth, thereby reducing the risk of endodontic failure.

12. Avoidance and treatment of complications.

[update 2022/3: The term procedural errors has been replaced by complications].

Inform the patient of a complication that has occurred.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to informing the patient after the occurrence of a complication.

Consider the following factors when deciding whether or not to remove or have removed the *aborted instrument*:

- position of the aborted fragment;
- cleaning degree of the root canal;
- available resources;
- risk of complications and
- Presence of periapical lesion.

Consider leaving the aborted instrument in situ under the following conditions: - There is no periapical radiolucency visible on the solo recording at the root where the instrument fracture occurred, AND
- The root canal apical to the aborted instrument is sufficiently clean by thorough irrigation prior to the instrument fracture, AND
- The fragment is inaccessible (located in the apical part of the root canal or beyond the bend).

In all other conditions, removal of the aborted instrument should be considered. This should include the risk of complications; if the aborted instrument is not in the coronal part of the root canal, removal of the fragment will involve tissue loss to make the fragment accessible.

If the practitioner considers himself not competent in removing broken instruments and/or does not have the necessary tools, he should refer the patient to a dental endodontist.

[unchanged after update 2022/3]

Rational

The guideline working group places great importance on preventing harm from repairing complications.

Non-surgical repair of a *root perforation* using *MTA material* is preferred. The defect to be repaired should be cleaned. When the perforation is above bone level, composite or glass ionomer cement is the material of choice.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to repairing complications and the correct choice of material.

Accident prevention with sodium hypochlorite:

- Identify risk factors such as perforations and resorptions, and
- prevent jamming of the irrigation needle in the root canal.

Treatment in the same session in which accident occurred:

For mild damage (mild pain, swelling <30%, local hematoma, no ulcerations or necrosis), the general practitioner or dental endodontist should:

- explanation to the patient;
- prescribe analgesics, preferably an NSAID to control swelling;
- cool by applying cold compresses or a cold pack to control swelling and
- perform an intra-oral radiograph or OPT to determine the cause of jacking and to aid in further management.

With moderate or severe damage (moderate or severe pain, swelling >30%, diffuse hematoma, intraoral

ulcerations, necrosis, airway obstruction or neurovascular damage), the patient should be referred to the MKA surgeon.

Follow-up treatment in the first week after the accident

For *mild damage* (mild pain, swelling <30%, local hematoma, no ulcerations or necrosis), the general practitioner or dental endodontist should:

- recommend using warm compresses to stimulate blood flow and
- perform regular monitoring to detect a deterioration in the patient's condition in a timely manner.

Longer-term follow-up treatment

With mild damage (mild pain, swelling <30%, local hematoma, no ulcerations or necrosis) or *After referral back by the MKA surgeon*, the general practitioner or dental endodontist should complete the root canal treatment.

Also when completing root canal treatment, use sodium hypochlorite as a root canal irrigant. In some cases, physiological saline may be chosen as a root canal irrigant in consultation with patient, even though it may adversely affect treatment outcome.

[unchanged after update 2022/3]

Rational

The guideline working group places great importance on avoiding sodium hypochlorite injury, distinguishing between mild on the one hand and moderate or severe on the other, and verifying the correct estimation of the level of injury.

Good practice statements

As a *good practice point**, the guideline working group emphasizes the importance of always preceding root canal treatment by making a *diagnosis* and identifying risk factors (such as by determining a DETI score; see Appendix 2 of Chapter 7 in this guideline).

As a *good practice point**, the guideline working group emphasizes the importance of using cofferdam because of the following benefits:

- protection: by using a cofferdam, the chance of aspiration is very small;
- Endodontic treatment with a cofferdam prevents contamination of the work area;
- better visibility of the work area and
- treatment can be carried out more efficiently.

As a *good practice point**, the working group emphasizes the importance of using an augmentation tool because of the following benefits:

- better view of the work area;
- tool for diagnostics and
- better work attitude.

As a *good practice point**, the working group recommends the following:

- Inform the patient prior to treatment about the prognosis of endodontic treatment and the possible effect of preoperative status on it.
- *[update 2022/3] Please note that the following factors may have a negative effect on the healing of periodontitis apicalis he:*
filling of the root canal more than 2 mm from the radiographic apex endend;
 - coarseoverfilling;
 - voids.

* A good practice point is considered important for good dental practice for which, however, significant evidence may be lacking.

1. General introduction

1. 1Rationale for creating the guideline

In 2012, the Health Council issued the report *The Oral Care of Tomorrow* to the Minister of Health, Welfare and Sport. One of the recommendations from that report was to motivate oral health care professionals to develop clinical practice guidelines that describe the best treatment for each diagnosis based on scientific evidence. The Dutch Association for Endodontology (NVvE) wants to take the initiative to start guideline development in the field of endodontology.

Why is it important to develop a guideline for this topic?

NVvE believes it is important to have guidelines for endodontology because it is a complex and widely practiced part of dentistry. Endodontology is practiced by both general practitioners and differentiated dentists (dental endodontologists). Diagnostics is very important in this. Once the correct diagnosis is made, one can prescribe and implement the best treatment based on it.

1.2 Purpose of the Directive

Develop an evidence-based guideline for endodontic diagnosis and treatment .

1.3Absence of the directive

Which patient group is involved?

The guideline targets all patients with permanent dentition who present with suspected endodontic pathology.

What are the most important and patient-relevant outcome measures?

- postoperative pain
- postoperative swelling
- Survival and functional status of dentition
- quality of life
- costs.

1.4 Intended users of the guideline

This guideline is intended for general practitioners, dental students and dental endodontists.

1. 5Definitions and terms.

What are the key definitions used in this guideline?

A list of definitions is available on the NVvE website (<https://nvve.com/wp-content/uploads/2018/03/Begrippenlijst-Endodontologie.pdf>).

2. Methodology guideline development

2.1 Validity

No later than 2027, the NVvE Board will determine whether this guideline is still current. If necessary, a new working group will be installed to revise the guideline. The validity of the guideline will expire earlier if new developments warrant initiating a revision process. The responsibility for identifying new developments (new evidence, bottlenecks presented from practice) lies with the guideline committee of the NVvE.

The NVvE, as holder of this guideline, is primarily responsible for keeping this guideline current.

2.2 General data

Updating the guideline published in 2018 was methodologically supported by J.J.A. de Beer, independent guideline methodologist, and funded by the NVvE.

2.3 Purpose and Target Group

Target

The goal of the guideline is to create clarity and uniformity for practitioners about endodontic diagnostic and treatment methods.

Specific goal is to develop evidence-based recommendations for the following topics:

- diagnostics of the pulp;
- Imaging diagnostics of periapical tissues;
- Treatment of teeth with inflamed pulp;
- *[update 2022/3] regenerative endodontic treatment*
- Treatment of teeth with necrotic pulp;
- orthograde revision of endodontic treatment*;
- Treatment of acute symptoms and pain management;
- Permanent and temporary restoration of teeth that have undergone root canal treatment;
- Understanding risks of and exacerbation of disease in other organs due to inflammation of the pulp and periapical tissues and
- avoiding and treating complications.

* Regarding retrograde treatment of a previously endodontically treated element, the guideline working group refers to the guideline apical surgery (apical resection) of the Dutch Association for Oral, Maxillofacial and Maxillofacial Surgery (NVMKA).

Target

The guideline aims to provide practical guidance for professional groups involved in endodontic diagnosis and treatment: general practitioners, dental endodontists and dental students.

2.4 Declarations of Interest

The working group members declared in writing whether they maintained any (financially supported) relationship in the last five years with commercial companies, organizations or institutions related to the subject of the guideline. Inquiries were also made about personal financial interests, interests through personal relationships, interests through reputation management, interests because of externally funded research, and interests through knowledge valorization. The declarations of interest can be requested from the NVvE. An overview can be found below:

Working Group Member	Function	Side functions	Person ly finan cial interests	Person ly relations-hips	Reputa-tie-manage-ment	Externally financed under search	Knowled-ge Valorisa-tie	Other interests
A. Feiz Barazandeh (member until 2018)	dentist-endodon toloog	no	no	no	no	no	no	no
A.G.M. Bouwman	dentist-endodon interpreter, dentist-teacher	committee member guideline advisory committee committee member scientific committee NVvE committee member training committee	no	no	no	no	no	no
E. Eggink	dentist-endodon toloog	Until November 202 chairman committee(re-) recognition ning T(andarts) E(ndodontolo gist) NVvE (unpaid)	no	no	Until November 2022 chairman committee on recognition ning and re-registrati on T(andarts) E(ndo dontolo-gist) NvvE (unpaid)	no	no	no
E.S. Hin (chairman)	dentist-endodon toloog	Until October 2020 chair-man/member of NVvE board (un-paid); until 2020 member be steer FWTv (un-paid); Until 2023 member Directive Advisory Committee (RAC) KiMO (unpaid) From 2023 board mem-ber KNMT	no	no	see addi-tional functions	no	no	no
B. Lacquer	dentist-endodon toloog	From No- vember 2022 chairman committee on	no	no	until May 2016 president of TEN	no	no	no

<i>Working Group Member</i>	<i>Function</i>	<i>Side functions</i>	<i>Person ly finan cial interests</i>	<i>Person ly relations-hips</i>	<i>Reputa tie- manage ment</i>	<i>Externally financed ciedr under search</i>	<i>Knowled-ge Valorisa tie</i>	<i>Other interests</i>
		recognition ning and re- registration T(andarts) E(ndo donto- logist) NVvE (un taald) Until Novem- ber 2022 member of the afore- mentioned committee (unpaid) From No- vember 2023 NVvE board member			(Dentist Endodon tologen Neder land)			
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A.R. Ozok	dentist- endodon interpreter, uni versi tary lecturer	no	no	no	no	no	no	no
H. Shemesh (member until 2018)	dentist- endodon toloog, secti- on chairman department of endodonto logy ACTA	no	no	no	no	no	no	no
L.W.M. van der Sluis (member until 2018)	dentist- endodon interpreter, department head UMCG- CTM	NVvE scienti- fic committee (unpaid)	no	no	no	no	disinfect- ant compo sition and its use in dental treat ment WO 20111027 24 A3	no
B.M.T. Tulp	dentist- endodon to loog, lectu-	From 2022 Endodontolo- gist at the	no	no	no	no	no	no

Working Group Member	Function	Side functions	Person ly finan cial interests	Person ly relations-hips	Reputa tie- manage ment	Externally financed ciera under search	Knowled-ge Valorisa tie	Other interests
	rer/section head Endo dontology ACTA	Foundation forSpecial Dentistry						

2.5 Input patient perspective

Attention was paid to the patient perspective by conducting literature searches, in particular studies on values and preferences regarding treatment methods and treatment outcomes, and shared decision-making (see appendix literature search patient perspective). The Patient Federation of the Netherlands (formerly the Dutch Patients' Consumer Federation (NPCF)) was asked to comment on the draft guideline. It did not wish to do so because it was not given the opportunity to provide bottlenecks and concerns during the preparation phase.

[update 2022/3] Due to the small number of studies on patient values and preferences found in 2017 that are informative for the Dutch situation, the literature review on this topic has not been updated.

2.6 Implementation

At the various stages of guideline development, the implementation of the guideline and the practical feasibility of the recommendations were taken into account. In doing so, explicit attention was paid to factors that may promote or hinder the implementation of the guideline in practice (see implementation chapter).

2.7 Methodology

AGREE and GRADE

This guideline was prepared in accordance with the requirements according to the report Medical Specialist Guidelines 2.0 of the Guideline Advisory Committee of the Council for Quality (www.kwaliteitskoepel.nl). This report is based on the AGREE II tool (Appraisal of Guidelines for Research & Evaluation II) (www.agreecollaboration.org), which is an internationally widely accepted tool, and on "guidelines for guideline quality assessment" (www.cvz.nl).

It was also prepared in accordance with the GRADE methodology (Guyatt et al., 2008).

[update 2022/3] Between 2017 and 2023, some important changes were made to the GRADE methodology. These are explained in the section "Assessing the strength of the scientific evidence."

Bottleneck analysis, baseline questions and outcome measures

No bottleneck inventory was conducted during the preparatory phase. The reason is that the NVvE Board's assignment was to update and make applicable the systematic review *Methods of Diagnosis and Treatment in Endodontics* written under the auspices of the *Swedish Council on Health Technology Assessment*. June 2012.

The (global) starting questions in *Methods of Diagnosis and Treatment in Endodontics*. June 2012 were adopted by the guideline working group. These read:

- How well can different diagnostic methods determine the condition of the pulp in teeth with different types of injury (caries, trauma, restorative interventions and other causes)?
- How well can different imaging methods demonstrate bone loss at the root tip?
- Are there effective methods for treating an inflamed pulp so that the pulp is preserved when affected by caries, trauma or other injury?
- [Update 2022/3] How effective are regenerative endodontic techniques?
- How effective are different treatment modalities when the pulp is necrotic?
- How effective are orthograde treatments of elements that have undergone root canal treatment, and show signs of periodontitis apicalis?

- How effective are different methods of treating acute symptoms and pain management?
- Can elements that have undergone root canal treatment be effectively restored with multi-year survival of element and restoration?
- Is there a risk that acute and chronic infections emanating from the pulp cause pathological conditions in other organs?
- What complications are associated with root canal treatment?

For the specific exit questions, the reader is referred to Appendix exit questions.

Strategy for searching and selecting the literature for the 2022/3 update

The study group searched PubMed/Medline and the Cochrane Database of Systematic Reviews (CDSR) for systematic reviews and meta-analyses, commentaries and editorials using the literature search strategy shown in Appendix "Update Literature 2022." The choice of this search strategy was based on Shekelle et al. (2001).

1015 titles/abstracts were found in PubMed/Medline using this search strategy. CDSR had no additions. Each working group member screened several hundred titles/abstracts for relevance to one of the existing chapters or to a possible new chapter. The second step involved two working group members checking the attribution of titles/abstracts to the various chapters and adjusting them if necessary. The third step was to determine whether diagnostic and therapeutic interventions that had not yet been discussed in the guideline would be included in the update. Criterion for this was whether the working group believed that there was discussion in the field about the advantages and disadvantages of these interventions. This was decided by majority vote. As a final step, all systematic reviews were assessed for methodological quality using the AMSTAR-I criteria. Only systematic reviews of sufficient methodological quality were included, i.e., when they met at least six of the 11 AMSTAR-I criteria. The reviews are included in appendix "update literature 2022" which can be requested through the NVvE Secretariat.

Strategy for literature search and selection first version of the guideline

Additional searches were performed in the Cochrane Library and PubMed/Medline. The search strategies listed in *Methods of Diagnosis and Treatment in Endodontics* were used for this purpose. *June 2012*. In principle, the selection of relevant studies adopted the criteria used by the authors of *Methods of Diagnosis and Treatment in Endodontics. June 2012*, unless the working group considered these criteria too limited. This means that clinical studies were sought as much as possible, and where efficacy and safety of treatment were concerned, studies with a direct comparative design, that is, studies with a control group.

The working group members selected the articles found through the search based on pre-established selection criteria. The selected articles were used to answer the starting question. The selection criteria used can be found in the selection criteria tables in the different chapters of the relevant starting question.

Quality assessment of individual studies

The risk of biased outcomes in individual studies was systematically assessed, based on pre-established methodological quality criteria

(<http://netherlands.cochrane.org/beoordelingsformulieren-en-andere-downloads>):

- For studies on diagnostic tests/procedure, this is the QUADAS tool;
- For studies on treatment and/or therapeutic interventions, this is the Cochrane risk of bias tool and
- For prognostic studies, an adapted version of the QUIPS tool was used. Practically, this means, in particular, dropout rates, corrections for confounding variables, and quality of statistical analysis were examined.

Summarizing the literature

The relevant research data from all selected articles were conveniently presented in evidence tables and/or evidence profiles. The main findings from the literature were described in the literature summary.

[update 2022/3] For the "update 2022/3" it was chosen not to create evidence tables, but to describe the summary of the literature in more detail. The existing evidence tables are included in a separate appendix "evidence tables" which can be requested through the NVvE Secretariat.

Assessing the strength of the scientific evidence

The quality of evidence ("quality of evidence") was assessed using GRADE (Guyatt et al., 2008). GRADE is a method that assigns a grade to the quality of evidence for each outcome measure of an intervention, or for a risk or prognostic factor, based on the degree of confidence in the estimate of effect size. High quality of evidence means there is high confidence that the actual effect is close to the estimated effect; low quality of evidence means confidence in the estimated effect is limited: the actual effect may differ substantially from the estimated effect.

[update 2022/3] The definition of quality of evidence as of 2017 reads as follows: 'the quality of evidence indicates how confident we are that the true effect is within a certain range of outcomes or on one side of a threshold' (Hultcrantz et al., 2017). This is illustrated in Figure 2-1 and Table 2-1 and Table 2-2.

A second change is that instead of two levels, three levels can be downgraded for imprecision ("imprecision"). The width of the confidence interval is the most important criterion in relation to the range of outcomes or a threshold to assess the degree of imprecision (Schunemann et al., 2022; Zeng et al., 2022).

This is illustrated in Figure 2-2.

Figure 2-1 Illustration revised GRADE definition quality of evidence

Suppose intervention A reduces pain intensity by -24 on a 0-100 VAS scale and intervention B by -10 on a 0-100 VAS scale. The difference is -14 with a 95% confidence interval of (-20, -8). For a patient-relevant difference in pain intensity, there is a threshold of -10. I.e., -11, -12 etc. all indicate a relevant difference, while -9, -8 etc. indicate an undetectable or barely detectable difference in pain intensity.

In this example, the quality of evidence is about how certain it is that the difference in pain intensity (outcome -14) is to the left of the threshold value of -10 or smaller than -10.

Figure 2-2 Illustration markdown for severe, very severe or extremely severe inaccuracy

In the illustration above, the difference in pain intensity between interventions A and B is -14 with a 95% confidence interval of (-20, -8). This is in favor of intervention A. A threshold value of -10 applies for a patient-noticeable difference in pain intensity. Looking now at the confidence interval, we find that it includes outcomes -8 and -9. These are values that do not indicate a noticeable difference in pain intensity between interventions A and B. In this case, we downgrade by one level for severe imprecision because the confidence interval crosses the threshold value of -10. The conclusion would be: intervention A *probably* reduces pain intensity *slightly* compared to intervention B. Would the confidence interval have been (-17, -11) instead of (-20, -8), then the threshold value -10 is *outside* the confidence interval and there is certainty that the lowest possible value of the confidence interval (-11) gives greater pain reduction than the threshold value of -10. The conclusion would then be: intervention A, compared to intervention B, reduces pain intensity *slightly*.

Now instead of -14, let the difference in pain intensity be -31 on a 0-100 VAS scale. The 95% confidence interval is (-54, -8). The study group defined a reduction of 0-<10, 10-<20, 20-<30 and 30 and above as no relevant difference, small but significant difference, medium difference and large difference. Looking at the difference (-31) and the confidence interval (-54, -8), we find that the confidence interval crosses three thresholds: <-10 (no relevant difference), <-20 (medium difference) and <-30 (large difference). In this case, we downscale by three levels and the conclusion would be: intervention A *seems to* result in a *large* reduction in pain intensity compared to intervention B, but the evidence is very uncertain. After all, it cannot be excluded that there is no relevant reduction, or that there is a small but significant reduction or a medium reduction. Had the confidence interval been (-31, -26) instead of (-54, -8), we would downgrade by one level for severe imprecision, because the confidence interval only crosses the threshold of -30, but not those of -20 and -10. The conclusion would then be: intervention A *is likely to* result in a *large* reduction in pain intensity compared to intervention B.

Table 2-1 Classification of quality of evidence according to GRADE [update 2022/3].

High	It is <i>almost certain</i> that the true effect lies <i>within some range of values or on one side of a threshold value</i>
Fair	It is <i>likely</i> that the true effect lies <i>within a certain range of values or on one side of a threshold value</i>
Low	It is <i>possible</i> that the actual effect lies <i>within a certain range of values or on one side of a threshold value</i>
Very low	It is <i>possible</i> that the true effect lies <i>within a certain range of values or on one side of a threshold</i> , but the evidence is very uncertain.

Table 2-2 The quality of evidence is determined based on the following criteria [update 2022/3]

Type of evidence	<p><i>For studies on therapeutic interventions:</i></p> <p>RCT starts in the 'high' category. Observational study starts in the 'low' category. All other study types start in the 'very low' category.</p> <p><i>For studies on diagnostic accuracy:</i></p> <p><i>Cross-sectional study with consecutive patients and acceptable reference test starts 'high'</i></p> <p><i>For studies on a risk or prognostic factor:</i></p> <p>Prospective or retrospective cohort study starts in the 'high' (Phase 2) or 'moderate' (Phase 1) category. For other study designs, downgrading is done via 'risk of bias' only.</p>	
Write-down	'Risk of bias'	<ul style="list-style-type: none"> - 1 Serious - 2 Very serious
	Inconsistency	<ul style="list-style-type: none"> - 1 Serious - 2 Very serious
	Indirect evidence	<ul style="list-style-type: none"> - 1 Serious - 2 Very serious
	Inaccuracy	<ul style="list-style-type: none"> - 1 Serious - 2 Very serious - 3 <i>Extremely severe</i>
	Publication bias	<ul style="list-style-type: none"> - 1 Likely - 2 Very likely
Upgrade	Big effect	<ul style="list-style-type: none"> + 1 Large + 2 Very large
	Dose-response relationship	+ 1 Evidence for gradient
	All plausible 'confounding'	<ul style="list-style-type: none"> + 1 Could reduce an effect + 1 Might suggest an opposite effect while the results show no effect.

Formulating the conclusions

A conclusion does not refer to one or more articles, but is drawn based on all studies combined (body of evidence).

Considerations

In arriving at a recommendation, other aspects besides the quality of scientific evidence on the desired and undesired effects of an intervention, on the accuracy of a diagnostic study, or on the effect size of a risk or prognostic factor, are often important.

Mention may be made of:

- the balance of desired and undesired effects (including costs);
- values, preferences and experiences of patients and practitioners regarding interventions and outcomes of care;
- applicability of a recommendation.

Preferably, scientific evidence is also sought for these aspects. The working group that drafted this guideline has refrained from doing so, with the exception of patient values and preferences, because the time required for this would be out of all proportion to the expected yield. Where it was deemed necessary, the working group inventoried the aforementioned aspects based on its own experience and expertise.

These aspects are discussed after the "conclusion" under the heading "considerations."

Formulating recommendations

The recommendations answer the baseline question and are based on the best available scientific evidence and key considerations. The overall quality of evidence with respect to desired and undesired effects (increases in costs are also an undesired effect), the importance the study group assigns to outcome measures (e.g., pain reduction or periapical healing), and the balance of desired and undesired effects together determine the strength of the recommendation.

The overall quality of evidence is determined by the lowest level of evidence of an individual effect. For example, if the quality of evidence for periapical healing is low and the quality of evidence for reduction of postoperative pain is high, then the overall quality of evidence is low. Overall quality of evidence indicates how confident we are about the balance of desired and undesired effects.

The GRADE methodology has strong and weak recommendations. Strong and weak recommendations can be identified by verbs used. A **notional** strong recommendation might read, "Remove the smear layer after chemo-mechanical preparation. A **notional** weak recommendation could read, 'Consider removing the smear layer after chemo-mechanical preparation'. In general, low and very low overall quality of evidence will result in a weak recommendation and reasonable and high overall quality of evidence will result in a strong recommendation.

Indicator development

Simultaneously with the development of the draft guideline, internal quality indicators were developed to monitor and strengthen the application of the guideline in practice. For this purpose, the methodology described in *Programm für Nationale VersorgungsLeitlinien von BÄK, KBV und AWMF Qualitätsindikatoren. Manual für Autoren: 6. Qualitätsindikatoren für Nationale VersorgungsLeitlinien* (2009). This methodology focuses on deriving indicators from strong recommendations. In addition, the presence of improvement potential, measurability and influenceability play an important role. [update 2022/3] The indicators have not yet been implemented, and will be retained - with a new indicator.

Knowledge gaps

During the development of this guideline a systematic search was made for research whose results contribute to an answer to the starting questions. For each key question, the study group examined whether (additional) scientific research is required. An overview of recommendations for further research or follow-up research can be found in the chapter Knowledge gaps.

2.8 Comment Phase

After the draft guideline was developed, it was submitted to a sounding board group of general practitioners and dental endodontists (see Appendix members sounding board group). Its comments were then incorporated as far as possible.

Literature

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 336: 924-6.

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3. Diagnosing the condition of the pulp

Introduction

The importance of making an accurate diagnosis of the condition of the pulp in elements affected by caries, dental injury or dental treatment can hardly be overstated. Accurate diagnosis is crucial for appropriate treatment. The goal of endodontic diagnostics is to identify elements with inflamed or necrotic pulp.

Signs and symptoms of various kinds can provide information as to whether, and to what extent, the pulp is inflamed or if, on the contrary, it is necrotic. There are several tests based on measuring a response to sensory stimuli (sensitivity) and tests to measure blood circulation in the pulp (vitality). Currently, vitality tests are poorly available and sensibility tests are mainly used in practice (Donnermeyer et al., 2022; Balevi, 2019; Mainkar & Kim, 2018). Thereby, these tests can be divided into thermal tests (cold and heat) and the electrical tests. Of course, this is always in combination with the clinical history and extra- and intra-oral examination.

How do you make a reliable diagnosis of the condition of the pulp? This question has two parts:

1. How accurate (sensitivity, specificity, positive and negative predictive value) are the various methods for determining pulpal sensitivity and vitality? Methods: thermal testing, electrical testing, percussion, pulse oximetry and laser Doppler flowmetry.
2. What is the predictive value of methods or markers for the outcome of treatment aimed at keeping the pulp vital, healthy and asymptomatic? Methods/markers: bleeding of the pulp, preoperative pain of mild intensity, thermal testing, electrical testing, percussion, and color and hardness of dentin around the affected pulp (depth of caries lesion).

Search and selection

The starting point is the systematic review by Mejare et al. (2012). This review is the same as the Swedish Council on Health Technology Assessment's systematic review. The review by Mejare et al. (2012) searched for literature in PubMed, EMBASE, The Cochrane Central Register of Controlled Trials and Cochrane Reviews published up to June 2011. Eighteen studies were found that met the inclusion criteria. Some of these studies involved examination of signs and symptoms as indicators of pulpal inflammation. Another part of the studies involved examination of pulpal sensitivity and vitality. The search strategy included in the Swedish Council on Health Technology Assessment's systematic review was used to update this review via PubMed (Appendix 3.1). In addition to the systematic review by Mejare et al. (2012), several other systematic reviews were found that were relevant to the starting question, but whose methodological quality (design and conduct of the review) was insufficient (Abu-Tahun et al., 2012; Jafarzadeh & Abbott, 2010a and 2010b; Barnes & Pattel, 2011). In part because no search strategy was specified (Barnes & Pattel, 2011), the selection of studies was unclear, and/or the methodological quality of the studies (Abu-Tahun et al., 2012; Jafarzadeh & Abbott, 2010a and 2010b) had not been assessed. Of the primary studies found, 1 met the inclusion criteria (Karayilmaz & Kirzioğlu, 2011). The reviews by Abu-Tahun et al. (2012, Jafarzadeh & Abbott (2010a; 20120) are briefly discussed in the considerations (under the heading professional perspective).

Selection Criteria

Type of studies	- SRs - original observational studies - ex and in vivo studies - publications from 2010
Type of patients	- adult patients in whom the pulp may be affected by caries, injury or dental treatment and who are undergoing diagnostic testing
Reference Standard	- histological examination or inspection of pulpal tissue

Type of outcome measures	<ul style="list-style-type: none"> - sensitivity and specificity - likelihood ratio - odds ratio - ROC curves - AUC (area under the curve). - or data from which the above outcomes can be derived
Type of setting	<ul style="list-style-type: none"> - general practitioners - dental endodontists

Summary of literature

How accurate (sensitivity, specificity, positive and negative predictive value) are the various methods for determining pulpal sensitivity and vitality? Methods: thermal testing, electrical testing, percussion, pulse oximetry and laser Doppler flowmetry?

10 studies (Dummer 1980; Evans 1999; Georgopoulou 1989; Gopikrishna 2007; Johnson 1970; Kamburoğlu 2005; Petersson 1999; Seltzer 1963; Weisleder 2009; Karayilmaz 2011) examined the sensitivity and specificity of the *electrical* test. 10 studies (Dummer 1980; Evans 1999; Garfunkel 1973; Georgopoulou 1989; Gopikrishna 2007; Kamburoğlu; Petersson 1999; Seltzer 1963; Tyldesley 1970; Weisleder 2009) evaluated the diagnostic accuracy of the *cold test*.

The diagnostic accuracy of the *heat test* was evaluated in 6 studies (Dummer 1980; Garfunkel 1973; Georgopoulou 1989; Petersson 1999; Seltzer 1963; Tyldesley 1970). The diagnostic accuracy of *laser Doppler flowmetry* was verified in 3 studies (Evans 1999; Olgart 1988; Karayilmaz 2011). The diagnostic accuracy of *pulse oximetry* was examined in 1 study (Gopikrishna 2007). *Percussion* was tested as a diagnostic test in 2 studies (Seltzer 1963; Tyldesley 1970).

5 of the 13 studies (Dummer 1980; Garfunkel 1973; Johnson 1970; Seltzer 1963; Tyldesley 1970) involved histological examination of the pulp; 7 studies (Evans 1999; Georgopoulou 1989; Gopikrishna 2007; Kamburoğlu 2005; Olgart 1988; Petersson 1999; Weisleder 2009) involved visual inspection, and 1 study (Karayilmaz 2011) involved a control group with elements deemed healthy (Table 3-1).

Table 3-1 Characteristics of diagnostic accuracy studies to determine pulpal sensitivity and vitality

Study ID	Patients	Index Tests of vitality of the pulpa	Reference Tests
Dummer 1980	75 permanent teeth to be extracted mainly because of pain	Electrical Cold Heat	Histology of pulp after extraction: Classification according to criteria by Seltzer et al. (1963) Dichotomized into: saveable pulp (chronic partial pulpitis) (n = 50) and nonsaveable pulp (severe inflammation/necrosis) (n = 25) Disease prevalence: Nonsaveable pulp: 67% Nonvital pulp: 25%
Evans 1999	Sample 1: 67 teeth in 55 patients aged 8-35 years. Anterior teeth subjected to dental trauma with at least two signs of pulp necrosis (loss of pulp sensitivity, discoloration, radiographic signs of pathology)	Laser Doppler flowmetry Electrical Cold	Visual examination after pulp exposure Classification: Whole pulp necrotic (n = 60) Coronal pulp necrotic (n =

Study ID	Patients	Index Tests of vitality of the pulpa	Reference Tests
	Sample 2: 77 non-injured intact teeth from the same or other patients		7) Disease prevalence: (Sample 1) Total pulp necrosis: 90% Coronal pulp necrotic: 100%
Garfunkel 1973	132 teeth with painful pulp conditions in need of endodontic therapy. Exclusion criteria: Teeth with radiographic signs of apical periodontitis, incomplete case history, technical difficulties (n = 23)	Cold Heat	Histology of extirpated pulp Classification: Acute pulpitis (n = 35) Chronic pulpitis (n = 27) Chronic pulpitis with partial necrosis (n = 39) Total necrosis (n = 8) Disease prevalence: Pulpitis = 57% Partial or total necrosis = 43%.
Georgopoulou 1989	Patients scheduled for endodontic treatment 168 patients (one tooth per patient) aged 11-78 years	Electrical Cold Heat	Visual examination after pulp exposure Classification: Vital (n = 100) Necrotic (n = 68) Disease prevalence: Necrotic pulp: 40%
Gopikrishna 2007	80 patients with one single-rooted incisor, canine or pre-molar requiring endodontic therapy because of either deep caries or prosthodontics Control: Contra-lateral sound tooth	Oxygen saturation Electrical Cold	Visual examination after pulp exposure (test sample only) Classification: Bleeding (vital) (n = 38) No bleeding (necrotic) (n = 42) Disease prevalence: No bleeding (necrotic) 53% Controls subjected to EPT and cold test only
Johnson 1970	706 extracted teeth in 94 consecutive patients because of full-mouth extraction or because of caries, tooth ache, marginal periodontitis, and prosthodontics 361 teeth pulp vitality tested	Electrical	Histology of pulp after extraction Classification: Hyperaemic stage (no inflammatory cell infiltrates) 'Irreversible' cellular inflammation or necrosis Disease prevalence: Hyperaemia: 31% Severe inflammation: 10% Necrosis: 7%
Kamburoğlu 2005	93 teeth in 97 patients aged 15-65 years (mean 33 ears) in need of endodontic therapy because of caries Comparison group: Adjacent or contralateral sound teeth (n = 49)	Electrical Cold	Visual inspection of exposed pulp Classification: Bleeding (n = 50) No bleeding (necrotic) (n = 43) Disease prevalence: Necrotic pulp: 46%
Olgart 1988	Sample 1: 33 teeth in 25 patients aged	Laser Doppler flow-	Visual examination and

Study ID	Patients	Index Tests of vitality of the pulpa	Reference Tests
	7-20 years with 1 year history of injury from trauma scheduled for endodontic treatment Control: 33 non-injured teeth Sample 2: 20 teeth in 18 patients aged 7-16 years subjected to moderate trauma and initially non sensitive to EPT	metry	probing pulp exposure Classification: Vital (n = 37) Necrotic (n = 16) Disease prevalence: (controls excluded): Necrotic pulp (no bleeding): 70%
Petersson 1999	Sample 1: 59 teeth in 56 patients (21-79 years) scheduled for endodontic treatment. Sample 2: (controls): 16 teeth in nine dental students with intact teeth	Electrical Cold Heat	Visual inspection after pulp exposure. (not sample 2) Classification: Vital (bleeding pulp) (n = 46) Nonvital (no bleeding) (n = 29) Disease prevalence: (sample 2 included): Nonvital pulp: 38%
Seltzer 1963	166 teeth scheduled for extraction because of tooth ache, orthodontic, periodontal or prosthetic reasons	Pain (presence/absence) Percussion Electrical Cold Heat Heat and cold combined	Histology of pulp after extraction Classification: a. Intact uninflamed (n = 23) b. Atrophic (n = 40) c. Intact with scattered inflammatory cells (n = 19) d. Chronic partial pulpitis with partial necrosis (n = 24) e. Chronic total pulpitis with partial necrosis (n = 14) f. Chronic total pulpitis (n = 22). g. Total necrosis (n = 22). Dichotomized in a-d = non-suppurative (n = 106) And e-g = suppurative (n = 60) Disease prevalence: Total pulpitis/necrosis (e-g): 35%
Tyldesley 1970	142 teeth scheduled for extraction because of toothache	Percussion Cold Heat	Histology of pulp after extraction Classification: a. Normal/hyperaemic (n = 16) b. Acute localized pulpitis (n = 25) c. Acute generalized and or chronic pulpitis (n = 69) d. Degeneration or necrosis (n = 32) Disease prevalence: Localized pulpitis: 18% Generalized pulpitis: 49% Degenerated/necrotic pulp:

Study ID	Patients	Index Tests of vitality of the pulpa	Reference Tests
Weisleder 2009	150 patients (18-76 years) undergoing endodontic treatment. One tooth per patient	Electrical Cold Electrical and Cold test combined	23% Visual inspection after pulp exposure Classification: Vital (bleeding) (n = 64) Necrotic (no bleeding, Bleeding in apical part only) (n = 86) Disease prevalence: Necrotic pulp: 57% Case control design 52-56/59 vital in control group (electrical test-LDF)
Karayilmaz 2011	59 pairs of maxillary anterior teeth (38 pairs of central, 21 pairs of lateral incisors) in 51 patients (range 12-18 years, mean age 14.6 ±1.73 years, 28 women, 23 men). The teeth with complete endodontic fillings constituted the study group, and the healthy, contralateral teeth of the same patients were constituted the control group	Electrical Laser Doppler flowmetry	

Source: Mejàre et al., 2012; Karayilmaz & Kirzioğlu, 2011

The following comments can be made on the results of diagnostic accuracy studies of pulpal sensitivity and vitality:

- Electrical, cold and heat tests have been the most researched, while studies of newer diagnostic tests, such as laser Doppler flowmetry and pulse oximetry, have been little explored.
- For any test for which four or more studies have been conducted, both the fraction of false positives and the fraction of false negatives can be high. The large variation of the fractions of false positives and false negatives of almost every test studied is difficult to explain in terms of variation in patient group et cetera.
- Therefore, no single test or combination of tests is sufficiently accurate to demonstrate or rule out pulpal vitality.

What are the outcomes of the various diagnostic tests (Table 3-2)?

Table 3-2 Outcomes of diagnostic accuracy studies of pulpal sensitivity and vitality.

Diagnostic test	Reference test: histological examination of the pulpa		Visual inspection of the pulp (or healthy controls)	
	Sensitivity	Specificity	Sensitivity	Specificity
Electrical	Se (nonvital) = 0.21 Se (necrosis) = 0.57 Se (necrotic) = 0.72	Sp = 1.00 Sp = 0.99 Sp = 0.92	Se = 0.87 Se = 0.94 Se = 0.84 Se = 0.72 Se = 0.75 Se = 0.71 Se = 0.915	Sp = 0.96 Sp = 0.73 Sp = 0.96 Sp = 0.90 Sp = 0.92 Sp = 0.92 Sp = 0.881
Range	Se: 0.21- 0.72 Proportion of false negatives: 28/100 - 79/100	Sp: 0.92-1.00 Proportion of false positives: 0/100 - 8/100	Se: 0.71-0.94 Proportion of false negatives: 6/100 - 29/100	Sp: 0.73-0.96 Proportion of false positives: 4/100 - 27/100
Cold	Se (nonvital) = 0.68 Se (necrosis) = 0.75 Se (necrotic) = 0.89 Se (necrotic) = 0.94	Sp = 0.70 Sp = 0.57 Sp = 0.24 Sp = 0.10	Se = 1.00 Se = 0.93 Se = 0.83 Se = 0.89	Sp = 0.62 Sp = 0.98 Sp = 0.90 Sp = 0.76

Diagnostic test	Reference test: histological examination of the pulpa		Visual inspection of the pulp (or healthy controls)	
	Sensitivity	Specificity	Sensitivity	Specificity
Range	Se: 0.68-0.94 Proportion of false negatives: 6/100 - 32/100	Sp:0.10-0.70 Proportion of false positives: 30/100-90/100	Se = 0.81 Se: 0.81-1.00 Proportion of false negatives: 0/100 - 19/100	Sp = 0.92 Sp: 0.62-0.98 Proportion of false positives: 2/100 - 38/100
Heat	Se (nonvital) = 0.95 Se (necrosis) = 0.63 Se (necrotic) = 0.94 Se (necrotic) = 0.89	Sp = 0.41 Sp = 0.61 Sp = 0.29 Sp = 0.05	Se = 1.00 Se = 0.86	Sp = 0.66 Sp = 0.57
Range	Se:0.63-0.95 Proportion of false negatives: 5/100 - 37/100	Sp: 0.05-0.61 Proportion of false positives: 39/100-95/100	Se: 0.86-1.00 Proportion of false negatives: 0/100 - 14/100	Sp: 0.57-0.66 Proportion of false positives: 34/100 -43/100
Cold and heat combined	Se (necrotic) = 0.78 Proportion of false negatives: 32/100	Sp = 0.86 Proportion of false positives: 14/100	Se = 0.92 Proportion of false negatives: 8/100	Sp = 0.89
Laser Doppler Flowmetry Range			Se = 1.00* Se = 0.88 Se: 0.88-1.00 Proportion of false negatives: 0/100 - 12/100	Sp = 1.00* Sp = 1.00 Sp:.,00 Proportion of false positives: 0/100
Pulse oximetry Range			Se = 1.00 Se = 0.813 Se: 0.813-1.0 Proportion of false negatives: 0/100 - 19/100	Sp = 0.95 Sp = 0.949 Sp: 0.95 Proportion of false positives: 5/100
Percussion	Se (necrotic) = 0.28 Proportion of false negatives: 72/100	Sp = 0.89 Proportion of false positives: 11/100		

* flux values at <7.0 and amplitude values at <1.6:

Source: Mejàre et al., 2012; Karayilmaz & Kirzioğlu, 2011

What is the predictive value of methods or markers for the outcome of treatment aimed at keeping the pulp vital, healthy and asymptomatic? Methods/markers: bleeding of the pulp, preoperative pain of mild intensity, heat test, cold test and percussion test, and color and hardness of dentin around the affected pulp?

Six studies (Seltzer 1963; Johnson 1970; Tyldesley 1970; Dummer 1980; Kamburoğlu 2005; Hasler 1970) examined the accuracy of testing for signs and symptoms that may indicate an inflamed pulp. Almost all studies involved histologic examination. The signs and symptoms looked at were quite heterogeneous (Table 3-3). Also, sensitivity or specificity were not always reported. In Table 3-4 sensitivity and specificity are listed for the studies that involved histological examination. As with tests for vitality and sensitivity of the pulpa, sensitivity and specificity for tests for signs and symptoms that may indicate pulpitis show strong variation.

1 study (Matsuo et al., 1996) examined the extent to which different clinical signs and symptoms could predict the outcome of pulpal overcapping. The material consisted of 44 permanent elements with affected pulp after excavation for deep caries. Pulp with profuse and persistent bleeding had a significantly worse outcome than when there was moderate bleeding or bleeding of short duration. Preoperative pain of mild intensity did not affect the likelihood of treatment success.

Table 3-3 Characteristics of diagnostic accuracy studies of signs and symptoms that may indicate an inflamed pulp

Study ID	Patients	Markers of the inflammation status of the pulpa	Reference Tests
Dummer 1980	75 permanent teeth to be extracted mainly because of pain	Presence/absence of pain Character of pain Tenderness at apex Intraoral swelling Tenderness to percussion Hypersensitivity to cold and heat	Histology of pulp after extraction: Classification according to criteria by Seltzer et al. (1963) Dichotomized into: saveable pulp (chronic partial pulpitis) (n = 50) and nonsaveable pulp (severe inflammation/necrosis) (n = 25) Disease prevalence: Nonsaveable pulp: 67% Nonvital pulp: 25%
Hasler 1970	47 patients age 13-56 years (mean 28 years). One tooth per patient Control: Adjacent or contra-lateral sound tooth	Electrical Cold Heat Percussion test Radiographic findings	Histology of pulp after extraction Classification: No or minimal pulpitis (n = 34) Moderate/severe pulpitis (n = 13) Disease prevalence: Moderate/severe pulpitis: 28%
Johnson 1970	706 extracted teeth in 94 consecutive patients because of full-mouth extraction or because of caries, tooth ache, marginal periodontitis, and prosthodontics	Hypersensitivity to heat and cold	Histology of pulp after extraction Classification: Hyperaemic stage (no inflammatory cell infiltrates) 'Irreversible' cellular inflammation or necrosis Disease prevalence: Hyperaemia: 31% Severe inflammation: 10% Necrosis: 7%
Kamburoğlu 2005	93 teeth in 97 patients aged 15-65 years (mean 33 years) in need of endodontic therapy because of caries Comparison group: Adjacent or contra-lateral sound teeth (n = 49)	History of pain Caries removal without anesthesia Sensibility to probing exposed pulp Percussion test Radiographic examination	Visual inspection of exposed pulp Classification: Bleeding (n = 50) No bleeding (necrotic) (n = 43) Disease prevalence: Necrotic pulp: 46%
Klausen 1985	74 patients with acute dental pain Exclusion criterion: Patients with dubious or mixed diagnosis	Ability to point out tooth interference with sleep Constant pain Tenderness to temperature changes and	Visual examination and probing of exposed pulp Classification: vital or necrotic pulp radiography: normal or apical rarefaction, marginal bone loss.

Study ID	Patients	Markers of the inflammation status of the pulpa	Reference Tests
		chewing Tooth feels extruded Impaired mouth opening. Reddening of the apical oral mucosa. Tenderness at apex, percussion, digital pressure Tooth mobility Swollen regional lymph nodes	Marginal periodontium: normal or deepened pocket Disease prevalence: 1. Pulpitis 38% 2. AP 41% 3. MP 12% 4. Pulpo-periodontitis 9%. (excluded from analysis)
Matsuo 1996	44 teeth in 38 patients (age 20-69 years) with carious exposure and without extensive pain Exclusion criteria: Severe damage to the pulp during caries excavation (n = 3)	History of pain Heat, cold and percussion test Color, hardness of dentin surrounding pulp exposure Pulp exposure size Bleeding character	Success of treatment (pulp capping) Criteria: No clinical signs or symptoms of irreversible pulpitis, tooth sensitive to EPT Follow-up: ≥12 months
Seltzer 1963	166 teeth scheduled for extraction because of tooth ache, orthodontic, periodontal or prosthetic reasons	Presence and character of pain Sensibility to percussion Radiographic signs Abnormal reaction to heat or cold Electrical	Histology of pulp after extraction Classification: a. Intact uninflamed (n = 23) b. Atrophic (n = 40) c. Intact with scattered inflammatory cells (n = 19) d. Chronic partial pulpitis with partial necrosis (n = 24) e. Chronic total pulpitis with partial necrosis (n = 14) f. Chronic total pulpitis (n = 22). g. Total necrosis (n = 22). Dichotomized in a-d = nonsuppurative (n = 106) And e-g = suppurative (n = 60) Disease prevalence: Total pulpitis/necrosis (e-g): 35%
Tyldesley 1970	142 teeth scheduled for extraction because of toothache	Character of pain Heat Cold Percussion	Histology of pulp after extraction Classification: a. Normal/hyperaemic (n = 16) b. Acute localized pulpitis (n = 25) c. Acute generalized and or chronic pulpitis (n = 69) d. Degeneration or necrosis (n = 32) Disease prevalence: Localized pulpitis: 18% Generalized pulpitis: 49% Degenerated/necrotic pulp: 23%

Source: Mejäre et al., 2012

Table 3-4 Outcomes of diagnostic accuracy studies of signs and symptoms that may indicate (the severity of) an inflamed pulp

Diagnostic test	Reference test: histological examination of the pulpa	
	Sensitivity (Se)	Specificity (Sp)
Presence and character of pain		
• presence of pain	Se (nonsaveable pulp) = 0.88 Se (total pulpitis) = 0,65 Se (generalized pulpitis/necrosis) = .68	Sp = 0.60 Sp = 0.76 Sp = 0.41
• mild versus severe pain	Se (generalized pulpitis/necrosis) = 0.37	Sp = 0.61
• intermittent versus constant pain		
Cold	Se (nonsaveable) = 0.40 Se (moderate/severe pulpitis) = 0.85 Se (irreversible inflammation) = 0.35 Se (total pulpitis) = 0.23 Se (generalized pulpitis/necrosis) = 0.92	Sp = 0.84 Sp = 0.12 Sp = 0.49 Sp = 0.80 Sp = 0.12
Heat	Se (nonsaveable) = 0.18 Se (moderate/severe pulpitis) = 0.54 Se (irreversible inflammation) = 0.59 Se (total pulpitis) = 0.31 Se (generalized pulpitis/necrosis) = 0.92	Sp = 0.92 Sp = 0.21 Sp = 0.39 Sp = 0.84 Sp = 0.02
Tenderness to percussion	Se (nonsaveable) = 0.66 Se (moderate/severe pulpitis) = 0.77 Se (total pulpitis) = 0.38 Se (generalized pulpitis/necrosis) = 0.16	Sp = 0.88 Sp = 0.21 Sp = 0.92 Sp = 0.93
Pulp exposed to caries	Se (moderate/severe pulpitis) = 0.77	Sp = 0.88
Character of bleeding of the pulp	Se (conspicuous bleeding not arresting at 30 s past exposure) = 0.50	Sp = 0.86

Source: Mejàre et al., 2012

Quality of evidence

According to the review by Mejare et al. (2012), the *risk of bias* for both sensitivity and specificity is severe in most studies. The main reasons for this are:

- No information on the reliability of the reference test;
- no confidence interval presented for sensitivity and specificity;
- in most studies, it is unclear whether the results of the index test and the reference test were independently assessed and
- ambiguity about the extent to which the patients represented a representative spectrum.

The study added by the Working Group by Karayilmaz & Kirzioğlu (2011) that evaluated the diagnostic accuracy of the electrical test and laser Doppler flowmetry for the detection and exclusion of necrosis of the pulp can be characterized as a study with severe risk of bias (Appendix 3.2).

In addition, for all tests, there was *inconsistency either strong heterogeneity* of sensitivity and specificity, or *imprecision* due to the fact that only 1 or 2 small studies examined the accuracy of a test. For all tests, therefore, *the quality of evidence* is low because there is considerable uncertainty in the outcomes of sensitivity and specificity.

Conclusions

Low GRADE	<p><i>Sensibility and vitality of the pulp</i></p> <p>There is considerable uncertainty regarding the diagnostic value of thermal (heat and cold) tests and electrical tests. Cold tests, more so than heat tests, seem to have higher sensitivity (necrotic pulp) than specificity (vital pulp), whereas electrical tests, on the contrary, seem to have higher specificity (vital pulp) than sensitivity (necrotic pulp). Therefore, cold tests seem more appropriate for demonstrating a necrotic pulp in the event of a negative test result, while electrical tests seem more appropriate for demonstrating a vital pulp in the event of a positive test result.</p> <p>There is considerable uncertainty about the diagnostic value of pulse oximetry and laser Doppler flowmetry. Both techniques appear to have high sensitivity and specificity.</p> <p>Mejàre et al., 2012; Karayilmaz & Kirzioğlu, 2011;</p>
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Low GRADE	<p><i>Signs and symptoms that may indicate (severity of) inflammation of the pulp</i></p> <p>There is considerable uncertainty about the diagnostic significance of hypersensitivity to heat, response to cold, electrical stimulation, or sensitivity to percussion in asymptomatic elements with deep caries lesions.</p> <p>The presence or absence of pain, the nature and duration of this pain are not conclusive about the condition of the pulp.</p> <p>Mejàre et al., 2012</p>
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Low GRADE	<p><i>Success pulp capping</i></p> <p>There is considerable uncertainty about the predictive value of nature and extent of bleeding from the pulp, preoperative pain of mild intensity, heat, cold and percussion testing, and color and hardness of dentin around the affected pulp for the outcome of treatment aimed at keeping the pulp vital, healthy and asymptomatic.</p> <p>Mejàre et al., 2012</p>
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Considerations

Quality of evidence

The quality of evidence is low, meaning that there is considerable uncertainty about the value of various diagnostic tests. Recognizing that accuracy parameters are *surrogates* for patient-relevant outcomes, such as absence of pain, reduction of periodontitis apicalis, or restoration of dental function, the overall quality of evidence is very low.

Patient values and preferences

The guideline working group has no evidence that patients differ in preference for one test or another. All are generally not perceived as very pleasant.

Professional perspective

Abu-Tahun et al. (2012) in their review do not provide figures on sensitivity and specificity of the various diagnostic tests, but conclude (p. 11): "*Currently, no single pulp testing technique can reliably diagnose all pulpal conditions nor it has been proven to be superior in all aspects.*"

Jafarzadeh & Abbott (2010a) found significantly fewer studies on thermal and electrical testing than Mejàre et al. (2012): a total of 5, of which 2 reported either sensitivity or specificity, but not both. Incidentally, these are 2 studies that Mejàre et al. (2012) excluded because of "inadequate reference standard" and "healthy teeth only." Their conclusion "*It should be emphasized that EPTs and thermal tests are simple non-invasive tests, but they are not completely reliable. Heat (...) is the least accurate overall of the three common pulp tests due to its low specificity (Petersson et al. 1999), whereas the cold test is more accurate than the EPT*" (Moody et al. 1989, Peters et al. 1994), is therefore based on a limited number of studies.

Convincing evidence to use or not use specific diagnostic tests is lacking. Therefore, there is no reason to strongly recommend or discourage specific tests or combinations of tests. Especially important is *that* a diagnostic test be performed to determine the sensibility, vitality, inflammatory status of the pulp, and in conjunction with a detailed history, symptoms, clinical findings and radiologic observations to determine further management.

Cost

Thermal tests are generally not very expensive and are ubiquitous in dental practices. The electric pulpate tester is slightly more expensive. The new tests such as pulse oximetry and laser Doppler flowmetry would be more costly once they become available. The working group assumes that, for the time being, general practitioners will have little or no access to the equipment needed for pulse oximetry and laser Doppler flowmetry.

Recommendation

Always perform a test to determine the sensibility, vitality, and inflammatory status of the pulp (to determine further management in conjunction with a detailed history, symptoms, clinical findings, and radiologic observations).

To determine the sensibility and - indirectly - the vitality of the pulp, the working group suggests the use of the cold test and electrical test.

Rational

Of none of the tests to determine the sensitivity and - indirectly - the vitality of the pulp, the diagnostic value has been scientifically demonstrated with a reasonable to high degree of certainty. Of the tests based on measuring a response to sensory stimuli, the cold test and electrical test seem to be the most sensitive/specific. Moreover, they are noninvasive, inexpensive tests.

Tests based on the measurement of blood circulation to determine the vitality of the pulp have not yet been investigated in a sufficiently robust manner to be applied routinely, and are also relatively expensive. Therefore, the study group assumes that pulse oximetry and laser Doppler flowmetry, in part because of the costs associated with them, are not or rarely used by general practitioners for the time being.

At this time, one cannot rely purely on the results of sensibility tests for an accurate diagnosis of the condition of the pulp.

The working group believes that in combination with the medical and clinical history, intraoral examination and the additional X-ray diagnosis, one can ultimately arrive at a working diagnosis.

Knowledge gaps

Future scientific research should focus on exploring methods that clarify whether a vital but affected pulp can be preserved or should be removed and replaced with filling material.

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Appendix 3.1. Search strategy

Retrieved from PubMed September 3, 2015

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((("dental pulp diseases/classification"[MeSH Major Topic] OR "dental pulp diseases/
diagnosis"[MeSH Major Topic] OR "dental pulp test"[MeSH Major Topic] OR ((diagnos*
[Title] OR test*[Title] OR indication*[Title] OR clinical symptom*[Title]) AND pulp*
[Title]) OR ("dental pulp diseases"[MeSH Terms] AND "tooth discoloration"[MeSH
Terms])) NOT ("case reports"[Publication Type] OR "clinical conference"[Publication
Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "editorial"[
Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type].
OR hasabstract[text])) OR (("dental pulp diseases/classification"[MeSH Terms] OR
"dental pulp diseases/diagnosis"[MeSH Terms] OR "dental pulp test"[MeSH Terms].
OR ((diagnos*[Title] OR test*[Title] OR indication*[Title] OR clinical symptom*[Title]))
AND pulp*[Title]) OR ("dental pulp diseases"[MeSH Terms] AND "tooth discoloration"
[MeSH Terms])) NOT ("case reports"[Publication Type] OR "clinical conference"[Publication
Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR
"editorial"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication
Type]) AND hasabstract[text]))
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Appendix 3.2. Risk of bias assessment of Karayilmaz & Kirzioğlu (2011).

Quadas criteria for assessing risk of bias

Representative patient spectrum	unclear
Population adequately described	yes
Reference test classifies the target condition correctly	case-control design (healthy controls)*
Time interval between index and reference test adequate	unclear
Reference test applied on all or on a randomized sample of patients	not applicable
The same reference test irrespective of results of index test	not applicable
Index test adequately described	yes
Reference test adequately described	not applicable
Index test interpreted without knowledge of results of reference test	no (one examiner)
Reference test interpreted without knowledge of results of index test	no (one examiner)
Uninterpretable test results reported	no
At least two independent examiners of reference test	no
Reliability concerning reference test reported	no
Precision of test results reported	no

Assessment: serious risk of bias

* Case-control studies tend to overestimate sensitivity and specificity because of plausible spectrum bias.

4. Imaging diagnostics

Introduction¹

X-ray examination is an essential *complement* to the clinical examination for a diagnosis of the condition of the periapex. Changes in the bone tissue around the root tip are a very important indicator of a severely inflamed or necrotic, infected pulp. These changes in the bone tissue around the root tip may appear on an x-ray image as an increase in bone density (sclerosis) or as periapical bone loss.

Both conditions may indicate inflammatory reactions due to an infected pulp.

Periodontitis apicalis/lateralis is diagnosed by radiographic evidence of periapical bone loss, combined with clinical signs of the periradicular tissue and/or the absence of a positive response of the pulp on the sensibility test.

The ability of imaging to reveal periapical bone loss depends on several factors. The extent and location of the bone loss are important features and actually determine whether the lesion can be detected at all using imaging techniques.

Conventional intra-oral X-ray examination is the most widely used technique. Meanwhile, digital techniques are increasingly used in dental practice. In the 1990s, the so-called cone beam computed tomography (CBCT) was developed. Clinical studies comparing periapical radiographs, either conventional or digital, with CBCT have shown significantly more periapical lesions detected with CBCT (Saidi, Naamen & Zogheib, 2015; Davies et al., 2015) or root canals identified (Davies et al., 2015). Not only in terms of detecting periapical lesions, but also in verifying the nature of periapical lesions, conventional periapical radiographs have limitations.

With color Doppler ultrasound, it may be more possible to distinguish between various types of lesions, for example, a cyst or a granuloma (Sandhu et al., 2015).

It is important to emphasize that a radiolucent-associated inflammatory lesion cannot be diagnosed with sufficient accuracy based solely on clinical or radiographic findings. For example, a New Zealand study with thousands of specimens examined histopathologically (Becconsall-Ryan, Tong & Love, 2010) showed that a preliminary diagnosis based on clinical presentation and imaging examination, which incidentally was unclear which imaging technique was used, was correct for a periapical granuloma in only 48.3% of cases and for a radicular cyst in 36% of cases.

Imaging diagnostics is not a matter of 'reading' but of interpreting X-rays. It is known that both inter-rater and intra-rater reliability is low in interpreting conventional X-rays (Tewary et al., 2011). As far as interpretation of digital images is concerned, inter-rater reliability appears to be moderate, as evidenced by a kappa coefficient of 0.35 (percentage agreement was 25%). This is equally true for intra-assessor reliability (kappa coefficient: 0.5). Both figures are from a study in which six evaluators (radiologists and endodontologists) had to assess 150 periapical images of molars from maxilla and mandible in two rounds (Tewary et al., 2011).

Using a virtual simulation platform and digitally reconstructed radiographs, based on a micro-CT scan of a specimen of the mandible, Gao et (2010) showed that conventional radiographs cannot detect early stages of periapical lesions, and that the image of the lesions obtained is influenced by the shape, location and size of the lesion.

Specific questions are:

1. How accurate (sensitivity, specificity, positive and negative predictive value) is a digital X-ray image compared to a conventional X-ray image for detecting changes in periapical tissue?
2. How accurate (sensitivity, specificity, positive and negative predictive value) is a CBCT compared to a periapical X-ray image for detecting changes in periapical tissue?
3. How accurate (sensitivity, specificity, positive and negative predictive value) is color Doppler ultrasound compared to X-ray for detecting changes in periapical tissue?

¹ This introduction is partly an adaptation of introduction to section 3.2 of the Swedish report.

4. How accurate (sensitivity, specificity, positive and negative predictive value) are color Doppler ultrasound, CBCT and periapical radiographs for determining the nature of the condition (including degree of inflammation, presence of cyst or granuloma, or healing with scar tissue)?
5. How accurate (sensitivity, specificity, positive and negative predictive value) is subtraction radiography compared to an X-ray image for detecting minor bone lesions?
6. Is there a relationship between the width and shape of the paradontal ligament and the vitality of the pulp?
7. [update 2022/3] How accurate (sensitivity, specificity) is CBCT in detecting vertical root fractures in (permanent) elements with canal filling compared to a reference standard (direct visualization by surgical exploration, extraction or orthograde re-treatment)?
8. [update 2022/3] How accurate is CBCT (sensitivity, specificity) in detecting an extra canal in permanent teeth with no root anomalies and no calcification compared to reference standard (micro-CT or 'staining & clearing' or sectioning of the root)?

Search and selection

The starting point for the specific questions 1, 3, 5 to 6 is the systematic review by the Swedish Council on Health Technology Assessment (2012) and published as Petersson et al. (2012). This review searched for literature in PubMed, EMBASE, The Cochrane Central Register of Controlled Trials and Cochrane Reviews published up to June 2011. Twenty-six studies were found that met the inclusion criteria.

The search strategy included in the Swedish Council on Health Technology Assessment's systematic review was used to update this review via PubMed (Appendix 4.3). 278 studies were found, of which 47 were potentially relevant based on title/abstract/language. Among these studies were 4 systematic reviews (Rosen et al., 2015; Kruse et al., 2015; Todd, 2014; Tyndall & Kohlfarber, 2012). No relevant reviews were found in the Cochrane Database of Systematic Reviews. None of the reviews adequately met the selection criteria. 1 primary study was found that met the selection criteria (Raghav et al., 2010).

[Update 2022/3] Two and one systematic review(s) of good methodological quality, respectively, were used to update the text related to specific questions 2 and 4 (Yapp, Brennan & Ekpo, 2021; Ramis-Alario et al., 2021 and Natanasabapathy et al., 2021). For the specific questions 7 and 8 added in 2022, the systematic reviews of good methodological quality by PradeepKumar et al. (2021) and Aung & Myint (2021) were used.

Selection Criteria

Type of studies	- SRs - original observational studies - ex and in vivo studies - publications from 2010
Type of patients	- adult patients expected to undergo examination in a dental setting - post-mortem studies
Index Test	- various x-ray or ultrasound methods compared to a reference standard
Reference Standard	- histological examination or bony cavity in skeletal material or other methods (see starting questions)
Type of outcome measures	- sensitivity and specificity - likelihood ratio - odds ratio - ROC curves - AUC (area under the curve). - data from which the above outcomes can be derived
Type of setting	- general practitioners - dental endodontists

Remark:

An evidence-based guideline from the European Commission entitled *Radiation Protection No 172 Cone beam CT for dental and maxillofacial radiology (Evidence-based guidelines)* was published in 2012 as a result of the SEDENTEXCT project. This guideline is partly based on a systematic review of the literature. The synthesis of the evidence found was done in a narrative manner. This means, among other things, that numbers about sensitivity and specificity cannot be found in this guideline. Since quantitative representation of accuracy parameters is a selection criterion (see later), this guideline was not used for a review of the literature related to CBCT, but is used in the considerations for the recommendations (see there).

Summary of literature

How accurate (sensitivity, specificity, positive and negative predictive value) is a digital X-ray image compared to a conventional X-ray image for detecting changes in periapical tissue?

In 5 studies reported in Petersson et al. (2012), conventional radiographs were compared with digital radiographs using phosphor plates (Barbat & Messer 1998; Holtzmann et al., 1998) or sensors (Kullendorff & Nilsson 1996; Kullendorff et al., 1996; Raghav et al., 2010). See Table 4-1.² All studies show that the conventional film technique and digital techniques have similar diagnostic accuracy, as evidenced by the similarity in the 'areas under the curve', and sensitivity and specificity (Table 4-1). Two studies show that image enhancement does not yield greater diagnostic accuracy (Kullendorff & Nilsson 1996, Barbat & Messer 1998).

Table 4-1 Diagnostic accuracy of conventional x-rays, digital techniques with storage on phosphor plates or with sensors, and cone beam computed tomography for the diagnosis of small lesions of bone tissue

	Material/ reference test/ index test	Number of jaws/type of lesions	Number of observati- ons/ observers	Sensitivi- ty/ PPV	Specificali- ty/ NPV	ROC curve, AUC	Risk of bias*
Barbat & Messer 1998	Post-mortem mandibles, molars/ Artificial lesions/ D-speed film and storage phosphor plates (SPP)	8 Jaws/19 roots, artificial (bur) lesions with 4 depths	116 Images/8 observers	-	-	Anova; Film and SPP comparable	Serious
Holtzmann et al., 1998	Post-mortem lower and upper jaws/. Histology/ D-E - films and storage phosphor plates (SPP)	28 Cadavers/50 teeth lower jaw, 50 teeth upper jaw, histology	300 Images/3 observers	-	-	<u>AUC:</u> SPP: 0,74-0,88 D-film 0,80-0,91 E-film 0,75-0,88	Serious
Kullendorff & Nilsson, 1996	Dry human mandibles, premolars and molars/ Artificial	6 jaws / artificial (bur) lesions 1, 3 and	20 Images with lesions, 16 images without lesions/7	-	-	<u>AUC:</u> Movie 0.84 Sensor 0.79	Serious

² AUC Interpretation:

1.0: Perfect test; 0.9 to 0.99: Excellent test; 0.8 to 0.89: Good test; 0.7 to 0.79: Fair test; 0.51 to 0.69: Poor test; 0.5: Worthless test

	Material/ reference test/ index test	Number of jaws/type of lesions	Number of observati- ons/ observers	Sensitivi- ty/ PPV	Specifi- ty/ NPV	ROC curve, AUC	Risk of bias*
Kullendorff et al., 1996	lesions/ E - film and CCD sensor Dry human mandibles, premolars and molars/ Artificial Lesions/ CCD sensor and image processing	5 mm 6 Jaws/ artificial (bur) le- sions 1-5 mm	observers 293 Observa- tions/7 ob- servers	-	-	<u>AUC:</u> Sensor original 0.79 Image processing 0.79	Serious
Raghav et al., 2010	Clinical study /histology/ D-film and CCD in- traoral sen- sor and ultrasound with color Doppler	21 patients aged 15-45 years with periapical radiolucen- cy in rela- tion to anterior maxillary or mandib- ular teeth as a sequel to dental caries or trauma indicated for extrac- tion or root canal treatment	D-movie: 3 observers CCD: 3 ob- servers Ultrasound: 3 observers	D-film: 0.714 (0.359- 0.918)) CCD: 0,857 (0,487- 0,974)	D-film: 0.500 (0,268- 0,732) CCD: 0,567 (0,326- 0,786)		Moderate
Estrela et al., 2008	Clinical/ CBCT/ periapical F- film or panoramic radiographs	888 Pa- tients/PAI scoring	1508 Teeth/3 observers	Periapical radio- graphs: 0,55	Periapical radio- graphs: 0.98		Moderate
Patel et al., 2009	Dry human mandibles, molars/ Artificial lesions/ CBCT and CCD sensor	Jaws/lesion s with bur 2 and 4 mm CBCT mean 1/1 Periapical radio- graphs mean 1/0.38 CBCT	10 First molars/6 observers	Periapical radio- graphs: 0,25 CBCT: 1,0	Periapical radio- graphs: 1.0 CBCT: 1,0		Moderate
Sogur et al., 2009	Dry human mandibles, premolars/	12 jaws/ chemically created	924 Ima- ges/252 periapical	Movie: 0,68	Movie: 0,52		Moderate

	Material/ reference test/ index test	Number of jaws/type of lesions	Number of observati- ons/ observers	Sensitivi- ty/ PPV	Specificty/ NPV	ROC curve, AUC	Risk of bias*
	Artificial lesions/ CBCT, peri- apicals F- film and SPP	lesions after 0, 1, 1.5 and 2 h	areas/6 observers	SPP: 0.739	SPP: 0.67		
Christian- sen et al., 2009	Clinical/ root-end resection/ CBCT and periapical radiographs with SPP	50 Pa- tients/ Surgically treated teeth with retrograde root fillings	58 Teeth ex- amined after 1 week and 52 teeth after 12 months/3 observers	-	-	A bone defect was observed at all teeth with both methods after 1 week. After 12 months 28% more bone de- fects were seen with CBCT, but in 5% a bone defect was seen only in the periapical radio- graphs.	Moderate

*Note: sources are Petersson et al. (2012) and the Working Group (2015). The latter assigned levels of risk of bias (no serious, serious, very serious risk of bias) based on Table 2 from Petersson et al. In this regard, small, moderate or high risk of bias (Table 2 from Petersson et al., included in Appendix 4.2 of this guideline) was converted by the working group to no serious, serious, very serious risk of bias, respectively. The risk of bias assessment of Raghav et al., 2010 was done by the working group (Appendix 4.1).

Quality of evidence

In the GRADE methodology, diagnostic accuracy studies whose study design is cross-sectional and involves consecutive patients initially start as high quality of evidence. Based on the following GRADE criteria, risk of bias, indirectness, inconsistency, imprecision and publication bias can be downgraded by one or more levels.

According to the review by Petersson et al. (2012), most studies have low to very low quality of evidence.

Conclusion

Diagnostic accuracy	<i>Conventional versus digital x-ray recording</i>
	There appears to be no essential difference in accuracy between conventional and digital X-ray imaging for detecting changes in periapical tissue. ³
Low	Petersson et al., 2012 (Barbat & Messer 1998; Holtzmann et al., 1998; Kullendorff & Nilsson 1996; Kullendorff et al., 1996; Raghav et al., 2010)

³ In the text of the conclusions, the word "seems" rather than "is" is used throughout to indicate that the conclusions are based on low quality evidence.

GRADE	
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For information: In 1 study (Estrela et al., 2008) reported by Petersson et al. (2012), periapical radiographs on F-speed films were compared with panoramic radiographs for detecting periodontitis apicalis, using CBCT as a reference test. Panoramic radiographs appear to have lower sensitivity than periapical radiographs, while specificity appears to be nearly equal.

How accurate (sensitivity, specificity, positive and negative predictive value) is a periapical X-ray image compared with CBCT for detecting changes in periapical tissue?

[Update 2022/3] The purest way to compare the diagnostic accuracy of periapical radiographs to CBCT is to compare both of them to histological data (the reference standard). This is what Yapp, Brennan & Ernest Ekpo (2021) examined. On the other hand, many studies have been conducted in which CBCT and periapical radiographs were only compared among themselves. From a pragmatic perspective, it is desirable to also summarize the results of these studies, as Ramis-Alario et al. (2021) have done.

Yapp, Brennan & Ekpo (2021) present two cadaveric studies (Kanagasingam et al. 2017, Kruse et al., 2019) using histological data as a reference standard. Kanagasingam et al. (2017) examined 67 teeth; Kruse et al., 2019 examined 222 teeth. The index test was "presence of a periapical lesion" or "periodontitis apicalis" determined using a 5-point scale. Multiple endodontists assessed the outcomes of the tests. The *sensitivity* [identifying periodontitis apicalis] of periapical x-rays ranged from 27 to 60%, that of CBCT from 80 to 89%. The *specificity* of a periapical x-ray image [excluding periodontitis apicalis] - only 1 study provided data on this - was 99%, that of CBCT ranged from 79 to 100%. In both studies, sensitivity and specificity concerned roots, not teeth.

Quality of evidence

In the GRADE methodology, diagnostic accuracy studies whose study design is cross-sectional and involves consecutive patients initially start as high quality of evidence. Based on the following GRADE criteria, risk of bias, indirectness, inconsistency, imprecision and publication bias can be downgraded by one or more levels.

[Update 2022/3] Yapp, Brennan & Ekpo (2021) assessed the risk of bias with the QUADAS tool. There is potential for bias for most criteria. The numbers of patients were small. Based on this, the quality of evidence can be downgraded from high to low because of severe risk of bias and imprecision. There is no downgrade for other GRADE criteria.

Conclusion

Diagnostic accuracy	<i>X-ray image versus CBCT versus histological data</i>
Low GRADE	Regarding the <i>exclusion</i> of periapical changes (absence of periodontitis apicalis), there seems to be no difference between a periapical radiograph and CBCT. Regarding the <i>detection</i> of periapical changes (presence of periodontitis apicalis), CBCT seems to be more accurate than X-ray imaging. Yapp, Brennan & Ekpo, 2021 (Kanagasingam et al. 2017; Kruse et al., 2019)

[Update 2022/3] Ramis-Alario et al. (2021) used CBCT as the starting point in their systematic review. Their considerations were (see Ramis-Alario, p. e154):

- 1) while histological data are the purest reference standard, histological examination is not applicable in practice;
- 2) there are many studies comparing periapical x-rays with CBCT.

They included cohort studies, case-control studies, cross-sectional studies, randomized clinical trials that aimed to detect persistent periapical lesions after root canal treatment using conventional (periapical and panoramic) radiographs as well as CBCT (the chosen reference standard). Ramis-Alario et al. (2021) included 27 studies. Thirteen studies compared digital periapical radiographs with CBCT. Five studies compared conventional radiographs with CBCT. Three studies compared panoramic radiographs with CBCT. The remaining six studies compared different radiographs (conventional, digital and panoramic) among themselves and with CBCT.

The lowest value for sensitivity was 27.83%, the highest was 94.83%. Regarding specificity, there was no variation at all. Ramis-Alario et al. (2021) performed a meta-analysis to make a combined estimate of the sensitivity and specificity of the individual studies. They arrived at a sensitivity of 0.58 and a specificity of 1.00, These results may have been influenced by financial sponsorship of some studies: sponsored studies seem to overestimate sensitivity. Sensitivity may be negatively affected the more time elapsed between diagnosis and root canal treatment.

Table 4-2 provides information on the number of false negatives and number of false positives. At a low prevalence of periodontitis apicalis, periapical radiographs miss approximately 75 cases per 1,000 patients. At a high prevalence of periodontitis apicalis, this number rises to nearly 25%, i.e. 244 cases per 1,000 patients. Missing the diagnosis of (persistent) periodontitis apicalis may increase the risk of loss of function or extraction of a tooth (Kirkevang et al., 2017). However, periapical radiographs rarely misdiagnose cases as periodontitis apicalis.

Table 4-2 Summary findings from Ramis-Alario et al. (2021)

Should periapical radiographs be used to diagnose (persistent) apical periodontal disease in patients w/ root canal treatment?

Patient or population: patients w/ root canal treatment

Setting: endodontologists; dentists

New test: periapical radiographs

Reference test: CBCT

Pooled sensitivity:0.58 (95% CI: 0.53 to 0.64)|Pooled specificity:1.00 (95% CI: 1.00 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI)		Number of participant (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence16% Jimenez-Pinzon et al. (2004)	Prevalence52%. Tibúrcio-Machado et al. (2021)			
True positives	93 (85 to 102)	302 (276 to 333)	8367 (26)	⊕⊕○○ Low ^{a,b}	When prevalence of apical periodontitis is low, 67 cases per 1,000 patients may be missed. When prevalence of apical periodontitis is high, 218 cases per 1,000 patients may be missed.
False negatives	67 (58 to 75)	218 (187 to 244)			
True negatives	840 (840 to 840)	480 (480 to 480)	8019 (23)	⊕⊕⊕○ Moderate ^a	The number of false positives is probably near zero.
False positives	0 (0 to 0)	0 (0 to 0)			

CI: confidence interval

Explanations

a. There were serious methodological flaws in the index test and the flow and timing risk of bias according to the QUADAS instrument. Therefore rated down by one level.

b. There is serious inconsistency (serious fluctuation of point estimates; p-value <0.001). Therefore rated down by one level.

Conclusion

Diagnostic accuracy	<i>Periodontitis apicalis: x-ray versus CBCT (considered acceptable reference standard)</i>
Fair to low GRADE	A periapical radiograph is probably an <i>accurate*</i> test particularly for <i>excluding</i> periodontitis apicalis. A periapical radiograph appears to be a <i>less accurate</i> test for <i>detecting</i> periodontitis apicalis.
	Ramis-Alario et al., 2021

* A test is considered accurate when the sum of sensitivity and specificity ≥ 1.5 .⁴

How accurate (sensitivity, specificity, positive and negative predictive value) is color Doppler ultrasound compared to X-ray for detecting changes in periapical tissue?

Raghav et al. (2010) examined the use of ultrasound with color Doppler in a study with severe risk of bias (Appendix 4.1; Table 1). They found a sensitivity of 0.952 and a specificity of 1.000. This study also addressed the question of the extent to which ultrasound with color Doppler allows differentiation of the nature of lesions. That question is addressed elsewhere.

Quality of evidence

In the GRADE methodology, diagnostic accuracy studies whose study design is cross-sectional and involves consecutive patients initially start as high quality of evidence. Based on the following GRADE criteria, risk of bias, indirectness, inconsistency, imprecision and publication bias can be downgraded by one or more levels.

There is low quality of evidence because there is serious risk of bias (unclear whether results from one test were determined without prior knowledge of the other test; unclear whether consecutive patients were involved) and very high imprecision of outcomes (no reporting of confidence intervals).

Conclusion

Diagnostic accuracy	<i>X-ray image versus color Doppler ultrasound</i>
Low GRADE	Color Doppler ultrasound appears to be more accurate than X-ray for detecting changes in periapical tissue.
	Raghav et al., 2010

How accurate (sensitivity, specificity, positive and negative predictive value) is subtraction radiography compared to an X-ray image for detecting minor bone lesions?

In 2 in vitro studies (Kullendorff et al., 1988, Dove et al., 2000) with moderate risk of bias, conventional radiographs were compared with subtraction radiography for the detection of periapical bone lesions in 2 consecutive studies (Table 4-3). In both studies, diagnostic accuracy - especially sensitivity by all appearances - improved in the detection of small bone lesions. Moreover, there was less assessor variation with (Kullendorff et al., 1988).

Table 4-3 Diagnostic accuracy of conventional X-ray images and digital X-ray images with sensors for diagnosis of small lesions of bone tissue, ex vivo studies

⁴ A test is (sufficiently) accurate when the sum of sensitivity and specificity is at least halfway between one (completely inaccurate) and two (perfectly accurate). See Power, Fell & Wright (2013).

	Material/ reference test/ index test	Number of jaws/type of lesions	Number of observati- ons/ observers	Sensitivity/ PPV	Specificity/ NPV	ROC curve, AUC	Risk of bias
Dove et al., 2000	Dry human mandible/ Artificial lesions/ Conventional technique and subtraction radiography	1 Mandible/6 locations 'bone chips' with different weights	78 Images with 234 sites/4 observers	Conventional: 57,4 Subtraction: 88,1	Conventional: 98,0 Subtraction: 88,8	-	Serious
Kullendorff et al, 1988	Dry human mandibles/ Artificial lesions/ Conventional technique and subtraction radiography	6 Jaws/26 artificial (bur) lesions with different depths	26 Pairs of images/10 observers			<u>Depth ≤ 1 mm:</u> Conventional: 0.601 Subtraction: 0.819 <u>Depth ≤ 2 mm:</u> Conventional: 0.767 Subtraction: 0.955	Serious

Source: Petersson et al. (2012). See also the note to Table 4-1.

Quality of evidence

In the GRADE methodology, diagnostic accuracy studies whose study design is cross-sectional and involves consecutive patients initially start as high quality of evidence. Based on the following GRADE criteria, risk of bias, indirectness, inconsistency, imprecision and publication bias can be downgraded by one or more levels.

According to the review by Petersson et al. (2012), there is low quality of evidence due to serious risk of bias and high imprecision of outcomes.

Conclusion

Diagnostic accuracy low GRADE	<i>Conventional radiograph compared with subtraction radiography</i>
	Subtraction radiography appears to be more accurate than x-ray for detecting minor bone lesions.
	Petersson et al., 2012 (Kullendorff et al., 1988, Dove et al., 2000)

How accurate (sensitivity, specificity, positive and negative predictive value) are color Doppler ultrasound, CBCT and periapical radiographs for determining the nature of the condition (including degree of inflammation, presence of cyst or granuloma, or healing with scar tissue)?

In a dissertation (Brynolf, 1967) in which intra-oral periapical radiographs were compared with histologic specimens from the same periapical area, the ability of radiographs to distinguish between normal conditions and conditions indicative of inflammation of any severity was found to increase as more radiographs were taken. However, this study only looked at anterior elements in the maxilla, which

limits the generalizability of the findings. A similar study (Green et al., 1997) concluded that even if normal conditions appear on an X-ray image, inflammation may still be histologically detectable. A study with severe risk of bias (Rosenberg et al., 2010) showed that CBCT is not a reliable imaging technique for differentiating radicular cysts and granulomata. The accuracy rate (true-positive and true-negative test results combined) was 51% and 63% for the two radiologists involved, respectively. In 2 other studies with severe risk of bias, the presence of a lesion on an X-ray image did not appear to provide accurate information regarding a histologic diagnosis of granuloma or cyst (Linenberg et al., 1964; Ricucci et al., 2006). There was agreement between practitioner and pathologist for only 60% of assessments (Linenberg et al., 1964). In the study by Ricucci et al., (2006), only 3 of 10 radiopaque lamina recordings were confirmed histologically as the presence of cysts (Table 4-4). Of the 47 digitized periapical radiographs without a radiopaque lamina, 40 were found to be granulomas or abscesses after histological examination, while 7 were cysts. See Table 4-4.

Table 4-4 Diagnostic value of conventional radiographs and CBCT for accurate information on the nature of the condition.

	Material/ reference test/ index test	Number of jaws/type of lesions	Number of observations/ observers	Sensitivity/ PPV	Specificity/ NPV	Risk of bias
Brynolf 1967	Biopsy specimens from upper incisors, teeth with normal periapical conditions/ Histology of periapical tissue specimens/ Periapical film (Radia-Tized) radiographs, short cone bisecting angle technique and tubular diaphragm.	142 subjects, 320 periapical biopsy specimens from upper incisors, 292 teeth radiographed. 93 teeth with normal periapical conditions	Histology of periapical tissue specimens. One observer (same for histology and radiology)			Serious
Rosenberg et al., 2010	Clinical study / Histopathology/ CBCT (i-CAT)	45 patients referred for endodontic surgery. Periapical lesion with a minimum diameter of 5 mm	2 oral and maxillofacial Radiologists (index test) 2 oral pathologists (reference test)	Accuracy (true-positives plus true-negatives) for the two radiologists was 51% and 63% respectively		Serious
Linenberg et al., 1964	Biopsies/ Histology of periapical biopsies/ Complete mouth roentgenograms and clinical impression at surgery of periapical lesion.	68 healthy male basic recruits. Specimens from apices of non-restorable teeth.	110 periapical biopsy specimens	Strong interrater reliability between pathologists (kappa=0.79, z=5.46, p<0.0001) Weak interrater reliability between radiologists (kappa=0.14, p=not significant). The surgeon was in agreement of the pathologists' findings in 66 of the 110 cases (60%)		Serious
Ricucci et al., 2006	Clinical material/ Histologic exami-	60 teeth with periapical	2 observers recorded	Out of 57 electronic images that could be interpreted,		Serious

Material/ reference test/ index test	Number of jaws/type of lesions	Number of observations/ observers	Sensitivity/ PPV	Specificity/ NPV	Risk of bias
nation/ Paralleling film radiographs scanned and digitized.	radiolucencies	the presence or absence of a radiopaque lamina on periapical lesions	10 lesions had a radiopaque lamina, but of these only 3 were histologically diag- nosed as cysts, while 7 were granulomas or abscesses. Out of 47 lesions without a radiopaque lamina, 40 were histologically diagnosed as granulomas or abscesses, while 7 were cysts.		

Source: Petersson et (2012). See also the note to Table 4-1.

[Update 2022/3] Natanasabapathy et al. (2021) examined the diagnostic accuracy of ultrasound for differentiating periapical lesions (cysts and granulomas) from histopathologic data. They included eleven cross-sectional studies and one case report. These included histopathologic data for 191 patients (the reference standard). Ultrasound was used for the differential diagnosis of periapical lesions localized in the anterior region of the maxilla (45 elements) and/or mandibula (14 elements) in five studies. In four studies, periapical lesions were diagnosed in all regions of the maxilla (38 anterior elements, 16 posterior elements) and mandibula (13 anterior elements, 15 posterior elements). The remaining studies did not specifically state exactly where periapical lesions were found. Ultrasound was color/power Doppler ultrasound in different planes (apical region of the element and/or the sulcus buccalis) with frequencies ranging from 7 to 12 MHz.

Natanasabapathy et al. (2021) calculated a sensitivity of 0.94 (95% BI: 0.68-0.99) and a specificity of 0.98 (0.90-1.00) for periapical granulomas. For periapical cysts, they calculated a sensitivity of 0.98 (95% BI: 0.85-1.00) and specificity of 0.99 (95% BI: 0.71-1.00).

Table 4-5 and Table 4-6 provide information on the number of false negatives and number of false positives. At a low prevalence of 29% granulomas, approximately 17 cases per 1,000 patients are missed. At a high prevalence of 70% granulomas, this can reach 42 missed cases per 1,000 patients. The number of cases incorrectly labeled as "granuloma" is less than 2%.

At low and high prevalence of 6-55% cysts, approximately 1 and 11 cases per 1,000 patients, respectively, are missed. Granulomas can become cysts. Untreated cysts may possibly lead to periapical infections, loss of an element, and jaw fracture or tumor. The number of cases incorrectly referred to as "cyst" is barely 1%.

Table 4-5 Summary findings from Natanasabapathy et al. (2021) regarding granulomas⁵

Should Ultrasound imaging be used to diagnose granulomas in individuals with periapical lesions?

Patient or population: individuals with periapical lesions

Setting: dentists / endodontologists

New test: Ultrasound

Reference test: histological data

Pooled sensitivity:0.94 (95% CI: 0.68 to 0.99)|Pooled specificity:0.98 (95% CI: 0.90 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants	Certainty of the Evi-	Comments
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⁵ The GRADE assessment was not fully adopted from Natanasabapathy et al. (2021). The GRADE assessment was partially redone by the guideline working group.

	Prevalence46% From references in Natanasabapathy et al. (2021)	Prevalence84% From references in Natanasabapathy et al. (2021)	(studies)	certainty (GRADE).	
True positives	432 (313 to 455)	790 (571 to 832)			
False negatives	28 (5 to 147)	50 (8 to 269)	79 (11)	⊕⊕⊕○ Moderate ^{a,b,c}	In case of a low prevalence of granulomas 28 cases per 1,000 patients may be missed. In case of a high prevalence of granulomas 50 cases per 1,000 patients may be missed.
True negatives	529 (486 to 540)	157 (144 to 160)			
False positives	11 (0 to 54)	3 (0 to 16)	95 (11)	⊕⊕⊕○ Moderate ^{a,c}	In case of both low and high prevalence of granulomas the number of false positives is probably very small.

CI: confidence interval

Explanations

a. Based on the QUADAS-2 criteria, in the patient selection domain, the risk of bias and concerns regarding applicability were serious for all the included studies. articles. Therefore rated down by one level.

b. There is some heterogeneity (I² = 47%) but not enough to rate down certainty.

c. Borderline risk of publication bias; p-value Egger test 0.062. Not rated down.

Table 4-6 Summary findings from Natanasabapathy et al. (2021) regarding cysts⁶

Should Ultrasound imaging be used to diagnose cysts in individuals with periapical lesions?

Patient or population: individuals with periapical lesions

Setting: dentists / endodontologists

New test: ultrasound

Reference test: histological data

Pooled sensitivity:0.98 (95% CI: 0.85 to 1.00)|Pooled specificity:0.99 (95% CI: 0.71 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI)		Number of participant (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence6%. From references in Natanasabapathy et al. (2021)	Prevalence55% From references in Natanasabapathy et al. (2021)			
True positives	59 (51 to 60)	539 (468 to 550)			
False negatives	1 (0 to 9)	11 (0 to 82)	90 (11)	⊕⊕⊕○ Moderate ^{a,b,c}	In case of a low prevalence of cysts 1 case per 1,000 patients is likely to be missed. In case of a high prevalence of cysts 11 cases per 1,000 patients are

⁶ The GRADE assessment was not fully adopted from Natanasabapathy et al. (2021). The GRADE assessment was partially redone by the guideline working group.

Test result	Number of results per 1,000 patients tested (95% CI)		Number of participant (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence 6%. From references in Natanasabapathy et al. (2021)	Prevalence 55%. From references in Natanasabapathy et al. (2021)			
True negatives	931 (667 to 940)	445 (319 to 450)	84 (11)	⊕⊕⊕○ Moderate ^{a,c,d}	likely to be missed.
False positives	9 (0 to 273)	5 (0 to 131)			In case of a low prevalence of cysts 9 cases may be falsely classified as a cyst. In case of a high prevalence of cysts 5 cases per 1,000 patients may be falsely classified as a cyst.

CI: confidence interval

Explanations

a. Based on the QUADAS-2 criteria, in the patient selection domain, the risk of bias and concerns regarding applicability were serious for all the included studies. Therefore rated down by one level.

b. There is some heterogeneity (variation in estimates of sensitivity) but not enough to rate down certainty.

c. p value Deeks test = 0.069. Borderline risk of publication bias. Not rated down.

d. I² is 67%. However, only one estimate is substantially higher. Therefore not rated down.

Quality of evidence x-rays and CBCT

In the GRADE methodology, diagnostic accuracy studies whose study design is cross-sectional and involves consecutive patients initially start as high quality of evidence. Based on the following GRADE criteria, risk of bias, indirectness, inconsistency, imprecision and publication bias can be downgraded by one or more levels.

According to the review by Petersson et al. (2012), the quality of evidence is (very) low due to very serious risk of bias and/or high imprecision of outcomes.

Conclusions

Diagnostic accuracy	<i>X-ray and CBCT (nature of the condition)</i>
low GRADE	Neither an X-ray nor CBCT provides accurate information about the nature of the condition (including degree of inflammation, cyst or granuloma, or healing with scar tissue). Petersson et al., 2012 (Brynolf, 1967; Green et al., 1997; Rosenberg et al., 2010; Linenberg et al., 1964; Ricucci et al., 2006)

Diagnostic accuracy	<i>Granulomas and cysts: color Doppler ultrasound versus histological data</i>
Fair GRADE	Ultrasound is probably an <i>accurate*</i> test for <i>detecting</i> and <i>excluding</i> granulomas and cysts.
	Natanasabapathy et al. (2021)

* A test is considered accurate when the sum of sensitivity and specificity ≥ 1.5 .⁷

Is there a relationship between the width and shape of the paradontal ligament and the vitality of the pulp?

This question has been addressed in only 1 study with very serious risk of bias (Kaffe & Gratt 1988). This study with 28 patients/dentures with pain and 28 "healthy" dentures showed that radiological signs such as changes in the width and shape of the paradontal ligament, and an interrupted lamina dura, were associated with a non-vital pulp.

Quality of evidence x-ray recording

In the GRADE methodology, diagnostic accuracy studies whose study design is cross-sectional and involves consecutive patients initially start as high quality of evidence. Based on the following GRADE criteria, risk of bias, indirectness, inconsistency, imprecision and publication bias can be downgraded by one or more levels.

According to the review by Petersson et al. (2012), there is very low quality of evidence due to very serious risk of bias and high imprecision of outcomes.

Conclusion

Diagnostic accuracy	<i>X-ray image</i>
very low GRADE	Changes in the width and shape of the paradontal ligament, and an interrupted lamina dura, appear to be associated with a nonvital pulp.
	Petersson et al., 2012 (Kaffe & Gratt 1988)

[Update 2022/3] How accurate (sensitivity, specificity) is CBCT in detecting vertical root fractures in (permanent) elements with canal filling compared to a reference standard (direct visualization by surgical exploration, extraction or orthograde re-treatment)?

PradeepKumar et al. (2021) investigated the diagnostic accuracy of CBCT in detecting vertical root fractures in elements with canal filling compared with direct visualization as the reference standard. They found eight studies that met the inclusion criteria (clinical studies that used CBCT for diagnosis of root fracture in permanent teeth), with a total of 363 cases. The index test used was CBCT with different parameters/models. The images were mainly interpreted by radiologists and/or endodontologists. The reference standard in the eight studies consisted of surgical exploration (four studies), extraction (three studies) or orthograde re-treatment (one study).

PradeepKumar et al. (2021) calculated a sensitivity of 0.78 (95% BI: 0.64-0.88) and a specificity of 0.80 (0.63-0.91).

Table 4-7 provides information on the number of false negatives and number of false positives. At a low prevalence of 64% vertical root fractures, approximately 141 cases per 1,000 patients are missed. At a high prevalence of 84% vertical root fractures, this can reach 185 missed cases per 1,000 patients. Delay in proper diagnosis can lead to the formation of a bone defect, which can complicate future tooth replacement.

⁷ A test is (sufficiently) accurate when the sum of sensitivity and specificity is at least halfway between one (completely inaccurate) and two (perfectly accurate). See Power, Fell & Wright (2013).

The number of cases incorrectly referred to as "vertical root fracture" at low, medium and high prevalence is less than 10%.

Table 4-7 Summary findings from PradeepKumar et al. (2021)⁸

Should CBCT be used to diagnose vertical root fractures in endodontically treated teeth?

Patient or population: endodontically treated teeth

Setting: dentists; endodontologists

New test: CBCT

Reference test: direct visualization

Pooled sensitivity:0.78 (95% CI: 0.64 to 0.88)|Pooled specificity:0.80 (95% CI: 0.63 to 0.91)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence: 64% PradeepKumar et al. (2021)	Prevalence: 74% PradeepKumar et al. (2021)	Prevalence: 84% PradeepKumar et al. (2021)			
True positives	499 (410 to 563)	577 (474 to 651)	655 (538 to 739)	262 (8)	⊕○○○ Very low ^{a,b,c}	In case of a low prevalence 141 vertical root fractures per 1,000 patients may be missed. In case of a high prevalence 185 vertical root fractures per 1,000 patients may be missed.
False negatives	141 (77 to 230)	163 (89 to 266)	185 (101 to 302)			
True negatives	288 (227 to 328)	208 (164 to 237)	128 (101 to 146)	101 (8)	⊕⊕○○ Low ^{a,c}	In case of a low prevalence 72 cases per 1,000 patients may be falsely classified as a vertical root fracture (VRF) .
False positives	72 (32 to 133)	52 (23 to 96)	32 (14 to 59)			

⁸ The GRADE assessment was not fully adopted from PradeepKumar et al. (2021). The GRADE assessment was partially redone by the guideline working group. The main reason is that the working group saw no reason to also upgrade for a large effect since the authors do not mention what the threshold for a large effect is and also otherwise it is hard to see why 0.78 (sensitivity) and 0.80 (specificity) with lower limits of the confidence interval just above 0.60 would be a large effect.

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence: 64% PradeepKumar et al. (2021)	Prevalence: 74% PradeepKumar et al. (2021)	Prevalence: 84% PradeepKumar et al. (2021)			
						When the prevalence is high, 32 cases may be falsely classified as VRF.

CI: confidence interval

Explanations

- High risk of bias in "reference test" domain of QUADAS ROB tool for 6 out of the 8 included studies. 2 of the included studies show high risk of bias with respect to "Flow and timing" domain
- substantial variation in accuracy estimates. Therefore rated down by one level.
- wide confidence interval. Therefore rated down by one level.

Conclusions

Diagnostic accuracy	<i>Vertical root fractures: CBCT versus direct visualization</i>
Low to very low GRADE	CBCT appears to be an <i>accurate*</i> test for <i>detecting</i> and <i>excluding</i> vertical root fractures. PradeepKumar et al. (2021)

* A test is considered accurate when the sum of sensitivity and specificity ≥ 1.5 .⁹

[Update 2022/3] How accurate is CBCT in detecting an extra canal in permanent teeth with no root anomalies and no calcification compared to reference standard (micro-CT or 'staining and clearing' or 'sectioning')?¹⁰

Aung & Myint (2021) investigated the diagnostic accuracy of CBCT in detecting the second canal of permanent teeth not previously endodontically treated, without internal or external resorption, compared with micro-CT, "staining and clearing" or "sectioning."¹¹ The authors used Vertucci's classification of a second canal. This means that all types of this classification except type I were denoted as second canal.

⁹ A test is (sufficiently) accurate when the sum of sensitivity and specificity is at least halfway between one (completely inaccurate) and two (perfectly accurate). See Power, Fell & Wright (2013).

¹⁰ It is usual to perform diagnostic examination of the anatomy of the root canal. Checking for the presence or absence of a "second" canal is part of this. The reason for writing this review by Aung & Myint is that missing a canal is one of the most common reasons for orthograde endodontic re-treatment. Prevalence rates of a "second" canal are: 5 and 14% respectively in permanent central and lateral incisors (in the mandibula); 37-97% in the first upper premolar ; 6-23% in the first lower premolar; 60% of MB2 in the mesiobuccal roots of the first upper molar and 94% of MB2 in the mesial roots of the first lower molar.

¹¹ 'Staining and clearing' is a procedure to examine the internal anatomy of 'calcified' tissue. The process of making a tooth transparent involves many physical and chemical changes. The tooth's inorganic components are first dissolved by decalcification and then water, air and lipid components are removed by dehydration. Subsequent immersion in a liquid makes the tooth transparent (Bansal., et al. 2019). Sectioning of the root: the root is embedded in a piece of resin after which it is cut at different heights. These can then be viewed under the microscope.

They found 12 studies, including 10 cohort studies and two case-control studies, with a total of 1086 roots. The index test used was CBCT. The images were mainly interpreted by radiologists and/or endodontologists.

Six studies reported the diagnostic accuracy of CBCT in detecting the MB2. Two studies reported the effectiveness of CBCT in detecting second canal anatomy in permanent molars in the mandibula. Three studies examined the second canal anatomy of premolars in the maxilla and mandibula. One study examined CBCT for detecting second canal anatomy of permanent canines in the mandibula.

Micro-CT was used as the reference standard in five studies of second channel anatomy. 'Staining and clearing' was used as the reference standard in three studies. 'Sectioning' was used as the reference standard in four studies.

Aung & Myint (2021) calculated for a sensitivity of 0.94 (95% BI: 0.81-0.98) and specificity of 0.93 (0.84-0.97). These results do not take into account the circumstance that the estimates seem to vary with location of second channel (molar, MB2 etc.) and reference test used (micro-CT, 'staining and clearing' and 'sectioning'), as mentioned by the authors themselves (p.8, p.10). The usual way to correct the estimate of - in this case - sensitivity and specificity for these 'confounding' variables is to perform a (weighted) regression analysis. The study group performed this analysis (see Appendix 4.4). It appears that when 'staining and clearing' is used as the reference standard the sensitivity is significantly underestimated and when it involves a molar in the mandibula the sensitivity is overestimated. Corrected for these variables, the sensitivity is 0.87 (95% BI: 0.76-0.98). Specificity does not require correction because none of the "confounding" variables has a statistically significant effect on specificity (see Appendix 4.4).

Table 4-8 provides information on the number of false negatives and number of false positives. At a low prevalence of 30% roots with a second channel, approximately 39 cases per 1,000 roots are missed. At a high prevalence of 70% roots with a second canal, this can reach 91 missed second canals per 1,000 roots. Missing a second canal can lead to failure of endodontic treatment, especially molars in the maxilla (Khademi et al., 2022), and necessitate re-treatment.

The number of cases mistakenly referred to as "second channel" at low, medium and high prevalence is less than 5%.

Table 4-8 Summary findings from Aung & Myint (2021)

Should CBCT be used to diagnose detection of the second canal of the root canal system in permanent teeth w/o root anomalies and calcification?

Patient or population: permanent teeth w/o root anomalies and calcification

Setting: endodontologists, dentists

New test: CBCT

Reference test: micro-CT, staining and clearing, and root sectioning

Pooled sensitivity:0.87 (95% CI: 0.76 to 0.98)|Pooled specificity:0.93 (95% CI: 0.84 to 0.97)

Test result	Number of results per 1,000 roots tested (95% CI).			Number of roots (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence30% Aung & Myint (2021)	Prevalence50% Aung & Myint (2021)	Prevalence70% Aung & Myint (2021)			
True positives	261 (228 to 294)	435 (380 to 490)	609 (532 to 686)	505 (12)	⊕○○○ Very low ^{a,b,c}	In case of a low prevalence of 2nd canals, 39 cases per 1,000 roots may be missed. In case of a high prevalence of 2nd canals, 91 cases
False negatives	39 (6 to 72)	65 (10 to 120)	91 (14 to 168)			

Test result	Number of results per 1,000 roots tested (95% CI).			Number of roots (studies)	Certainty of the Evidence (GRADE).	Comments
	Prevalence 30% Aung & Myint (2021)	Prevalence 50% Aung & Myint (2021)	Prevalence 70% Aung & Myint (2021)			
True negatives	651 (588 to 679)	465 (420 to 485)	279 (252 to 291)	581 (12)	⊕⊕○○ Low ^{a,c}	per 1,000 roots may be missed.
False positives	49 (21 to 112)	35 (15 to 80)	21 (9 to 48)			In case of a low prevalence of 2nd canals, 49 cases per 1,000 roots may be falsely classified as '2nd canal'. In case of high prevalence of 2nd canals, 21 cases per 1,000 roots may be falsely classified.

CI: confidence interval

Explanations

- a. For the patient selection domain, all of the included studies were stated as high risk of bias due to lack of randomization or consecutive series. Most studies unclear whether results of index test and/or reference test were blindly assessed. Therefore rated down by one level.
- b. Substantial variation in estimates of sensitivity, and presence of non-overlapping confidence intervals. Therefore rated down by one level.
- c. "funnel plot asymmetry" and six additional studies were needed to be filled for its symmetry! Publication bias seriously suspected. Rated down by one level.

Conclusions

Diagnostic accuracy	<i>Second channel: CBCT versus reference standard (micro-CT, 'staining and clearing,' section of root)</i>
Low to very low GRADE	CBCT appears to be an <i>accurate*</i> test for <i>detecting</i> and <i>excluding</i> second channel.
	Aung & Myint (2021)

* A test is considered accurate when the sum of sensitivity and specificity ≥ 1.5 .¹²

Considerations

Quality of evidence

The quality of evidence is low to very low for all diagnostic accuracy outcomes of the different imaging techniques. This means that there is high uncertainty about the value of the different diagnostic tests. However, the different imaging techniques seem to be more accurate in predicting healthy periapical conditions (high specificity) than in predicting lesions.

¹² A test is (sufficiently) accurate when the sum of sensitivity and specificity is at least halfway between one (completely inaccurate) and two (perfectly accurate). See Power, Fell & Wright (2013).

Recognizing that accuracy parameters are a surrogate for patient-relevant outcomes such as absence of pain, reduction of periodontitis, or restoration of dental function, the overall quality of evidence is very low.

Patient values and preferences

In principle, all patients will want to undergo as little radiation exposure as possible. However, patients will probably be willing to accept more radiation exposure if they are told that this will lead to a better diagnosis and more focused treatment. Most patients will prefer a better diagnosis to a moderate diagnosis.

Cost

Both CBCT and ultrasound are significantly more expensive than periapical X-rays, but CBCT is becoming cheaper and cheaper because of improvements the industry is making to the equipment.

Consideration of desired and undesired effects

In the context of diagnostic accuracy, sensitivity and specificity, or the fraction of true-positive and true-negative results, respectively, are the desired effects. The undesirable effects in this context are radiation exposure and cost.

CBCT

For the application of CBCT in the diagnostic process, European experts have considered the following: *"The current evidence suggests that high resolution CBCT may have higher sensitivity for detection of periapical lesions than conventional radiography in laboratory studies and that this is achieved without loss of specificity. However, the results should be interpreted with caution when based on the available studies. In practice, clinical signs and symptoms add significantly to the diagnostic process and radiological evidence is not always of critical importance. Furthermore, the relatively high economic cost of CBCT compared with intraoral radiography should not be ignored. Consequently, the Panel concluded that it was not appropriate to recommend CBCT as a standard method for diagnosis of periapical inflammatory disease"* (Radiation Protection No 172, 2012). The Working Group adopts this consideration.

[update 2022/3] A European Society of Endodontology position statement on CBCT cites a series of examples justifying application of CBCT. For example, this position statement states, "In those cases in which lower dose conventional radiography does not provide sufficient information for confident diagnosis a small FOV CBCT examination should be considered if the additional information from reconstructed three-dimensional images is likely to aid diagnosis and treatment planning and/or enhance clinical management. Examples include the following (...):

- detection of periradicular bone (secondary) changes indicative of root fractures, when clinical examination and conventional imaging modalities are not conclusive;
- nonsurgical re-treatment of cases with possible untreated canals and/or previous treatment complications (e.g. perforations);
- identification of the spatial location of extensively obliterated canals, also taking into account the possibilities of guided endodontics.

The working group accepts these opinions.

Ultrasound

[update 2022/3] Research on this seems promising, but ultrasound is not yet available in the daily practice of dentist and endodontist.

Digital versus conventional x-ray recording

In diagnostic accuracy, there seems to be no substantial difference.

Side note on a 2D image versus CBCT

On a 2D image, we can see that different structures overlap, even the small changes in bone structure are not always detectable. After all, there must be a large amount of bone loss before it becomes visible on a 2D image. Of course, this depends on the location, thickness of the cortical bone and amount of

different layers of tissue at the site we are examining. To overcome this problem, it is recommended to take multiple images from different angles to get more of a three-dimensional impression.

Of course if enough bone loss has occurred, the lesion will be clearly visible. Again, whether the size of the lesion on the 2D image matches reality is debatable. In most cases, this does not affect the treatment plan and healing much if the lesion is visible and not too large.

If the periapical image does not give a clear picture, the lesion is too large, the symptoms and the X-ray image do not indicate the same diagnosis, and for the purpose of treatment, more information is needed to provide more targeted and precise treatment, then a 3D image is helpful.

According to the position statement on indications justifying the use of CBCT formulated by the NVvE in 2012, one of the indications relevant here is: "When the diagnosis of periapical abnormalities in patients who show conflicting clinical symptoms, or who show poorly localized symptoms associated with an untreated or previously endodontically treated dentition, cannot be made using radiographs obtained by conventional means."

Application of CBCT should only be done by a dentist or endodontist who has been trained in it. Otherwise, referral to a dentist or endodontist trained in it is necessary.

Recommendations

A periapical X-ray image is preferred for radiologically assessing the condition of periapical tissue. If necessary, multiple images can be taken at different angles to avoid overlap and get a better view of different structures without a 3D image.

CBCT should not be routinely used as an imaging technique for identifying periapical pathology. The ALARA principle is applied here.

High-resolution CBCT with limited volume *should be considered* when

- 1) no clear diagnosis of periapical abnormalities can be made from the clinical signs and periapical radiographs because of:
 - (a) conflicting clinical symptoms, or
 - b. because of poorly localized symptoms associated with an un-treated or previously endodontically treated tooth.
- 2) [update 2022/3] on serious suspicion of the presence of an additional channel
- 3) [update 2022/3] in serious suspicion of the presence of a vertical root fracture.

Application of CBCT should only be done by a dentist or endodontist who has been trained in it. Otherwise, referral to a dentist or endodontist trained in it is necessary.

When using CBCT to image multiple teeth in one image, radiological abnormalities of other teeth should also be checked for. The entire image should be assessed, and thus all the different tissues and structures.

[modified after update 2022/3: added two indications for CBCT and formulated recommendation more strongly on this basis]

Rational

Despite the fact that the cost of CBCT versus that of a periapical X-ray image is higher, CBCT gives a higher radiation exposure than a periapical X-ray image [update 2022/3], the working group gave great weight to the evidence on presence of an extra canal and a vertical root fracture as well as the relevant opinions of European Society of Endodontology position statement on CBCT.

Knowledge gaps

There is a lack of reasonable to high quality evidence on the relative diagnostic usefulness of conventional and intra-oral radiographs and CBCT over histopathologic data.

A possible research approach could be, when one imaging technique has a negative result and the other indicates periapical pathology, to take a biopsy during surgical apical endodontic treatment and examine it histologically (source: Petersson et al., 2012).

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Appendix 4.1.

Assessment risk of bias from Raghav et al., 2010

Quadas criteria for assessing risk of bias

	Item	Assessment
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	Unclear
2.	Were selection criteria clearly described?	Not reported whether patients were consecutively enrolled or randomized
3.	Is the reference standard likely to correctly classify the target condition?	Yes
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Yes
6.	Did patients receive the same reference standard regardless of the index test result?	Yes
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	No
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes
13.	Were uninterpretable/intermediate test results reported?	No
14.	Were withdrawals from the study explained?	Not relevant

Note: **bold** are the criteria that received particular attention from Petersson et al. (2012)

Assessment: serious risk of bias.

Appendix 4.2

Criteria of high-, moderate- and low-study quality, mainly according to QUADAS

High: small risk or bias	<p>Study design either cross-sectional or prospective. A case-control design was not accepted, because it usually overestimates diagnostic accuracy. Particular emphasis was put on the following items:</p> <ul style="list-style-type: none"> - Randomly or consecutively selected, adequately described patients involving a representative and - clinically relevant sample (QUADAS items 1, 2) - The index test should not form part of the reference standard (item 7) - Evaluators should be masked to results of index test and reference test (items 10, 11) - The tests should be described in sufficient detail to permit replication (items 8, 9) - Sample size in subgroups ≥ 30 - Diagnostic accuracy presented as sensitivity and specificity
Moderate: moderate risk of bias	<p>A case-control design was accepted as well as nonrandom or nonconsecutive enrolment of patients. Otherwise the same criteria as for high quality. A sample size of ≥ 20 in subgroups was accepted</p>
Low: high risk of selection and/or verification bias	Criteria of moderate quality not met

Source: Petersson et al., 2012.

Appendix 4.3. Search strategy

Retrieved from PubMed on August 31, 2015

("sensitivity and specificity"[MeSH Terms] OR "Detection"[title/abstract] OR "ROC curve"[MeSH Terms] OR "diagnostic accuracy"[title/abstract] OR "Periapical diseases/diagnosis"[MeSH Terms] OR "Periapical diseases/radiography"[MeSH Terms] OR "Dental pulp diseases/diagnosis"[MeSH Terms] OR "Dental pulp diseases/radiography"[MeSH Terms] OR "Periapical lesions"[tiab] OR "Cadaver"[MeSH Terms])
AND ("Cone beam computed tomography"[MeSH Terms] OR "Radiography, panoramic"[MeSH Terms] OR "periapical radiography"[title/abstract] OR "cone beam computed tomography"[title/abstract] OR "CBCT"[title/abstract] OR "radiologic"[title/abstract] OR "radiology"[title/abstract] OR "radiological"[title/abstract] OR "radiography"[title/abstract] OR "radiographic"[title/abstract] OR "radiographical"[title/abstract]) AND (endodontic[title/abstract] OR "root canal"[title/abstract])"

Appendix 4.4

Outcomes of (weighted) regression analysis where sensitivity (se) or specificity (sp) are the dependent variable and the dependent variables are a set of dummy variables:

- Staining (0 or 1), root section (0 or 1); reference: micro-CT
- Maxillary and mandibular premolars (mmp: 0 or 1), mandibular molar (mm: 0 or 1), mandibular canine (mc: 0 or 1); reference: MB2.

Weighted variable: $1/(\text{unstandardized predicted value})^2$

Model	Coefficients ^{a,b}						
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	,869	,044		19,639	,000	,760	,977
staining	-,249	,071	-,832	-3,524	,012	-,421	-,076
root_section	,077	,059	,233	1,301	,241	-,068	,222
mpm	-,029	,065	-,093	-,455	,665	-,187	,128
mm	,162	,082	,398	1,973	,096	-,039	,363
mc	,050	,100	,115	,501	,634	-,194	,294

a. Dependent Variable: sensitivity

b. Weighted Least Squares Regression - Weighted by weight

Model	Coefficients ^{a,b}						
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	,907	,115		7,885	,000	,625	1,188
staining	-,028	,213	-,068	-,132	,900	-,549	,493
root_section	-,122	,143	-,352	-,854	,426	-,473	,229
mpm	,126	,169	,301	,742	,486	-,289	,540
mm	,023	,212	,049	,109	,917	-,496	,542
mc	,121	,327	,177	,370	,724	-,680	,923

a. Dependent Variable: specificity

b. Weighted Least Squares Regression - Weighted by weight²

5. Treatment of pulpitis

Introduction¹³

Causes of pulpitis

Caries is the most common cause of pulpitis. Several symptoms and clinical findings may indicate that the pulp is irreversibly inflamed, such as spontaneous or persistent pain, or unstoppable bleeding from an exposed pulp. The significance of these symptoms and signs for the prognosis of treatment aimed at preserving the pulp has not yet been adequately investigated.

The pulp can also be damaged by trauma. If the pulpa is exposed by a complicated fracture in the crown, the wound is often superficial. An infection will then be limited in the short term to the area at the site of exposure. If treated in time, the pulp has a good prognosis.

What are the benefits of keeping the pulp vital?

A tooth with an inflamed vital pulp, caused by a deep carious lesion or by a complicated fracture of the crown due to trauma, can be treated in two ways: preservation or removal of the pulp. The advantage of the first option is obvious when a young permanently incomplete tooth is involved, because pulpectomy brings root development to a halt. The root will remain undeformed and therefore weaker, increasing the risk of fracture. Also in general, the risk of fracture of an element and root is higher when the element has been treated endodontically. From a cost perspective, the option of preserving all or part of the pulp is also desirable.

Types of treatment

There are several treatment options to keep the pulp vital. With indirect pulp capping, the deepest layer of carious dentin is left undisturbed. The goal of this method is to avoid trauma to the pulp and pulpal exposure, thus promoting healing. Another treatment option is the complete removal of carious tissue, either during the same appointment (immediate complete removal of carious dentin) or in several treatment steps (stepwise excavation).

In the latter case, the goal is to avoid potentially unnecessary pulpal exposure. If the pulp is exposed during treatment, then the pulp can be immediately roofed. Another option is to remove inflamed pulpal tissue and apply a wound dressing to the remaining pulp (partial pulpotomy). Yet another option is to remove the entire contents of the pulpal chamber (pulpotomy). The most radical approach - apart from extraction - is pulpectomy.

The outcome of treatment (the effect measure) is determined by examination of the degree of healing. With stepwise removal of carious dentin and pulpal overdenture or partial pulpotomy, the following criteria apply for healing:

- treated element is asymptomatic;
- Positive response to sensitivity test;
- radiographically normal periapex and
- Continued development of the root in unformed teeth.

Criteria for lack of cure:

- treated dentition is symptomatic and
- Necrotic/infected pulp as determined by clinical and radiographic examination.

For elements treated by pulpotomy or pulpectomy, the outcome is determined primarily on the basis of radiographic examination and any complaints to the treated element. Subjective symptoms are important, as are other clinical findings that may indicate root canal infection.

[Update 2022/3] Post-operative pain may occur as a result of treatment. Ways to reduce the likelihood of afterpain include preoperative and/or postoperative medication. Instead of or in addition to this, some practitioners use occlusal reduction. This technique involves selective removal of hard tissue

¹³ This introduction is based in part on *Methods of Diagnosis and Treatment in Endodontics. A systematic review (2012)* and supplemented where necessary.

(enamel) with subsequent loss of some of the anatomical features of the occlusal surface of the affected tooth. The effect of occlusal reduction would be to reduce the mechanical stimulation of peripheral ends of nociceptors. Whether this technique merits recommendation is highly questionable: 1) it appears far from clear how great the analgesic effect is and 2) sacrificing natural tissue for a highly uncertain pain reduction is questionable.

Pulpa canopy material

When the pulp is directly exposed, it is roofed. Calcium hydroxide (CaOH₂) can be used for this purpose and has long been the material of choice. Despite its high pH, calcium hydroxide creates conditions that promote pulpal healing. Other agents contain steroids - with or without antibiotics - but are not routinely used.

In recent years, promising results have been reported for "mineral trioxide aggregate" (MTA).

Other factors affecting pulpal healing

The treatment outcome of a deep carious lesion - with or without pulpal exposures - depends largely on how infected the pulp is at the time of treatment.

The outcome may also depend on the age of the patient, the approach chosen (indirect or direct pulpal overdenture et cetera) and the choice of overdenture material. The ability of restorative material to prevent bacterial leakage is another factor. For pulpal reconstruction due to trauma, the treatment outcome may depend on the location of the fracture, the degree of root development of the element and the time elapsed between accident and treatment.

Factors affecting healing after pulpectomy

The goal of pulpectomy is to prevent infection of the pulpal cavity, keep the periapical tissues healthy and ensure asymptomatic conditions. To achieve this, proper disinfection during treatment, effective removal of pulpal tissue and compact filling of the instrumented root canal are crucial conditions to prevent infection of the root canal. A complicated anatomy of the root canal and the skills of the surgeon can influence the outcome.

Specific questions are:

1. Is there a difference in effect between incremental, partial or complete removal of carious dentin?
2. Is there a difference in effect between MTA *versus* other materials and among other materials (Biodentine, glass ionomer cement and calcium hydroxide) in *indirect* pulp capping?
3. Is there a difference in effect between direct pulpal overdenture *versus* partial or complete pulpotomy?
4. Is there any difference in effect between calcium hydroxide, MTA or other materials in *direct* pulp capping?
5. [update 2022/3] Is there any difference in effect between calcium hydroxide, MTA or other materials in pulpotomy?
6. Is there a difference in effect between pulpotomy, partial and total pulpectomy?
7. Is there a difference in effect between single-session pulpectomy versus two-session pulpectomy?
8. Is there a difference in effect between occlusal reduction versus no occlusal reduction?

Search and selection

As a starting point for the literature search, the systematic review *Methods of Diagnosis and Treatment in Endodontics* (2012) was taken as an update. The search strategy contained therein was used for this update. The criteria for selecting found studies were created by the working group itself, and do not entirely match the criteria used in *Methods of Diagnosis and Treatment in Endodontics* (2012).¹⁴

¹⁴ For example, a minimum of 15 dentures per group in controlled trials, or 30 dentures in cohort studies was not applied. Nor was a maximum dropout rate of 30 applied. Regarding follow-up duration, a minimum of 1 year

The search strategy was conducted in April 2016 through a search in PubMed. Details of the search strategy are provided in Appendix 5.1. A total of 168 articles were found, of which 20 were eligible for inclusion. These included 4 systematic reviews and 16 original studies. After reviewing the studies in the 4 systematic reviews, the 16 original studies and the relevant studies in *Methods of Diagnosis and Treatment in Endodontics* (2012), 30 studies that met the selection criteria could finally be included.

[update 2022/3] With regard to the update of the starting question on *incremental, partial, no or complete removal of carious dentin*, one systematic (Cochrane) review of very good methodological quality was included (Schwendicke et al., 2021). Regarding the basic question on *direct pulpal overdenture and pulpotomy*, one systematic review of good methodological quality was included (Jakovljevic et al., 2022). Regarding the baseline question on *calcium hydroxide, MTA or other materials in direct pulpal overdenture*, two systematic reviews of very good methodological quality were included (Cushley et al, 2021; Didilescu et al, 2018). One review looked at success as an outcome measure, the other review looked at whether or not dentin bridge formation occurred. Regarding the baseline question on *calcium hydroxide, MTA or other materials in partial or total pulpotomy*, one systematic review of good methodological quality was included (Li et al., 2019).

Regarding the starting question on *pulpotomy, partial and total pulpectomy*, one systematic review of good methodological quality was included (Jakovljevic et al., 2022) and a critical commentary by Brignardello-Petersen (2017).¹⁵ Regarding the baseline question on pulpectomy in one session versus pulpectomy in two over more sessions, one systematic review of very good methodological quality was included (Mergoni et al, 2022). Regarding the starting question on occlusal reduction, one systematic review of reasonable methodological quality was included (Nguyen et al, 2020).

Selection Criteria

Type of patients	- patients with permanent teeth with an inflamed vital pulp
Type of Intervention	- indirect and direct pulp capping - stepwise, partial and complete caries removal - (partial) pulpotomy
Type of outcome measures	- failure of therapy: a composite outcome measure, i.e. complications such as: * signs or symptoms of irreversible pulpitis, inflammation or mortality; * endodontic therapy (pulp capping, pulp therapy or root canal treatment; * extraction of the dentition; * Restorative failure or re-treatment (restore replace, restore), or both; * or a combination of the above. - clinical cure - X-ray-based healing (PAI) - extraction - quality of life - number of sessions - cost - postoperative pain - positive or negative bacterial culture - hard tissue barrier
Type of setting	- general practitioners - dental endodontists
Inclusion and exclusion criteria	- Inclusion criteria: - human in vivo studies - comparative observational studies - (quasi-) randomized) or controlled experimental studies - systematic reviews (with or without meta-analyses) - Exclusion criteria:

was not used. The study group believes that applying the GRADE criteria of 'imprecision' and 'indirectness' can sufficiently take into account limited study size and short follow-up duration, respectively.

¹⁵ Partial pulpectomy was examined only in the Brignardello-Petersen-commented study by Eren et al. (2017)

- case reports
- patient series
- in vitro, ex vivo (human) studies

Summary of literature

Is there a difference in effect between stepwise, partial or complete removal of carious dentin for teeth with (irreversible) pulpitis?

[update 2022/3]a. Comparison *complete versus stepwise* removal of carious dentin

Schwendicke et al. (2021) included three randomized studies with a total of 398 teeth with deep lesions (Bjørndal 2017, Orhan 2010 and Leksell 1996) in which there was permanent dentition.¹⁶ It is important to note that at least in Bjørndal's study there was caries in more than three-quarters of the dentin. For study characteristics, see Schwendicke et al, (2021, pp. 51-53, 73-74, 81-83).

Outcome measure failure

Failure was defined as a composite outcome measure (Schwendicke et al., 2021, p. 16):

- signs or symptoms of irreversible pulpitis, inflammation or mortality;
- Endodontic therapy (pulp capping, pulp therapy or root canal treatment);
- extraction of the tooth;
- restorative failure or re-treatment (restore replace, restore), or both;
- Or some combination of the above.

The outcomes on failure are listed in Table 5-1.

Quality of evidence failure follow-up duration 6-60 months

The quality of evidence is reasonable. It was downgraded by one level for severe risk of bias and by one level for imprecision. There was no downgrading for indirect evidence, inconsistency, imprecision and publication bias. The reasons for downgrading are that no blinding of the outcome assessor took place, and there are ambiguities about generation of randomization order and/or blinding of allocation to experimental or control group.

Outcome measures long-term survival and function of element, pain, swelling, fistula, patient satisfaction

These outcomes were not reported in Schwendicke et al. (2021). Nor were other systematic reviews of sufficient methodological quality *found* on this subject.

Conclusions

Fair GRADE	<i>Failure, follow-up duration 6-60 months</i>
	<i>Stepwise removal of carious dentin appears to confer a lower risk of failure than complete removal of carious dentin.</i>
	<i>Bjørndal et al, 2017; Orhan et al, 2010; Leksell et al, 1996</i>

b. *Partial* removal of carious dentin versus *complete* removal of carious dentin

[update 2022/3] Schwendicke et al. (2021) included two randomized studies (Khokhar et al, 2018; Orhan et al, 2010) with 179 teeth with deep lesions involving permanent dentition. For study characteristics, see Schwendicke et al (2021, pp. 70-71, 81-83).

The outcomes on failure are listed in Table 5-1.

¹⁶ Deep lesions are defined as lesions close to the pulp where there is a risk of exposure, extending into the inner third or quarter of the dentin (Schwendicke et al, 2021, p. 16).

Quality of evidence failure follow-up duration 12-18 months

The quality of evidence is very low. It was downgraded by one level for severe risk of bias and by two levels for imprecision. There was no downgrading for indirect evidence, inconsistency and publication bias. The reasons for downgrading are that the study size is small, no blinding of the outcome assessor took place, and there are ambiguities about generation of randomization order and/or blinding of allocation to experimental or control group.

Outcome measures long-term survival and function of element, pain, swelling, fistula, patient satisfaction

These outcomes were not reported in Schwendicke et al. (2021). Nor were other systematic reviews of sufficient methodological quality found on this subject.

Conclusions

Very low GRADE	<i>Failure; follow-up duration 12-18 months</i>
	<i>Partial removal of carious dentin appears to confer a lower risk of failure than complete removal of carious dentin.</i>
	Khokhar et al., 2018; Orhan et al., 2010

c. Is there a difference in effect between *partial removal versus incremental removal of carious dentin?* [update 2022/3] Schwendicke et al. (2021) included three randomized studies (Labib et al, 2019; Maltz et al, 2018; Orhan et al, 2010) with 371 teeth with deep lesions involving permanent dentition. For study characteristics, see Schwendicke et al. (2021, pp. 71-73, 77-79, 81-83).

The outcomes on *failure* are listed in Table 5-1.

Quality of evidence failure follow-up duration 12-24 months

The quality of evidence is reasonable. It was downgraded by one level for severe risk of bias. There was no downgrading for indirect evidence, inconsistency, imprecision and publication bias. Main reasons were flaws in statistical analysis and inadequate randomization procedure.

Outcome measures long-term survival and function of element, pain, swelling, fistula, patient satisfaction

These outcomes were not reported in Schwendicke et al. (2021). Nor were other systematic reviews of sufficient methodological quality found on this subject.

Conclusions

Fair GRADE	<i>Failure; follow-up duration 12-24 months</i>
	<i>Partial removal of carious dentin seems to be more likely to be successful than incremental removal of carious dentin.</i>
	Labib et al, 2019; Maltz et al, 2018; Orhan et al, 2010

Summary

Complete removal is probably a less good option, because leads to more failure, than stepwise and partial (or selective) removal of carious dentin. Stepwise removal of carious dentin appears to be a less good option than partial removal of carious dentin (Table 5-1).

Note: In general, young patients (<29 years) were recruited for the mentioned trials.

Table 5-1 Odds ratios and absolute effects related to failure of complete, partial and incremental removal of carious dentin

Interventions compared pairwise	Odds ratio (95% BI)	Absolute effect (95% BI)
<u>complete versus incremental</u> removal of carious dentin	206 (1.34; 3.17) (3 studies)	17% (7-28%) more failure with complete removal
<u>complete versus partial</u> removal of carious dentin	11.32 (1.96; 65.02) (2 studies)	11% (1-42%) more failure with complete removal
<u>incremental versus partial</u> removal of carious dentin	225 (1.33; 3.82) (3 studies)	13% (4-25%) more failure with stepwise removal

Is there a difference in effect between MTA versus other materials and among other materials (Biodentine, glass ionomer cement and calcium hydroxide) in indirect pulp capping?

A trio of publications compared the following materials: Biodentine versus glass ionomer cement, MTA versus calcium hydroxide and calcium hydroxide versus glass ionomer.

a. Calcium hydroxide cement versus glass ionomer cement.

Through a systematic review, Mickenautsch et al. (2010) sought to determine whether the pulmonary response of resin-modified glass ionomer cement placed in a deep cavity differs from that of calcium hydroxide cement. The reviewers found 6 trials, 1 of which was a randomized trial. However, this trial involved a primary dentition. The age of the patients in these trials ranged from 9 to 32 years. The teeth were premolars (Costa et al., 2003), 2^e maxillary molars and mandibular premolars (Murray et al., 2001), 1^e premolars (Mousavinasab et al., 2008), 1^e and 2^e premolars (About et al., 2001), 2^e premolars (Murray et al., 2002). All teeth were free of caries. Outcomes evaluated by Mickenautsch et al. were inflammatory cell response, hard tissue formation, soft tissue organization, bacterial leakage, odontoblast changes, numbers of intact odontoblasts, and lack of clinically identifiable symptoms of the pulp. These studies yielded 17 data sets. Because of clinical and methodological heterogeneity, meta-analysis was not an option for most outcomes. Summary of results provides the table below.

Table 5-2. Relative risks resin modified glass ionomer cement versus calcium hydroxide cement.

Outcome measure	Number of data-sets	Number of patients	Relative risk [range].
Inflammatory cell response	7	179	0.61 - 1.00 (5 studies) 0.13 (1 study)
Formation of hard tissue	3	85	0,34 - 2,00
Organization soft tissue	1	15	0,97
Leaking bacteria	2	28	0,88 - 0,94
Changes odontoblasts	2	23	0,60 - 2,00
Number of intact odontoblasts	2	124	0,45 - 0,66

Note: In 13 datasets, there was no statistically significant difference. Source: Mickenautsch et al. (2010)

Quality of evidence outcome measures in Table 5-2

The quality of evidence for the in Table 5-2 outcome measures listed is very low. The reasons are imprecise outcomes (downgraded by one level) and the studies not being randomized (downgraded by two levels for risk of bias).

Conclusion

	<i>Outcome measures in Table 5-2</i>
Very low	Calcium hydroxide cement may give slightly more favorable results than glass ionomer cement.
GRADE	Mickenautsch et al., 2010

b. Biodentine versus glass ionomer cement.

In a randomized trial, Hashem et al. (2015) examined the effectiveness of calcium silicate cement (Biodentine) versus glass ionomer cement in patients with reversible pulpitis. They also compared the effectiveness of CBCT periapical radiographs to detect periapical changes over 12 months postoperatively.

Important exclusion criteria were: clinical signs of irreversible pulpitis for which endodontic treatment is indicated, presence of fistula or swelling, mobile elements or sensitivity to percussion, women who are pregnant and patients younger than 18 years. Important inclusion criteria were: a deep carious lesion with extension to at least three-quarters into the dentin based on radiograph, clinical signs of reversible pulpitis, positive response of the pulp to electrical test or heat stimulation, and no periapical changes on a periapical radiograph.

72 restorations (36 Biodentine and 36 glass ionomer cement) were performed in 53 patients (40% female) patients ranging in age from 18 to 76 years (median 28 years). 85% of restorations occurred in a molar. Superficial and softly infected dentin was removed under local anesthesia and with rubber dam isolation. Deeper carious dentin (more than three-quarters) was removed with chemo-mechanical gel and hand instrumentation. The outcome measures were as follows:

- *Clinical success*: positive response to cold test/electrical pulp test, absence of spontaneous pain, negative sensitivity to percussion, absence of fistula/swelling and abnormal motility, and absence of a periapical radiolucency as determined by periapical radiographs;
- *Detection of presence or absence of periapical lucency with CBCT*;
- *Intra-rater and inter-rater reliability for periapical radiographs and CBCT*.
- *Diagnostic accuracy parameters of periapical radiographs (CBCT 'gold' standard)*.

Clinical success after 12 months

In both groups, the success rate was 83.3 (RR: 1.00; 95% BI: 0.81 - 1.23). There were 5 dropouts. Neither cavity size nor gender had any effect on pulpal vitality.

Detection of presence or absence of periapical lucency with CBCT after 12 months

Based on CBCT, 65.4% (34/52) of the pulp was healthy and 90.4% (47/52) based on the X-ray image. A significant difference in the presence of periapical radiolucency ($p = 0.02$) was observed when using CBCT between Biodentine (71%) and glass ionomer cement (88%). It should be noted that in the glass ionomer group, the number of elements with severe pulpitis was higher. On the other hand, after 12 months the distribution of severe/mild lesions in the glass ionomer cement group was similar to that in the Biodentine group.

Intra-assessor and inter-assessor reliability for periapical radiographs and CBCT

Kappa values for intra-rater reliability were 0.68 and 0.66 for CBCT and periapical radiographs, respectively. Kappa values for inter-rater reliability were 0.53 and 0.26 for CBCT and periapical radiographs, respectively.

Diagnostic accuracy parameters of periapical radiographs (CBCT 'gold' standard)

The sensitivity of periapical radiographs was 0.24, the specificity 1, the positive predictive value 1 and the negative predictive value 0.63. The low sensitivity of periapical radiographs means that relatively few periapical changes were detected with this imaging technique.

Quality of evidence clinical success and detection periapical lesions

The quality of evidence regarding *clinical success after 12 months* is low because of ambiguity regarding blinding of allocation to experimental and control group, and imprecision of outcome (clinical success). It was downgraded by one level for risk of bias and by one level for imprecision. There was no downgrading for indirect evidence, inconsistency and publication bias. See also evidence profile 1 in appendix.

The quality of evidence for the outcome the *detection of presence or absence of periapical lesions* with CBCT, diagnostic accuracy parameters, and intra- and inter-rater reliability cannot be determined with GRADE. This is because these outcomes have not been determined through diagnostic testing.

Conclusions

Low	<i>Clinical success after 12 months</i> Biodentine and glass ionomer cements do not appear to differ in terms of clinical success at 12 months in patients with reversible pulpitis.
GRADE	Hashem et al., 2015

-----	<i>Detection of presence or absence of periapical lesions with CBCT after 12 months</i> CBCT appears better than X-ray in detecting periapical changes in patients with reversible pulpitis.
GRADE	Hashem et al., 2015

-----	<i>Intra- and inter-rater reliability periapical radiographs</i> Intra-assessor reliability for radiographs and CBCT do not seem to differ for detecting periapical changes in patients with reversible pulpitis. However, inter-rater reliability appears to be better for CBCT than for periapical radiographs.
GRADE	Hashem et al., 2015

c. MTA versus calcium hydroxide cement.

Leye Benoist et al (2012) investigated the effectiveness of MTA and calcium hydroxide cement in forming a dentin bridge in a randomized controlled trial. Important inclusion criteria were: an active deep carious lesion on the occlusal or approximal surface, reversible inflammation of the pulp (determined based on a painful response to pulp testing). Important exclusion criteria were: elements with periodontal lesions, internal or external root resorptions, and systemic medical conditions of the patient. Patients were 24 years old on average. The MTA group (n=30) included 40% women, and the calcium hydroxide group (n=30) 47%. Of the teeth, 30% were premolar and 15% the 1^e molar in the maxilla, 28% the 1^e molar and 15% the 2^e or 3^e molar in the mandible. After local anesthesia and rubber dam isolation, the carious lesions were removed in three steps: high-speed removal of carious enamel with a round drill; mechanical excavation of dentin with a low-speed drill; manual dentin excavation with a spoon-shaped excavator. Glass ionomer cement was applied over MTA or calcium hydroxide paste. Outcome measures were:

- Clinical success: the pulp remained vital with normal response to thermal and electrical testing with no signs of spontaneous pain.
- X-ray success: dentin bridge was present over the lesions, without radiolucency, widening of periodontal ligament, internal or external root resorption. All radiographs were digitized and analyzed by an operator.

Follow-up took place up to 6 months.

Clinical success after 6 months

In the MTA group, 90.0% (27/30) of the elements were successful. In the calcium hydroxide group, it was 73.3% (22/30). This corresponds to a relative risk of 1.23 (95% BI: 0.96 - 1.57). For every 1,000 elements treated, 169 more were successful (95% BI: 29 fewer to 418 more) with MTA than with calcium hydroxide.

X-ray success after 6 months

The dentin bridge thickness was 0.235 mm ± 0.110 mm in the MTA group and 0, 221 ± 0.059 mm in the calcium hydroxide group. This difference was not statistically significant at the 5% level.

Using logistic regression, the researchers determined which of the following variables influenced clinical success: age, gender, localization of the dentition, type of dentition (premolar et cetera), location of caries (occlusal et cetera), type of capping material (MTA or calcium hydroxide). Disto-occlusal caries was found to have a significant negative and MTA a significant positive effect on outcome. However, this analysis only refers to the outcome after 3 months. Moreover, it cannot be ruled out that the outcome is not due to the site of the caries but to the practitioner.

Quality of evidence clinical and radiographic success after 6 months

The quality of evidence is low. It was downgraded by one level for risk of bias and by one level for imprecision. The reasons are imprecision of outcomes due to small study size, and no adequate randomization and blinding of allocation to study groups. See evidence profile 2 in appendix.

Conclusions

Low	<i>Clinical success after 6 months</i>
	MTA compared with calcium hydroxide could slightly increase clinical success after 6 months in patients with deep carious lesions.
GRADE	Leye Benoist et al., 2012

Low	<i>X-ray success after 6 months</i>
	Between MTA and calcium hydroxide there appears to be little difference in radiographic success after 6 months in patients with deep carious lesions.
GRADE	Leye Benoist et al., 2012

Is there a difference in effect between direct pulpal overdenture versus partial or complete pulpotomy?

[update 2022/3] Jakovljevic et al, 2022 included two randomized studies (Asgary et al, 2018; Bjørndal et al, 2010, 2017) that compared direct pulpal overdenture with partial and/or complete pulpotomy. A group of patients from the previously discussed trial of Bjørndal 2010, 2017 had pulpal exposure (n=58). This group was divided into two groups via a randomized trial, where either direct pulpal overdenture (n=27) or partial pulpotomy (n=31) was performed. Important inclusion criterion was that pulpal exposure was due to removal of carious dentin. Exclusion criteria were prolonged excruciating pain or pain that disturbed sleep, and pus drainage from the exposed pulp. Direct pulp capping was performed after complete removal of carious dentin using hand instruments for excavation. For partial pulpotomy, the same procedures and materials were used as for direct pulpal overdenture except that 1-1.5 mm of pulpal tissue was removed with a round drill. What the patient characteristics were and whether they differed between the two groups was not reported. In the direct pulpal overdenture group, 5 patients dropped out, in the other group 2 patients. To what extent the dropouts in one group differed from the dropouts in the other group was not reported. Outcome measure was suc-

cess, defined as vitality of the pulp (positive response to cold or electrical stimulation) without periapical radiolucency.

The Asgary 2018 trial involved pulpal exposure (n=218). This group was divided into three groups via a randomized trial where either direct pulpal overdenture (n=73) or partial pulpotomy (n=76) or complete pulpotomy (n=69) was performed. After pulpal exposure, 1 mm of pulpal tissue was removed with a diamond drill. The same procedures and materials were used for partial and complete pulpotomy as for direct pulpal overdenture. The outcome measure success was defined as clinical (absence of signs and symptoms of inflammation/infection) and radiographic success (normal contour of periodontal ligament was rated as "healed," evident decrease periapical lesion was rated as "healed"). The outcomes on success are listed in Table 5-3, Table 5-4, Table 5-5.

Table 5-3. Success at 12-month follow-up of direct pulpal overdenture versus partial pulpotomy

	direct pulp capping (I)	partial pulpotomy (II)	relative risk (95% BI) (I)/(II)
Bjørndal 2010	7/27 (26%)	10/31 (32%)	0,80 (0,36; 1,82)
Asgary 2018	45/73 (62%)	31/76 (41%)	1,51 (1,09; 2,09)

Table 5-4. Success at 60-month follow-up of direct pulpal overdenture versus partial pulpotomy

	direct pulp capping (I)	partial pulpotomy (II)	relarisk (95% BI) (I)/(II)
Bjørndal 2017	1/27 (4%)	3/31 (10%)	0,38 (0,04; 3,47)

Table 5-5. Success at 12-month follow-up of direct pulp capping versus full pulpotomy

	direct pulp capping (I)	complete pulpotomy (II)	relative risk (95% BI) (I)/(II)
Asgary 2018	45/73 (62%)	39/69 (57%)	1,09 (0,83; 1,44)

Quality of evidence success after 12 and 60 months

The quality of evidence for *success* of direct pulpal overdenture versus partial pulpotomy *after 12 months* is low. It was downgraded by one level for severe risk of bias, and by one level for severe inconsistency. The main reasons are the possible selective dropout of study participants and no blinding of outcome assessor, and the conflicting outcomes of both trials.

The quality of evidence for *success* of direct pulpal overdenture versus partial pulpotomy *after 60 months* is very low. There are so many study dropouts that it has been downgraded by two levels for very serious risk of bias. In addition, it has been downgraded by two levels for very serious imprecision.

The quality of evidence for *success after 12 months* of direct pulpal overdenture versus complete pulpotomy is low. It was downgraded by one level for severe risk of bias, and by one level for severe imprecision. The main reasons are the large dropout rate of study participants (>20%), no blinding of outcome assessor and the fact that the confidence interval crosses the "no effect line."

Outcome measures long-term survival and function of element, pain, swelling, fistula, patient satisfaction

These outcomes were not reported. Nor were other systematic reviews of sufficient methodological quality found on this subject.

Conclusion

Low GRADE	<p><i>Success after 12 months</i></p> <p>Because of conflicting study outcomes, it is unclear whether direct pulp capping and partial pulpotomy differ in terms of success .</p> <p>Asgary et al., 2018; Bjørndal et al., 2010, 2017</p>
Very low GRADE	<p><i>Success after 60 months</i></p> <p>Direct pulp capping seems less successful than partial pulpotomy but the evidence is very uncertain.</p> <p>Bjørndal et al., 2010, 2017</p>
Low GRADE	<p><i>Success after 12 months</i></p> <p>Direct pulp capping does not seem to differ from full pulpotomy in terms of success .</p> <p>Asgary et al., 2018</p>

Is there any difference in effect between calcium hydroxide, MTA or other materials in direct pulp capping?

[update 2022/3] Cushley et al. (2021) included nine comparative studies, including four randomized studies (Suhag et al. 2019; Awawdeh et al. 2018; Parinyaprom et al. 2018; Kundzina et al., 2017; and five non-randomized studies (Çaliskan et al. 2017; Mente et al. 2014; Cho et al., 2013; Mente et al. 2010). Nine studies, some with multiple follow-up dates ranging from 6 months to 2-3 years, examined MTA versus calcium hydroxide. Five studies some with multiple follow-up dates ranging from 6 months to 3 years examined Biodentine versus MTA. Inclusion criteria were: permanent dentition, dentition with deep caries and an exposed pulp with a clearly formulated pulp diagnosis (normal or reversible pulpitis).

Almost all studies had included patients with reversible pulpitis. In terms of radix development, most cases had a closed apex. As for the type of dentition, molars and premolars were in the majority. A few studies also included incisors. The mean age ranged from 10 to mostly 30-40 years. Women were overrepresented in some studies, men in others.

Good luck

Success was defined as *absence of signs and symptoms of irreversible pulpitis, periodontitis apicalis or loss of vitality of the pulp.*

The outcomes on success are listed in Table 5-6. This shows that at any follow-up duration, MTA gives more success than calcium hydroxide. Here a difference of 5% is taken as a *significant difference in success*. Furthermore, when 5% is again taken as a *significant difference in success*, the table shows that Biodentine appears to be little or no different from MTA. Finally, there also seems to be a significant difference in success between Biodentine and calcium hydroxide. Indeed, the difference in success is always greater than 5% at different follow-up durations.

Table 5-6. Odds ratios and absolute effects related to success of MTA, calcium hydroxide and Biodentine in direct pulpal overdenture

Interventions compared among themselves	Follow-up duration	Odds ratio (95% BI).	Absolute effect (95% BI).
MTA versus calcium hydroxide*	6 months	2.30 (0.91; 5.78) (2 studies)	13% (-2%; 20%) more successful with MTA
	1 year	2.66 (1.46; 4.84) (3 studies)	16% (7%; 21%) more successful with MTA
	2-3 years	2.21 (1.42; 3.44) (4 studies)	16% (8%; 22%) more successful with MTA
MTA versus Biodentine*	6 months	2.56 (0.25; 25.00) (2 studies)	4% (-16%; 7%) more successful with MTA
	1 year	1.12 (0.31; 4.17) (3 studies)	1% (-20%; 10%) more success with MTA
	2 years	1.56 (0.28; 9.09) (2 studies)	5% (-23%; 13%) more successful with MTA
<i>Indirect evidence:**</i>			
Biodentine versus calcium hydroxide	6 months	-	9% (-7%; 25%) more success with Biodentine
	1 year	-	15% (-2%; 32%) greater success with Biodentine
	2 years	-	11% (-8%; 30%) more success with Biodentine

* Subgroup analysis showed no significant effect of study design (randomized/not randomized) on effect estimates (odds ratio). ** Calculated from absolute effects MTA versus calcium hydroxide and MTA versus Biodentine.

For information: Didilescu et al. (2018) compared the effects of various pulp capping materials on *hard tissue* formation.¹⁷ After applying the exclusion criteria, meta-analyses were performed for 22 randomized and non-randomized comparative studies. Non-randomized studies far outnumbered randomized studies by 75% of the total. The inclusion criteria were:

- Permanent dentition with mechanical exposure that underwent vital pulp therapy,
- Use of commercially available materials for pulp capping,
- Use of calcium hydroxide as a control material,
- histological evaluation performed on an extracted tooth,
- formation of a dentin bridge as an outcome measure and
- A minimum follow-up duration of 30 days.

The meta-analyses involved a total of 190 teeth for which MTA was used and which were compared to 142 teeth for which calcium hydroxide was used and 161 teeth for which a resin material was used and which were compared to 93 teeth for which calcium hydroxide was used.

Use of MTA resulted in 2.5 times more frequent dentin bridge formation than calcium hydroxide (odds ratio: 2.45, 95% BI: 1.39; 4.29). Compared with calcium hydroxide, resin materials provided less positive outcomes with respect to dentin bridge formation (odds ratio: 0.02, 95% BI: 0.01; 0.05).

These meta-analyses support the conclusions that can be drawn from Cushley et al. (2021). These seem to indicate that MTA forms a more homogeneous dentin bridge than calcium hydroxide and resin materials.

Quality of evidence success 1-3 years and formation dentin bridge

¹⁷ A critical review by Shenkin & Wilson (2019) was used for this summary.

Regarding the comparison MTA versus calcium hydroxide in terms of *success for a follow-up duration 1-3 years*, the quality of evidence is reasonable. It was downgraded by one level for severe imprecision (wide confidence interval). There was no downgrading for risk of bias, indirect evidence, inconsistency and publication bias.

Regarding the comparison of MTA versus Biodentine in terms of *success for a follow-up duration 1-3 years*, the quality of evidence is very low. It was downgraded by two levels for very severe imprecision (very wide confidence interval). It was downgraded by one level for severe risk of bias (no blinding of allocation interventions and of study participants) but not for indirect evidence, inconsistency and publication bias.

With regard to the indirect comparison Biodentine versus in terms of *success for a follow-up duration 1-3 years*, the quality of evidence is very low. It was downgraded by two levels for very severe indirect evidence and by two levels for imprecision (very wide confidence interval). There was no downgrading for risk of bias, inconsistency and publication bias.

Regarding the comparisons MTA versus calcium hydroxide and resin materials versus calcium hydroxide in terms of *dentin bridge formation*, the quality of evidence is very low. It was downgraded by one level for severe risk of bias: most studies were non-randomized. In addition, two levels were downgraded for very severe imprecision: the ratio of upper limit and lower limit of the confidence interval is greater than 2.5. No downgrading was done for other factors.

Outcome measures long-term survival and function of element, pain, swelling, fistula, patient satisfaction

These outcomes were not reported. Nor were other systematic reviews of sufficient methodological quality found on this subject.

Conclusion

	<i>Success after 1-3 years</i>
Fair	In <i>direct</i> pulpal overdenture, compared with calcium hydroxide, MTA likely increases the probability of success (absence of signs and symptoms of irreversible pulpitis, periodontitis apicalis or loss of pulpal vitality) of treatment.
GRADE	Cushley et al., 2021 (Suhag et al., 2019; Kundzina et al., 2017; Çaliskan et al. 2017; Cho et al., 2013; Mente et al. 2010)

	<i>Success after 1-3 years</i>
Very low	In <i>direct</i> pulp capping, MTA and Biodentine may not differ in the probability of success (absence of signs and symptoms of irreversible pulpitis, periodontitis apicalis or loss of pulp vitality) of treatment, but the evidence is very uncertain.
GRADE	Cushley et al., 2021 (Awawdeh et al. 2018; Parinyaprom et al. 2018; Linu et al. 2017;

	<i>Success after 1-3 years</i>
Very low	In <i>direct</i> pulp capping, Biodentine compared to calcium hydroxide may increase the probability of success (absence of signs and symptoms of irreversible pulpitis, periodontitis apicalis or loss of pulp vitality) of treatment, but the evidence is very uncertain.
GRADE	Cushley et al., 2021 (indirect comparison)

Very low	<p><i>Formation of a dentin bridge after 30 days</i></p> <p>In <i>direct</i> pulpal overdenture, compared with calcium hydroxide and with resin materials, MTA may increase the likelihood of successful dentin bridge formation, but the evidence is very uncertain. Resin materials seem to be the least effective in dentin bridge formation.</p>
GRADE	<p>Didilescu et al., 2018 (Shenkin & Wilson, 2019)</p>

[update 2022/3] Is there a difference in effect between calcium hydroxide, MTA or other materials in partial or full pulpotomy?

Li et al. (2019) included thirteen randomized studies investigating MTA, calcium hydroxide, calcium enriched mixture (CEM), platelet-rich fibrin and triple antibiotic paste. Inclusion criteria included presence of carious pulpal exposures or pulpitis associated with caries and clear definitions of success:

- clinical success defined as absence of clinical manifestations of such as pain on percussion/palpation and spontaneous pain, and absence of the need for further root canal treatment,
- radiographic success defined as healing or resolution of radiographic periapical lesions, and absence of need for further root canal treatment,
- overall success defined as achieving both clinical and radiographic success.

Three studies were conducted in India, two in Egypt, two in Jordan, two in Turkey, two in Iran, one in Australia and one in Thailand. Eight studies involved immature permanent teeth, four studies involved mature permanent teeth, and one study involved both mature and immature teeth.

Most of the evidence relates to the comparison between MTA and calcium hydroxide. For other comparisons, at most two studies were available, usually also implicitly comparing mature and immature teeth.

Good luck

Limiting ourselves to the comparison between MTA and calcium hydroxide (five studies [Taha, N. A., & Khazali, M. A., 2017; Özgür, Uysal & Güngör, 2017; Kumar et al., 2016; Chailertvanitkul et al, 2014; Qudeimat, Barrieshi-Nusair & Owais, 2007] and 315 dentitions), then the results can be summarized as follows: the meta-analysis showed that pulpotomies performed with MTA had 2.23 (95% BI: 1.16; 4.29), 2.19 (95% BI: 1.18; 4.14), and 2.20 (95% BI: 1.15; 4.20) were as likely to have clinical success at 12 months and radiographic and overall success at 12 months and radiographic and overall success at 24 months, respectively, than pulpotomies performed with calcium hydroxide. On a side note, four of the five studies performed a partial pulpotomy and only one study (Kumar et al., 2016) performed a full pulpotomy. This study shows a smaller effect of MTA versus calcium hydroxide, namely 1.44 (95% BI: 0.32; 6.53) as likely to be clinical and 1.45 (95% BI: 0.38; 5.54) as likely to be radiographic/complete success at 12 months,

Quality of evidence success after 12, 24 months

For most studies in which partial pulpotomy was used, there is serious risk of bias. In addition, there is serious imprecision for all outcome measures listed: the confidence intervals (approximately 2.3 to 18% greater success) cross the 5% threshold, considered a minimum for a significant difference. There was no downscaling for other factors. So there is two-level downscaling.

In the study in which complete pulpotomy was applied, there was very serious imprecision (ratio upper and lower limits of odds ratio greater 2.5) on the basis of which this was downgraded by two levels. In addition, there is serious risk of bias. So there is a three-level downgrade.

Outcome measures long-term survival and function of element, pain, swelling, fistula, patient satisfaction

These outcomes were not reported. Nor were other systematic reviews of sufficient methodological quality *found* on this subject.

Conclusion

Low	<i>Success after 12-24 months</i>
	In <i>partial</i> pulpotomy, MTA compared with calcium hydroxide may increase the likelihood of clinical, radiographic and overall success.
	Li et al., 2019 (Taha & Khazali, 2017; Özgür, Uysal & Güngör, 2017; Chailertvanitkul et al., 2014; Qudeimat, Barrieshi-Nusair & Owais, 2007)

Very low	<i>Success after 12 months</i>
	In <i>complete</i> pulpotomy, MTA compared to calcium hydroxide may increase the likelihood of clinical, radiographic and overall success, but the evidence is very uncertain.
	Li et al., 2019 (Kumar et al., 2016)

Is there a difference in effect between pulpotomy, partial and total pulpectomy?

Asgary et al. (2010a, 2010b, 2013, 2014, 2015) compared pulpotomy (vital pulp therapy using calcium-enriched cement) with pulpectomy in a large randomized multicenter trial. 23 general practitioners from Iran participated. 30 dentists attended a workshop in which the study protocol was discussed, training was given in standardized root canal treatment, as well as instructions for pulpotomy treatment. Seven dentists did not pass the exam, and did not participate in the trial. Each dentist was asked to include 18 patients with a permanent molar with irreversible pulpitis.

Important inclusion criteria were: molar with vital pulp, pain indicative of irreversible pulpitis, and patients had opted for extraction for pain relief. Important exclusion criteria were: patients with pockets with a depth of >3 mm, internal/external root resorption visible on radiograph, a non-restorable tooth (with amalgam), and pregnancy/lactation.

Patients, more than 60% of whom were women, had an average age of 26 years. In the pulpectomy group, there were 152 1st molars, 47 2nd molars and 3 3rd molars. In the pulpotomy group, the corresponding numbers were 144, 56 and 5.

During root canal treatment, the canals were frequently irrigated with sterile saline, filled with AHPlus and gutta-percha using the cold lateral condensation technique. The element was temporarily sealed with Cavit™, which was replaced with amalgam after 7 days. In the pulpotomy group, the tooth was anesthetized similarly to the root canal treatment. Pulpotomy was done with a round diamond drill in the air rotor. The pulpal tissue was removed up to the pulpal pump in the root canal. The pulp was covered with an approximately 2 mm thick layer of CEM cement. After covering with a sterile wet cotton pellet, the element was sealed with Cavit™, which was replaced with amalgam after 7 days.

Outcome measures were:

- Clinical success: determined based on subjective symptoms and objective observation of inflammation and/or infection. Objective signs included abscess, swelling, fistula, redness, tenderness, recorded by the dentist at each follow-up.
- X-ray success: success was classified using modified Strindberg criteria. Dental elements with normal contour and width of the periodontal ligament were rated as "cured," elements with

markedly reduced extent of periapical radiolucency were rated as "cured," and elements with unchanged, increased, or new periapical radiolucency were rated as "failed."

- Pain for 7 days postoperatively measured on a numerical scale.
- Costs.

The overall picture is that the results of pulpotomy appear comparable to those of root canal treatment, at least in terms of clinical and radiographic success. At 12-month follow-up, pulpotomy shows a higher success rate than pulpectomy that can be considered clinically relevant. Moreover, at 24-month follow-up, the rates are almost the same: clinical success rate in both study arms 98.19%; radiographic success rates were 79.5 and 86.7% for root canal treatment and pulpotomy, respectively. Postoperative pain is probably less in case of pulpotomy, but whether the effect is relevant to the patient is questionable. Indeed, the difference in pain intensity is only 0.59 on a 10-point scale, whereas a difference of at least 1 can be considered clinically relevant. According to Asgary et al. pulpotomy is cost-effective. To what extent this cost can be translated to the Dutch situation is unclear. They calculate 28 US dollars per molar for a root canal treatment, and over 7 US dollars for a pulpotomy.

For outcome measures at 60-month follow-up, Asgary et al. examined the extent to which age, gender and preoperative periapical lesion affected the clinical success rate. Table 5-7 summarizes this. According to Asgary et al. none of the three variables had any effect on the treatment outcome of pulpotomy compared with pulpectomy. For example, a preoperative periapical lesion present gave a less favorable treatment outcome with both pulpotomy and pulpectomy.

Table 5-7 Effect of age, gender and periapical status on treatment outcome

	Pulpotomy	Root canal treatment
Age	Clinical success rate	
• <21	75	68
• 21-29	81,4	77,9
• >29	76,1	75,6
Gender		
• Women	75,3	74,4
• Men	84,1	77,1
Preoperative periapical lesion		
• Present	65,7	66,7
• Absent	82,4	80,4

Source: Asgary (2015)

[update 2022/3]

Jakovljevic et al., 2022 included a randomized study (Galani et al., 2017) that compared pulpotomy¹⁸ with complete, two-session pulpectomy in patients with mature teeth with pulpal exposures associated with caries. They included 54 patients (mean age: 25 years, 48% female) with carious pulpal exposures in vital teeth without periapical lesions. Pain intensity was on average 1.32, 1.93, 1.34, 1.05, 0.64, and 0.44 points higher on a 0-10 VAS scale in patients who underwent pulpectomy than in patients who underwent pulpotomy after 1, 2, 3, 4, 5, and 6 days.

Regarding success after 18 months, 84.6% (22/26) had success in case of pulpotomy and 87.5% (21/24) had success in case of pulpectomy, giving a relative risk of 1.03 (95% BI: 0.83; 1.29). The researchers defined success as no pain, swelling, fistula, an intact restoration and a periapical index of no more than one.

Eren et al. (2017) compared three interventions, pulpotomy, partial and total pulpectomy, in terms of pain reduction.¹⁹ They included 66 patients with irreversible pulpitis in one vital molar. The mean age

¹⁸ The surgeon removed the pulpal tissue to the canal opening and covered the chamber floor with MTA, after checking bleeding and cleaning.

¹⁹ The working group draws on the critical discussion of Brignadello-Petersen (2017).

was 36 years; 58% were women; and 47% involved a molar in the maxilla. All patients received 600 mg ibuprofen after treatment. Pain intensity was reduced in all groups after 7 days. Comparing pre-operative and postoperative pain, the researchers found that patients experienced a mean pain reduction of 3.0, 1.0 and 5.5 points on a 0-10 VAS scale when they underwent partial pulpectomy, pulpotomy and total pulpectomy, respectively. Thus, pulpotomy seems to provide less pain reduction than partial and especially total pulpectomy.

Quality of evidence success at 1-2 years, 60 months and postoperative pain at 7 days, [update 2022/3] For the outcome measures regarding *success* measured by Asgary et al. *after 1 and 2 years*, the quality of evidence is mostly low. The reasons for downgrading the quality of evidence are: doubts about the randomization procedure; lack of information about differences in success rates between dental practices; composition of calcium-enriched-mixture cement is not known; no sodium hypochlorite solution was used during root canal treatment as is common in the Netherlands. The small study by Galani et al. (2017) was without serious risk of bias. On the basis that Asgary et al. evaluated many more patients, it was downgraded by one level for risk of bias, and by one level for indirect evidence. There was no downgrading for publication bias and inconsistency. *[update 2022/3]* For the outcome measure *postoperative pain after 7 days* was also downgraded by one level for severe risk of bias. Although Galani et al. and Eren et al. (2017) did not have severe risk of bias. However, the largest study (Asgary et al.) did have severe risk of bias (see 1^e paragraph). On this basis, we downgraded by one level. It was not downgraded for indirect evidence, but it was downgraded for severe inconsistency. No downgrading was done for imprecision and publication bias. For the outcome *clinical success after 60 months of follow-up*, there is very low quality of evidence. In addition to the aforementioned reasons, the dropout rate was high, and there is imprecision of the outcome, as reflected in a wide confidence interval, which includes both a clinically relevant and *no* clinically relevant effect. See also evidence profile 3 in appendix.

Outcome measures long-term survival and function of element, patient satisfaction

These outcomes were not reported. Nor were other systematic reviews of sufficient methodological quality found on this subject.

Conclusions

Low GRADE	<p><i>Postoperative pain (calculated over 7 days)</i></p> <p>Pulpotomy seems to give somewhat less pain reduction in some studies and somewhat more pain reduction than (partial) pulpectomy in some studies, if we take a value of 1 on a 10-point scale as a significant effect.</p> <p>Eren et al, 2017; Galani et al, 2017; Asgary et al, 2010a; Asgary et al, 2010b</p>
Low GRADE	<p><i>Clinical success at 12, 18 and 24 months</i></p> <p>Pulpotomy may have as much success at 12 and 24 months follow-up as pulpectomy.</p> <p>Galani et al, 2017; Asgary et al, 2013; Asgary et al, 2014</p>
Low GRADE	<p><i>X-ray success at 24 months</i></p> <p>Pulpotomy may have the same degree of success as pulpectomy.</p> <p>Asgary et al., 2014</p>

Very low	<i>Clinical success at 60 months</i>
GRADE	Pulpotomy may have the same degree of success as pulpectomy. Asgary et al., 2015

-----	<i>Cost</i>
GRADE	Pulpotomy seems cheaper than pulpectomy on a 5-year term. Asgary et al., 2015

Is there a difference in effect between single-session pulpectomy versus two-session pulpectomy?

[update 2022/3] Mergoni et al. (2022) included seven randomized and quasi-randomized trials (Dhyani et al., 2022; Patil et al., 2016; Pragya et al., 2016; Wang, 2016; Wang et al., 2010; Ince et al., 2009; Gesi et al., 2006) that investigated root canal treatment due to pulpitis and reported on one or more of the following outcome measures:

- Radiological failure after 1 year, i.e., periapical radiolucency
- Nap pain within 1 week
- Pain in the immediate postobturation period (< 3 days)
- Postobturation pain after 1 week
- Swelling or flare-up
- Use of pain medication.²⁰

The inclusion criteria were:

- Patients 10 years and older who needed root canal treatment.
- All patients had teeth with completely formed apex and no internal resorption.
- Root canal treatment was performed in one or two or more sessions.
- Treatment was to be carried out using a rubber dam and sodium hypochlorite (0.5% to 5.25%) as irrigant.
- Any systemic drug treatment (antibiotics, NSAIDs or analgesics) had to be the same in experimental and control groups.

Three studies were conducted in India, two in China, one in Turkey and one in Italy. Together, these studies counted 844 dentitions for the mentioned outcome measures. The sex ratio was (v/m) 0.84. The mean age was between 31 and 45 years. Almost all studies were conducted in a clinic affiliated with a university, hospital or military agency.

The results are listed in Table 5-8.

If 5% or more is taken for a significant difference in *effect on radiological failure*, then there appears to be no significant difference between root canal treatment in one versus two or more sessions.

If 10% or more is held for a significant difference in effect on *pain (post-pain within 1 week and pain in the immediate post-obturation period)*, then treating in a single session seems to lead to unfavorable outcomes.

For the other outcome measures (postobturation pain at 1 week, swelling or flare-up, use of analgesia), no significant difference in effect can be observed when a 10% margin is used for a significant difference).

²⁰ The Cochrane reviewers included studies on dentures with vital and necrotic pulp. In this chapter only the studies on a nonnecrotic pulp, in chapter 7 only the studies on a necrotic pulp are described in which the effects of treating in one session versus in multiple sessions were examined. The reviewers named the interventions for a necrotic or a nonnecrotic pulp, as root canal treatment or endodontic treatment. Extraction was also an outcome measure but there were no studies reporting on this separately for pulpitis and pulpal necrosis.

Table 5-8. Outcomes root canal treatment/pulpectomy in one session versus in two or more sessions

Outcome measure	Relative effect (95% BI).	Absolute effect
radiological failure after 1 year (1 study; n=184)	1,19 (0,4; 3,55)	1.1% more radiological failure at one session (-3.6%; 15.3%)
after pain within 1 week (2 studies; n=316)	2,16 (1,39; 3,36)	14.1% more after pain at one session (4.7%; 28.7%)
pain in the immediate postobturation period (<72h) (4 studies; n=402)	1.33 (0.94; 1.88)	16.2% more pain at one sitting (-2.9%; 43.10%)
postobturation pain after 1 week (5 studies; n=249)	1.52 (0.9; 2.55)	7.0% more pain at one sitting (-1.3%; 20.9%)
swelling or flare-up (2 studies; n=209)	0,53 (0.09; 3.0)	1.8% less swelling or flare-up at one sitting (-3.4%; 7.5%)
Use of pain relief (2 studies; n=149)	0.93 (0.71; 1.23)	2.8% less use of pain medication at one sitting (-10.3%; 8.2%)

Quality of evidence radiological failure, follow-up pain < 1 week, postobturation pain < 1 week, swelling and flare-up and use of analgesia

With regard to *radiological failure*, the quality of evidence is low. It was downgraded by one level for severe risk of bias due to ambiguity in allocation blinding. In addition, by one level for severe imprecision: confidence interval crosses threshold for a significant effect (5%). No downgrading was done for other GRADE criteria.

With regard to *post-pain within one week*, the quality of evidence is reasonable. One level was downgraded for severe imprecision: confidence interval crosses threshold for a significant effect (10%). There was no downgrading for other GRADE criteria.

With regard to *pain in the immediate postobturation period (<72h)*, the quality of evidence is low. It was downgraded by one level for severe risk of bias because of ambiguity about allocation blinding and randomization procedure in half of the studies. In addition, by one level for severe inconsistency: some studies showed a small but significant to large effect, others a trivial effect. There was no downgrading for other GRADE criteria.

Regarding *postobturation pain after 1 week*, the quality of evidence is low. It was downgraded by one level for severe risk of bias because of ambiguity about blinding allocation and randomization procedure in half of the studies. Additionally by one level for severe imprecision: confidence interval crosses threshold for a significant effect (10%). There was no downgrading for other GRADE criteria.

With regard to *swelling and flare-ups*, the quality of evidence is very low. It was downgraded by one level for severe risk of bias because of ambiguity about blinding allocation and randomization procedure in half of the studies. In addition, by two levels for very serious imprecision: ratio of upper and lower limits of confidence interval is >3. There was no downgrading for other GRADE criteria.

With respect to *use of analgesia*, the quality of evidence is low. It was downgraded by two levels for severe imprecision: confidence interval crosses threshold for a significant effect (-10%) and ratio of upper and lower limits of confidence interval equals 3. No downgrading was done for other GRADE criteria.

Outcome measures long-term survival and function of element, patient satisfaction

These outcomes were not reported. Nor were other systematic reviews of sufficient methodological quality *found* on this subject.

Conclusions

Low GRADE	<p><i>Radiological failure after 1 year</i></p> <p>Performing root canal treatment/pulpectomy in one session compared to treating in two or more sessions may have little or no effect on radiological failure.</p> <p>Mergoni et al., 2022 (Gesi et al., 2006)</p>
Fair GRADE	<p><i>Nap pain within 1 week</i></p> <p>Performing root canal treatment / pulpectomy in one session compared to treating in two or more sessions probably increases the risk of post-operative pain slightly.</p> <p>Mergoni et al., 2022 (Dhyani et al., 2022; Gesi et al., 2006)</p>
Very low GRADE	<p><i>Pain in the immediate postobturation period (<72h)</i></p> <p>Performing root canal treatment/pulpectomy in one session compared to treating in two or more sessions may slightly increase the risk of pain in the immediate postobturation period, but the evidence is very uncertain.</p> <p>Mergoni et al., 2022 (Dhyani et al., 2022; Pragya et al., 2016; Wang et al., 2010; Ince et al., 2009)</p>

Low GRADE	<p><i>Postobturation pain after 1 week</i></p> <p>Performing root canal treatment/pulpectomy in one session compared to treating in two or more sessions may have little or no effect on postobturation pain after 1 week.</p> <p>Mergoni et al., 2022 (Dhyani et al., 2022; Pragya et al., 2016; Wang et al., 2010)</p>
Very low GRADE	<p><i>Swelling and flare-up</i></p> <p>Performing root canal treatment/pulpectomy in one session compared to treating in two or more sessions may have little or no effect on swelling and flare-ups, but the evidence is very uncertain.</p> <p>Mergoni et al., 2022 (Wang, 2016; Wang et al., 2010)</p>
Low GRADE	<p><i>Use of pain relief</i></p> <p>Performing root canal treatment/pulpectomy in one session compared to treating in two or more sessions may have little or no effect on use of analgesia.</p> <p>Mergoni et al., 2022 (Dhyani et al., 2022; Wang et al., 2010)</p>

Is there a difference in effect between occlusal reduction versus no occlusal reduction?

[update 2022/3] Nguyen et al. (2020) included seven randomized studies with a total of 987 patients, both men and women aged approximately 25 to 35 years, in their systematic review related to the above question (Emara et al., 2019; Arslan et al., 2017; Raza et al., 2016; Zaman et al., 2016; Sheikh et al., 2015; Asghar et al., 2014; Parirokh et al., 2013).²¹ These studies were conducted in various countries (Pakistan [n=4], Turkey [n=1], Egypt [n=1], and Iran [n=1]). Studies that did not evaluate preoperative or postoperative pain intensity in a quantitative manner were excluded. Of these seven studies, only three could be used for a meta-analysis to determine the effect of occlusal reduction on postoperative pain on *day six*. The remaining four studies either had not evaluated pain intensity on day six or did not report mean and standard deviation of pain scores.

These three studies in the meta-analysis included in terms of diagnosis:

- (Acute) irreversible pulpitis of posterior teeth,
- pain on cold test or percussion (however: no information on preoperative pain intensity)
- No periapical peculiarities.

The interventions in these three studies involved reduction of occlusal contacts by 1 mm. Irrigation was done with sodium hypochlorite [1.3, 2.5 or 3%] and calcium hydroxide was used as an intracanal medication. In two studies, manual instrumentation was used. In the third study rotary instrumentation was used. Endodontic treatment took place in two sessions.

In the remaining four studies, the diagnosis involved:

- (symptomatic) irreversible pulpitis of posterior teeth with moderate to severe pain on cold test or percussion and no periapical peculiarities in three studies and periodontitis apicalis in one study.

²¹ Not all studies reported data on sex and age.

Two studies involved reduction by 1 mm ; two others involved "complete reduction" or "reduction where absence of contact was confirmed with articulation paper." Irrigation was done with sodium hypochlorite [1.25 or 1.3%] in two studies, and calcium hydroxide was used as an intracanal medication. The remaining two studies did not report on this. In three of the four studies, rotary, in one study hand instrumentation was used.

As from the above description of diagnoses and interventions, the three studies in the meta-analysis are not fully representative of the remaining four studies.

Postoperative pain

The meta-analysis performed refers to pain intensity on day 6 after surgery. The standardized mean difference (SMD) is -1.10 (95% BI: -2.06; -0.15). An SMD of -0.8 and smaller is considered a large effect. Thus, in this case there appears to be a large effect. Stated differently, occlusal reduction would significantly reduce pain intensity (on day 6).

A narrative analysis of the remaining four studies seems to confirm that the intervention and/or occlusal reduction has a beneficial effect on pain intensity:

- Emara et al. (2019): mean pain scores in the intervention group were lower than pain scores in the control group at all follow-up time points (6, 12, 24 and 48 hours)
- Raza et al. (2016): in three of the four age groups, there was more pain relief in the intervention group than in the control group after 24 hours
- Arslan et al. (2017): on days 3, 5 and 7, pain intensity was lower in the intervention group than in the control group except on day 1
- Parirokh et al. (2013): from 24 hours to day 7, the intervention group had only mild or no pain; in the control group there were some patients with moderate or severe pain.

Quality of evidence postoperative pain < 6 days

The quality of evidence is very low. It was downgraded by three levels for extreme imprecision: the confidence interval (-2.06; -0.15) crossed the thresholds for a small (-0.2), moderate (-0.5) and large (-0.8) effect. There was no downscaling for other factors.

Outcome measures long-term survival and function of element, swelling, fistula, patient satisfaction

These outcomes were not reported. Nor were other systematic reviews of sufficient methodological quality found on this subject.

Conclusion

Very low GRADE	<p><i>Postoperative pain up to 6 days after surgery</i></p> <p>Occlusal reduction seems to reduce pain intensity but the evidence is very uncertain.</p> <p>Nguyen et al., 2020 (Zaman et al., 2016; Sheikh et al., 2015; Asghar et al., 2014)</p>
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Considerations for use of MTA vs calcium hydroxide in pulpotomy (partial/full)

Quality of evidence

The overall quality of evidence is low (partial pulpotomy) to very low (full pulpotomy) for the outcome measure success.

Patient values and preferences

Success is an important outcome measure for patients (and practitioners).

Balance of desired effects versus undesired effects and costs

MTA is significantly more expensive than calcium hydroxide and may cause discoloration. However, compared with calcium hydroxide, MTA has a potentially large effect on clinical and overall success of a (partial) pulpotomy.

Applicability

Calcium hydroxide is still in limited practical use. This is in contrast to MTA. Even though applying MTA requires a certain amount of dexterity and practice. This apparently does not prevent the use of MTA.

Considerations for pulpotomy versus pulpectomy

Quality of evidence

The quality of evidence ranges from low to very low for the outcome measures pain, (clinical and radiographic) success (follow-up duration: 12-60 months). Thus, the overall quality of evidence is very low.

Patient values and preferences

There will be variation in the extent to which patients consider preservation of the dentition important. For many patients, preservation will be important regardless of cost. But a portion of patients will find extraction not an insurmountable problem, while another portion of patients opt for pulpotomy because of the lower cost. For example, a utility study by Ismail et al. (2004) shows that when patients with an element with reversible pulpitis are presented with a choice between filling, dentin regeneration, root canal treatment and extraction, most make the choice of filling, followed by dentin regeneration, then root canal treatment and lastly extraction.

According to Johnson et al. (2006), when there is an indication for root canal treatment or extraction, information about success, risks, prognosis, and costs can help with decision-making.

Balance of desired effects versus undesired effects and costs

Pulpotomy and pulpectomy may give similar results. However, pulpotomy is cheaper.

Applicability

A pulpectomy is the standard treatment in cases of irreversible pulpitis. A pulpotomy seems to give equal results as a pulpectomy. [update 2022/3] More studies with a higher strength of evidence (in GRADE terms: at least reasonable quality of evidence) and with a follow-up duration of at least 48-60 months are needed before pulpotomy is considered an equivalent alternative to pulpectomy in practice.

Considerations for treatment of deep caries

Quality of evidence

The quality of evidence for the outcome measure failure is (very) low.

Patient values and preferences

Almost all patients prefer one rather than two appointments for treatment.

Balance of desired effects versus undesired effects and costs

Exposition of the pulp should be avoided as much as possible. For this reason, but also because stopping the disease process does not require removing all carious tissue, complete removal of caries should be avoided. Stepwise removal of caries requires two appointments. Quite apart from the additional cost of two appointments, one appointment is preferable from a patient perspective.

Applicability

Given that it is widely known that to stop the disease process, removal of all carious tissue is unnecessary, preventing complete caries removal will be acceptable to all.

Considerations for direct pulp capping ("wound dressing")

Quality of evidence

The quality of evidence is fair (MTA vs. CaOH₂) to very low (Biodentine vs. MTA and CaOH₂) for the outcome measure success.

Values and preferences

Patients have no preference for applying MTA or calcium hydroxide or Biodentine.

Balance of desired effects versus undesired effects and costs

MTA and Biodentine are (probably) less likely to cause treatment failure than calcium hydroxide but are more expensive.

Applicability

MTA and Biodentine are the most studied, which is favorable for professional acceptability.

Considerations for indirect pulp capping

According to the guideline working group, it is far from certain whether or not overdenture material is necessary at all in indirect pulpal overdenture.

Treating considerations in one or two sessions

Quality of evidence

The quality of evidence ranges from reasonable (afterpain within 1 week) to very low (all other outcome measures including radiological failure). Thus, the quality of evidence is very low.

Values and preferences

Both follow-up pain and failure are critical outcome measures for patients. Frequency of sessions is an important outcome measure for patients with strong preference for one rather than two sessions.

Balance of desired effects versus undesired effects and costs

For most outcome measures, there is little or no difference between treatment in one or two sessions. Napache within one week may occur more frequently with single-session treatment. An additional advantage of treating in one session is a lower risk of leakage because there is no temporary restoration. In addition, there are fewer costs when treatment is done in one sitting. For most patients, the benefits of single-session treatment outweigh the greater risk of short-term afterpain, the study group believes.

Applicability

Treating in one session is acceptable and feasible for most patients. This is also true for the practitioner.

Considerations related to application of occlusal reduction

Quality of evidence

The quality of evidence is very low for the outcome measure postoperative pain up to 6 days after surgery.

Values and preferences.

Most patients consider pain a critical outcome measure, as well as loss of enamel due to occlusal reduction.

Balance of desired effects versus undesired effects

Virtually all patients and practitioners, in light of the very weak evidence for a beneficial effect of occlusal reduction on pain on the one hand, and of the available alternatives to pain relief such as medi-

cation, and loss of enamel on the other, see more disadvantages than advantages in applying occlusal reduction.

Recommendations

Consider the use of MTA when partial or total pulpotomy is chosen.*

[update 2022/3: new recommendation] see glossary (<https://nvve.com/wp-content/uploads/2018/03/Begrippenlijst-Endodontologie.pdf>).*

Rationale

The working group placed great weight on the more favorable clinical effect of MTA compared to calcium hydroxide, the multiple uses of MTA, and little weight on the fact that MTA is more expensive than calcium hydroxide.

When irreversible pulpitis is suspected, pulpectomy is the standard treatment. [update 2022/3] However, pulpotomy may be considered, with the advantages and disadvantages of pulpectomy for irreversible pulpitis discussed with the patient and weighed in concert.

[modified after update 2022/3: the old recommendation contained a passage that could be perceived as discriminatory. The passage read, "In case of limited financial resources, pulpotomy may be considered as an alternative."]

Rational

The Working Group gave considerable weight to the fact that despite new studies published since 2016, there are still insufficient studies available comparing the long-term effects (minimum follow-up duration of 48-60 months) of pulpotomy with those of pulpectomy. On this basis, pulpectomy is considered the standard treatment for the time being.

In patients with permanent dentition, try to avoid pulpal exposure.

[Update 2022/3] Selective removal of carious tissue is preferable to 'stepwise excavation'.

[modified after update 2022/3: partial removal has been replaced by selective removal to put more emphasis on targeted rather than partial removal of carious tissue]

Rational

The working group placed great weight on avoiding pulpal exposure. In addition, incomplete removal of carious tissue does not reduce clinical success, provided the enamel-dentin boundary is clean. Selective removal of *central* carious tissue can be done in one sitting, as opposed to "stepwise excavation".

For patients with permanent dentition and deep caries in whom pulpal exposure occurs, MTA and [update 2022/3] Biodentine are the agents of first choice as direct overdenture materials.

[modified after update 2022/3: Biodentine has been added due to new evidence].

Rational

The working group gave great weight to the fact that MTA is likely to be less likely to cause treatment failure than calcium hydroxide and is the most researched of the hydraulic calcium silicate-based cements (HCSCs), and gave little weight to the higher cost of MTA and Biodentine.

The working group does not recommend any of the overdenture materials for indirect pulpal overdenture.

[unchanged after update 2022/3]

Rationale

The working group placed great weight on the fact that it is far from certain whether or not overdenture material is necessary at all in indirect pulpal overdenture.

Consider treating (irreversible) pulpitis in one sitting. This may be deviated from when warranted by the presence of pain (emergency), the difficulty of treatment and/or the patient's wishes.

[update 2022/3: new recommendation]

Rationale

The study group gave great weight to the fact that treating in one session is more pleasant for the patient (convenience; time saving) than treating in two sessions, costs less and the risk of leakage is reduced (since there is no temporary restoration as when a second session takes place). The study group placed little weight on the possible more frequent occurrence of post-operative pain within one week.

*For pain relief, **do not** consider occlusal reduction.*

[update 2022/3: new recommendation]

Rationale

The working group gave great weight to the view that sacrificing natural tissue by occlusal reduction for highly uncertain pain reduction is undesirable.

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Appendix 5.1 Search strategy

Using the Search Terms below, a search was conducted April 1, 2016 in PubMed. This yielded 168 hits. During the search, the results were limited to English-language articles published as of 2010.

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((("dental caries"[MeSH Terms] OR "dental pulp exposure"[MeSH Terms] OR "dental pulp diseases"[MeSH Terms] OR "Tooth fractures"[MeSH Terms] OR ("caries"[Title] OR "carious"[Title] OR pulp*[Title]) AND (vital[title] OR expos*[Title] OR lesion*[Title]))) AND ("ultraconservative"[Title] OR "pulpotomy"[MeSH Terms] OR pulpotom*[Title/Abstract] OR "dental pulp capping"[MeSH Terms] OR "calcium hydroxide"[MeSH Terms] OR "pulp capping"[Title] OR ("stepwise"[Title/Abstract] AND "excavation"[Title/Abstract])) AND ("observational"[Title] OR "clinical report"[Title] OR "Follow-Up Studies"[Mesh Terms] OR "comparative study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "review"[Publication Type] OR "retrospective"[Title] OR "retrospective studies"[MeSH Terms] OR random*[Title/Abstract] OR allocat*[Title/Abstract] OR systematic[sb] OR "time factors"[MeSH Terms]) AND (Humans[MeSH Terms]) NOT ("case reports"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type]))
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6. Regenerative endodontic treatment

Introduction

Regenerative endodontic procedures (also referred to as revascularization or revitalization) are defined as biology-based procedures that aim to repair or replace damaged element structures and regenerate part of the pulpadentine complex. Several studies have shown that regenerative procedures can produce acceptable outcomes such as the disappearance of signs and symptoms and/or show complete healing of periapical tissues, thickening of root canal walls and continuation of root formation, along with apical closure. To what extent now are regenerative endodontic procedures an alternative to conventional endodontic treatment of mature teeth with pulpal necrosis and periodontitis apicalis? Especially since conventional endodontic treatment also leads to loss of proprioception and destruction of structure of the mature, permanent dentition (Glynis et al., 2021). Case reports and patient series with results of regenerative procedures or MTA Apical Plug methods (MAP) showed a survival of 97.8% and 97.1%, respectively, and a success rate of 91.3 and 94.6, respectively, summarized Torabinejad et al. in 2017. They concluded, "The existing literature lacks high-quality studies with a *direct comparison* of outcomes of MAP and RET. Randomized multicenter clinical trials with large sample sizes and long-term follow-ups are needed to address this gap in knowledge." Since the publication of the literature review by Torabinejad et al. (2017), several randomized studies have been published, examined whether irrigants used and cause of pulpal necrosis of an immature, permanent dentition have an effect on the outcome of regenerative therapy. As the literature review will show, the total number of patients is still relatively small and follow-up duration is limited. Regeneration is a procedure that is typically done in multiple sessions; however, it is possible to perform this procedure in one session. It is important for practitioners to know whether the effectiveness of treatment is affected by the number of sessions in which regeneration is performed.

Definitions

Success (clinical and radiographic): combination of clinical symptoms (elimination of pain, sensitivity, swelling) and radiographic findings (radiographic evidence of reduction in the size of an apical lesion and - possibly for immature teeth - radiographic evidence of increase in root thickness and length).

Specific questions are:

1. In patients with permanent, immature teeth with pulpal necrosis, what is the survival, healing and root development of regenerative endodontic treatment?
2. In patients with permanent, mature or immature teeth with pulpal necrosis, what is the clinical and/or radiographic success of regenerative endodontic treatment compared with conventional nonsurgical endodontic treatment?
3. Does the cause of pulpal necrosis (trauma, dens evaginatus and caries) of permanent teeth with immature roots in patients treated with a regenerative procedure affect the outcomes of this procedure?
4. In patients with permanent, immature teeth with pulpal necrosis, what is the clinical and/or radiographic success of regenerative endodontic treatment in one session compared with regenerative endodontic treatment in two sessions?
5. In patients with permanent, immature teeth with pulpal necrosis receiving regenerative endodontic treatment, what is the effect of using calcium hydroxide *versus* antibiotics as an intracanal medication on root canal calcification?

Literature search and selection

A literature search was performed in PubMed/Medline in May 2022 (appendix "update literature 2022," available from the Secretariat). Systematic reviews were searched, whether or not combined with a meta-analysis or network meta-analysis. The reviews found were selected according to, in ac-

cordance with the criteria below and methodologically assessed with AMSTAR-I.

Type of patients	- permanent (mature or immature) necrotic teeth with periodontitis apicalis
Type of Intervention	- regenerative endodontic treatment
Check	- conventional, nonsurgical endodontic treatment (<i>only in studies on effectiveness is a control group important, not in studies on prognosis</i>)
Type of outcome measures	- clinical and/or radiographic success - Positive response to/sensitivity to thermal/electrical pulp test - Discoloration and calcification in the root canal (side effects) - patient satisfaction - quality of life - cost
Type of setting	- general practitioners - dental endodontists
Inclusion and exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - regarding questions of effectiveness: systematic reviews of randomized clinical trials and/or <i>comparative</i> observational studies controlling for confounding variables - regarding prognostic questions: systematic reviews of randomized clinical trials and/or observational studies controlling for confounding variables <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - individual randomized clinical trials - non-comparative experimental and observational studies (<i>for prognostic questions, this is not an exclusion criterion</i>) - in vitro, ex vivo (human) studies

Four systematic reviews of good methodological quality were found: Nangia et al. (2021), Glynis et al. (2021), Meschi et al. (2022) and Almutairi et al. (2022).

The review by Meschi et al. (2022), unlike the reviews by Glynis et al. (2021) and Nangia et al. (2021), also covers *immature* permanent dentition. We utilize the review by Glynis et al. (2021) primarily for a scientific summary regarding *mature* dentition, because this review provides the most manageable overview of the characteristics of the included studies.²² Moreover, between the three reviews there is a very high degree of overlap in the studies that were included. The reviews by Nangia et al., Glynis et al. and Meschi et al. address the second starting question: regenerative endodontic treatment compared to conventional nonsurgical endodontic treatment. The review by Almutairi et al. discusses the fifth starting question on the risk of calcium hydroxide on root canal calcification.

In addition, three systematic reviews of moderate quality were found (Koc & Del Fabbro, 2020; Ong et al., 2020; Rossi-Fedele et al., 2019). The review by Ong et al. (2020) concerns the first baseline question on the prognosis of regenerative therapy. The review by Koc & Del Fabbro (2020) relates to the third starting question, which is about the prognostic significance of the cause of pulpal necrosis for the success of regenerative therapy. The review by Rossi-Fedele et al. (2019) concerns the fourth starting question: regenerative therapy in one versus two sessions?

Summary of literature

In patients with permanent, immature teeth with pulpal necrosis, what is the survival, healing and root development of regenerative endodontic treatment?

Ong et al. (2020) conducted a review of studies on the prognosis of regenerative endodontic treatment of permanent, *immature* teeth with pulpal necrosis. The reviewers examined the effect of this therapy on survival, healing and root development. Survival was defined as preservation of the tooth during

²² A very comprehensive overview of study characteristics is provided by Meschi et al. (2022) in appendix 1 of the review.

the follow-up period. Healing was defined as the absence of clinical symptoms combined with elimination of periapical radiolucency. Root elongation was defined as increase in root length. Root thickening was defined as an increase in root thickness. Apical narrowing/closure was defined as decreasing the apical diameter of the root.

Ong et al. (2020) included randomized studies as well as prospective and retrospective cohort studies with a minimum follow-up duration of 12 months. The follow-up period ranged from 12 to 93 months. In four of the 11 studies, it was 12 months. In almost all studies, anterior elements or premolars were treated. The causes of pulpal necrosis were trauma (all 11 studies), dental anomaly (seven of 11 studies) or caries (five of 11 studies). EDTA irrigation was used in five of the eleven studies, but not in the remaining studies. In all eleven studies, a blood clot was applied as a matrix. MTA was almost always applied for closure. Restoration was almost always with composite.

The outcomes are:

- *survival* was 97.3% (95% BI: 94.34-98.75%);
- the *cure* rate was 93.0 (95% BI: 88.16-96.00%).
- *Root extension* was present in 77.3% (95% BI: 66.34-85.41%) of cases. However, if a minimum 20% increase in root elongation was maintained as a clinically relevant increase, the said percentage dropped from 77.3% to 16.1% (95% BI: 5.59-38.35%).
- In 80.6% (95% BI: 71.53-87.31%) of cases, there was an *increase in root canal wall thickness*. However, if a minimum 20% increase in root thickness was taken as a clinically relevant increase, the mentioned percentage dropped from 80.6 to 39.8 (95% BI: 21.98-60.79%).
- *Apical stenosis/closure* was present in 79.1% (95% BI: 65.53-88.22%) of cases. However, if a minimum 20% increase in apical stenosis/closure was maintained as a clinically relevant increase, the said percentage increased from 79.1 to 90.7 (95% BI: 75.26-96.91%).

*Quality of evidence survival to 12 months, healing, root extension and thickness, apical narrowing/closure*²³

Studies on prognosis start for both randomized and observational studies as high quality of evidence. To assess the quality of evidence of prognostic studies, the following criteria are particularly important: was there a representative and well-defined sample of patients; was follow-up sufficiently long and complete; were objective outcome criteria used?

Survival: studies with a 12-month follow-up duration provided the lion's share of patients (163/289). Twelve months is short for evaluation of element survival; ≥ 24 months is a more patient-relevant follow-up duration. Ergo: one level is downgraded for severe risk of bias. There is no downgrading for inconsistency, indirect evidence, publication bias. As for imprecision, the confidence interval shows that at least 94% survive. This seems a high enough percentage (cutoff value: 90%) to consider a regeneration procedure at all. Thus, the quality of evidence is reasonable.

Healing: no downgrading is done for severe risk of bias. Unlike for survival, a follow-up duration of 12 months seems sufficiently long for evaluating healing. Well is downgraded for imprecision: the confidence interval shows that 12% (100-88%) do not heal. This is more than the 10% (100-90%) that is considered the threshold for considering a regeneration procedure at all. Thus, the quality of evidence is reasonable.

Root lengthening, root thickness and apical constriction/closure (20% increase): one level is downgraded for severe risk of bias. This is because it is highly questionable whether these outcome measures can be sufficiently objectively measured.²⁴ In addition, two levels are downgraded for very serious imprecision: the confidence intervals are very wide. Thus, the quality of evidence is very low.

²³ Ong et al, (2020, table 3) assess risk of bias with incorrect assessment criteria. These are primarily designed for efficacy studies and not appropriate for prognostic studies. Their assessment of the "level of evidence" is thus incorrect.

²⁴ From the review by Ong et al. (2020, p. 5): '(...) Besides, the different angulation in positioning of the X-ray beam could lead to radiographic image distortions, giving rise to the wrong interpretation of the result. A few studies showed some negative values in root development after RET, and this indicated the inconsistency in radiographic positioning. Likewise, it is arguable that some positive values in root development after RET could be caused by an error in radiographic positioning'.

Conclusions

Fair GRADE	<i>Survival and healing</i> A regenerative procedure is likely to have a favorable prognosis. Ong et al, 2020
Very low GRADE	<i>20% or more increase in root elongation, thickening of root, apical narrowing/closure</i> A regenerative procedure does not seem to have a favorable prognosis for said outcome measures, but the evidence is very uncertain. Ong et al, 2020

In patients with permanent, mature or immature teeth with pulpal necrosis, what is the clinical and/or radiographic success of regenerative endodontic treatment compared with conventional nonsurgical endodontic treatment?

a. Comparison of regenerative procedures with conventional nonsurgical endodontic treatment of mature permanent teeth with necrotic pulp and/or apical periodontitis

Glynis et al. (2011) found three randomized studies comparing regenerative procedures with conventional endodontic treatment (Table 6-1). A total of 112 patients were randomized. All studies involved mature, permanent teeth with periodontitis apicalis. Which teeth were involved were not specified by the studies, only in terms of "teeth of any type." Most patients were of adult age. Table 6-1 further shows what the regenerative procedure and conventional treatment consisted of. In addition, the follow-up period ranged from 12 to 18 months.

Table 6-1 Summary of study characteristics

Study	Population	Intervention	Comparison	Outcome	Notes
Arslan et al., 2019 [Turkey]	46 patients (11 female, 35 male; REP age, 20.58,±2.53; NSRCT age, 20.66±1.27), 46 teeth of any type (mature, necrotic with apical lesions)	REP [triple antibiotic paste and EDTA 5%/bleeding induction for blood clot formation]	NSRCT [calcium hydroxide and EDTA 5%/gutta-percha cones and epoxy resin-based sealer-cold lateral condensation technique]	1. successful cases [based on clinical and radiographic healing] 2. number of teeth positive to EPT	Clinical & radiographic assessment up to 12 mo follow-up
Brizuela et al., 2020 [Chile].	36 patients (25 female, 11 male; age range overall, 16-58), 36 teeth of any type (mature with apical lesions)	REP [calcium hydroxide/encapsulated human umbilical cord mesenchymal stem cells in a plasma derived biomaterial]	NSRCT [calcium hydroxide/gutta-percha cones + Topseal sealer-continuous wave condensation technique]	1. successful cases [based on clinical and radiographic healing] 2. response to thermal and EPT	Clinical & radiographic assessment at 12 mo follow-up
Jha et al, 2019 [India]	30 patients (age range 9-15); 30 teeth of any type (permanently mature with apical lesions)	REP [EDTA 17%/ SealBio technique, stimulating stem cells of the region and calcium sulfate-based cement]	NSRCT [gutta-percha cones-cold lateral condensation technique]	1.successful healing (combined radiographic and clinical criteria)	Clinical & radiographic assessment at 18 mo follow-up

EPT, electric pulp testing; EDTA, ethylenediaminetetraacetic acid; mo, months; MRI, magnetic resonance imaging; NSRCT, non surgical root canal treatment; PA, periapical; REP, regenerative endodontic procedure

The combined results of these trials are shown in Table 6-2. For the *critical* outcome measure "success," a regenerative procedure shows 28 more successes per 1,000 patients (2.8%) than conventional nonsurgical endodontic treatment. If we take 50 per 1,000 (±5%) as the cutoff value for a small but significant effect, there would be little or no difference in effect between the two treatments. However, the confidence interval shows that a regenerative procedure can have both a significant unfavorable effect (-7.4%) and a significant more favorable effect (+13.9%) than nonsurgical endodontic treatment. For the *important* outcome measure "positive response to electrical stimuli," a regenerative procedure shows a (very) favorable effect compared to nonsurgical endodontic treatment, namely 348 more successes per 1,000. However, there is a high degree of uncertainty about this effect (Table 6-2).²⁵

Other outcome measures (including quality of life; patient satisfaction; side effects) were not reported in the studies, if at all. Regarding adverse events, in one study (Arslan et al., 2019), more *discoloration* of the element was seen in the regeneration group (38.5%) than in the group with conventional nonsurgical endodontic treatment (0%). *Regarding oral health-related quality of life*, this was reported in Arslan et al. (2019): there was no difference after treatment between the two interventions.

Table 6-2 Summary of outcomes and assessment of quality of evidence

²⁵ Glynis et al. (2021) presented a more favorable GRADE rating: moderate rather than low. However, they did not adequately account for the (large) degree of uncertainty of the effect on "success" and on "positive response to electrical stimuli," as reflected in the wide confidence intervals (see Table 6-2).

Regenerative procedure compared with nonsurgical endodontic treatment

Patients or population: patients with necrotic teeth with periodontitis apicalis

Setting: academic **dentistry/endodontology**

Intervention: regenerative procedure (RP)

Control: conventional nonsurgical endodontic treatment (NCEB)

Outcomes	Number of participant (st) Follow up	Certainty of the evidence (GRADE).	Relative effect (95% CI).	Absolute effects	
				Risk with NCEB	Risk difference with RP
success follow up: 12 months on average	112 (3 RCTs)	⊕⊕○○ Low ^a	RR 1.03 (0.92 to 1.15)	925 per 1,000	28 more per 1,000 (74 less to 139 more)
positive response to electrical stimuli follow up: 12 months on average	82 (2 RCTs)	⊕⊕○○ Low ^b	RR 4.31 (1.36 to 13.62)	105 per 1,000	348 more per 1,000 (38 more to 1,328 more)

The risk in the intervention group (and the 95% confidence interval) is based on the risk in the control group and the **relative effect** of the intervention (and the 95% BI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanation

a. When >50 per 1,000 (>5% difference) is taken as the limit for a small but significant beneficial or adverse effect, the confidence interval crosses both a small but significant beneficial and adverse effect. Therefore, it is downgraded by two levels from high to low.

b. The ratio of the upper to lower limit of the confidence interval around relative risk (4.31), i.e., 13.62/1.36, is > 3. Therefore, it is downgraded by two levels.

For information: Nangia et al. (2021) who, like Glynis et al. (2021), compared regenerative procedures with nonsurgical conventional endodontic treatment, reached the same conclusion as stated below, namely, 'Based on a limited number of comparative studies, REP [regenerative endodontic procedures] has a similar success rate to NSET [nonsurgical endodontic treatment] in mature permanent teeth'. Meschi et al. (2022) concluded, 'The survival and success rates were favorable in all included studies and for all groups; however, these outcomes are not reliable due to the low certainty level'.

Conclusions

Low GRADE	<p><i>Clinical and/or radiographic success</i></p> <p>A regenerative procedure appears to be little or no less successful for permanent <i>mature</i> teeth than conventional nonsurgical endodontic treatment.</p> <p>Glynis et al, 2021; Nangia et al, 2021; Meschi et al, 2022 [Arslan et al, 2019; Jha et al, 2019; Brizuela et al, 2020].</p>
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Very low GRADE	<p><i>Positive response to electrical stimuli</i></p> <p>A regenerative procedure appears to result in a significant increase in positive response to electrical stimuli for permanent <i>mature</i> teeth compared with conventional nonsurgical endodontic treatment, but the evidence is highly uncertain.</p> <p>Glynis et al., 2021 [Arslan et al., 2019; Brizuela et al., 2020]</p>
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b. Comparison of regenerative procedures with conventional nonsurgical endodontic treatment of immature permanent teeth with necrotic pulp and/or apical periodontitis

Meschi et al. (2022) included one randomized study (Lin et al., 2017) examining immature teeth (34 central incisors, 69 premolars; 15 dropouts). This study involved children and adolescents aged 8-16 years. The sex ratio was not stated by the investigators. The causes of periodontitis apicalis were caries, trauma, dens evaginatus. The interventions compared were regeneration versus MTA apexification. *Irrigants* used in the regeneration procedure and MTA apexification: (first session) 20 ml 1.5% sodium hypochlorite, 0.9% saline, and 20 ml 17% EDTA; (second session) 0.9% saline and 20 ml 17% EDTA.

Intracanal medication used in the regeneration procedure: 0.1 mg/ ml mixture of ciprofloxacin, metronidazole, clindamycin (1:1:1 mixed with distilled water) and in the MTA apexification: calcium hydroxide, after 1 week Vitapex paste to apical barrier that was confirmed radiographically. *Filling of the root canal* at the regeneration procedure: blood clot plus absorbable collagen barrier and at the MTA apexification: warm gutta-percha. Composite was used for the coronal restoration.

Both MTA apexification and regeneration were 100% successful after one year (RR 1.0; 95% BI: 0.96-1.05). The regeneration procedure showed an increase in root length of 1.64 mm (SD: 1.43 mm). MTA apexification showed a smaller increase in root length of 0.60 mm (SD: 1.06 mm). Converted to a standardized mean difference (SMD), this is 0.788 (95% BI: 0.363 - 1.211). An SMD of 0.788 is a reasonably large effect.²⁶ The regeneration procedure showed an increase in root thickness of 0.24 mm (SD: 0.25 mm). MTA apexification showed a smaller increase in root thickness of 0.08 mm (SD: 0.21 mm). Converted to an SMD, this is 0.673 (95% BI: 0.252 - 1.094). An SMD of 0.673 is a reasonably large effect.

It seems that the root length of the immature dentition in case of regeneration increases particularly in the dens evaginatus group and less in the trauma group. Thus, a comparison of the increase in root length between the two regeneration groups (dens evaginatus *versus* trauma) showed a difference of 2.06 - 0.68 mm: 1.38 mm in favor of the dens evaginatus group.

Of the 69 cases with a regeneration procedure, 30 (43.5%; 95% BI: 32.4-55.2) developed discoloration in the root canal, while calcification in the root canal was found in 26 (37.7%; 95% BI: 27.2-49.5) cases.²⁷ These were the main complications of this procedure.

²⁶ SMDs of 0.2, 0.5 and 0.8 correspond to small, reasonable and large effect, respectively.

²⁷ Almutairi et al. (2022) estimated the overall prevalence of intracanal calcification in a regenerative procedure to be 30.7%.

For information: Santos et al. (2018) investigated the following question: are there alternative materials to conventional materials such as "triple antibiotic paste" (TAP) and "Grey MTA" in order to prevent discoloration of the dentition after revitalization of the pulp. They included prospective and retrospective studies, patient series and clinical trials, all *in vivo*. A total of 38 studies. Discoloration was found in more than 50% of the regenerated dentition. Particularly when TAP was used as an intracanal medication and gray MTA (GMTA) as a sealing material. The reviewers concluded that alternatives to TAP (DAP, calcium hydroxide, in TAP replacement of minocycline with cefaclor, amoxicillin, clindamycin) and to gray MTA (white MTA, Biodentine and calcium enriched mixture[CEM]) showed less discoloration: the TAP/ GMTA combination would cause discoloration in 93% of cases, while an alternative to TAP combined with an alternative to GMTA would still cause discoloration only in 33% of cases.

Quality of evidence success, root length and thickness, discoloration and calcification

Success, root length and thickness: there was difference in percentage of dropouts between the two groups of interventions: 11 dropouts for the regeneration procedure (5 cases of dens evaginatus and 6 cases of trauma) and 4 dropouts for MTA apexification (2 cases of dens evaginatus, 2 cases of trauma). There were ambiguities regarding randomization/blinding allocation. In addition, it strongly appears that the outcome assessors were not blinded. On this basis, two levels are downgraded for very serious risk of bias.

Success: the number of "events" is small (about 100), considerably less than the 200-300 usually required for an adequate study size. On this basis, we also downgrade for severe imprecision. No downgrading was done for other factors, so the quality of evidence for the outcome success is very low.

Increase in root length and root thickness: both involve wide confidence intervals and fall far short of the number of patients required (approx. 800) to demonstrate a small but significant effect (n=103: smaller than 30-50% of 800). On this basis, two levels were downgraded for very severe imprecision. There was no downscaling for other factors, so the quality of evidence for root length and root thickness is very low.

Discoloration and calcification in the root canal: the limitations in study design and conduct, as described for the outcomes success, root length and thickness, do not apply, or hardly apply, to the outcomes discoloration and calcification. Therefore, there is no downgrading for risk of bias. Nor for other GRADE factors. Thus, there is strong evidence for these side effects.

Conclusions

Very low GRADE	<p><i>Clinical and/or radiographic success</i></p> <p>A regenerative procedure appears to be no less successful than MTA apexification for permanent immature teeth but the evidence is very uncertain.</p> <p>Meschi et al., 2022 [Lin et al., 2017]</p>
Very low GRADE	<p><i>Root length and root thickness</i></p> <p>A regenerative procedure - especially in the case of dens evaginatus - for permanent immature teeth seems to have a greater effect on increasing root length and root thickness compared to MTA apexification, but the evidence is very uncertain.</p> <p>Meschi et al., 2022 [Lin et al., 2017]</p>

Very low GRADE	<i>Root length and root thickness</i> A regenerative procedure - especially in the case of dens evaginatus - for permanent immature teeth seems to have a greater effect on increasing root length and root thickness compared to MTA apexification, but the evidence is very uncertain. Meschi et al., 2022 [Lin et al., 2017]
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High GRADE	<i>Discoloration and calcification in the root canal</i> A regenerative procedure causes discoloration and calcification in the root canal in at least 25% of cases. Meschi et al., 2022 [Lin et al., 2017]
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Does the cause of pulpal necrosis (trauma, dens evaginatus and caries) of permanent teeth with immature roots in patients treated with a regenerative procedure affect the outcomes of this procedure?

Koc and Del Fabbro (2020) conducted a review of studies investigating whether the cause of pulpal necrosis of teeth with immature roots influenced the success of a regenerative procedure. Asymptomatic teeth-clinically and radiographically examined during the follow-up period-and teeth that required no further endodontic treatment after completion of the RET protocol were considered successful cases.

They included randomized and non-randomized and non-comparative studies. Inclusion criteria further included: specification of cause of pulpal necrosis, more than five patients, outcome based on clinical and radiographic examination, both pre- and postoperative, follow-up duration of at least 6 months. Eighteen studies met the inclusion criteria: randomized studies (n=8), patient series and retrospective studies (n=10).

In all studies, there were multiple sessions for performing a regeneration procedure.

Koc and Del Fabbro's (2020) analysis consists of two separate analyses:

- In part 1 of the analysis, they performed a number of univariate analyses (Table 6-3),
- In Part 2 of the analysis, they conducted meta-analyses of outcomes from *four* studies that *each* compared success rates for *different causes of pulpal necrosis*.

Univariate analyses

Univariate analyses have major limitations because prognostic factors tend to be correlated. Multivariate analyses are needed to evaluate the specific effect of an individual prognostic factor. In these types of analyses, other potential prognostic factors are corrected for. Table 6-3 lists all potential prognostic factors, including pulpal necrosis.²⁸ This table shows, first, that the cause of pulpa necrosis does not appear to statistically significantly influence the outcome of regenerative treatment although caries appears to have a slightly more favorable prognosis than either of the other two causes. The only statistically significant potential prognostic variables are the irrigation protocol used and whether or not EDTA irrigation is applied. Irrigation with the combination of sodium hypochlorite and EDTA appears to be less successful than sodium hypochlorite alone or the combination of sodium hypochlorite, EDTA and chlorhexidine. EDTA irrigation seems to reduce the likelihood of success.

²⁸ Table 6-3 is taken from Koc & Del Fabbro (2020). However, the p-values were recalculated because almost all p-values were *incorrect*. An example by way of explanation. Koc & Del Fabbro (2020) report for ear room of pulpal necrosis a p-value of 0.055, at the limit of statistical significance. Looking at the success rate of the individual causes of pulpa necrosis, the reader with some statistical knowledge will conclude that this p-value is borderline impossible. Calculation from: <https://www.socscistatistics.com/tests/chisquare2/default2.aspx>.

Table 6-3 Comparison of factors with possible influence on outcome of regenerative procedure

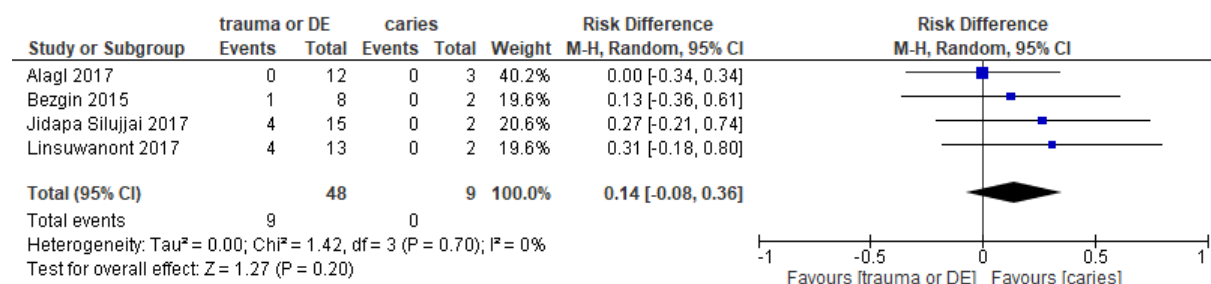
Factors		Success (n=422)	Failure (n=23)	% success	P value
Cause of pulpal necrosis	Trauma (T)	274	15	94,81	0,770
	Dens evaginatus (DE)	95	7	93,14	
	Caries (C)	24	1	96	
		Odds ratio T/C: 0.76 (95% BI: 0.096-6.012)			
		Odds ratio DE/C: 0.57 (95% BI: 0.066-4.819)			
Dentition	Anterieur	275	15	0,0	0,911
	Premolar	135	7	193,66	
	Miller	12	1	92,31	
Intrachannel medication	Ca(OH) ₂	63	0	100	0,179
	CHP (CaOH ₂ + CHX)	10	1	90,91	
	Double antibiotic paste	38	1	97,44	
	Triple antibiotic paste	287	13	95,67	
Irrigation protocol	NaOCl	111	0	100	0,003
	NaOCl+EDTA	240	21	91,95	
	NaOCl+EDTA+CHX	71	2	97,26	
		Odds ratio NaOCl+EDTA /NaOCl+EDTA+ CHX: 0.32 (95% BI: 0.074-1.406)			
EDTA irrigation	EDTA(+)	311	23	93,11	0,005
	EDTA(-)	111	0	100	
		Odds ratio EDTA+/EDTA-: 0.12 (95% BI: 0.016-0.921) ²⁹			
Matrix	Collagen	118	9	92,91	0,15
	No	279	11	96,21	
Matrices ("scaffold").	Blood clot	296	19	93,97	0,126
	Plate Concentration.	93	1	98,94	
	Blood clot +additives	8	0	100	
	No	25	3	89,29	

Meta-analyses

Two studies (Linsuwanont et al., 2017; Silujjai & Linsuwanont, 2017) compared outcome *failure* for caries and dens evaginatus as causes of pulpal necrosis. In case of caries, the failure rate was 0 (0/4); in case of dens evaginatus 33% (6/18). Four studies compared (Alagl et al., 2017; Linsuwanont et al., 2017; Silujjai & Linsuwanont, 2017; Bezgin et al., 2015) compared the outcome *failure rate* for caries and trauma as causes of pulpa necrosis. In case of caries, the failure rate was 0 (0/9); in case of trauma 10% (3/30). Caries appears to have a more favorable prognosis than either of the other two causes. See Figure 6-1, in which *failure* for both causes (trauma and dens evaginatus) is compared with caries as a cause of pulpal necrosis. Compared with caries, 14% (95% BI: -8%; 36%) more regenerative procedure failure occurs with trauma/dens evaginatus. Incidentally, all these studies used a blood clot ("blood clot") as a matrix ("scaffold").

²⁹ The odds ratio is in fact 0 because the failure rate for not applying EDTA is 0. However, to still calculate confidence intervals, 1 case of failure out of 110 successes was assumed.

Figure 6-1 Percent failure rate: trauma or dens evaginatus (DE) versus caries as a cause of pulpal necrosis



Quality of evidence failure

Prognostic studies start as high quality of evidence in case of randomized or observational studies. For risk of bias, it is downgraded by one level because of the lack of multivariable analysis. Prognostic factors are often correlated. Determining an *independent* prognostic factor - in this case, the cause of pulpal necrosis - requires multivariable analysis. In such an analysis, other potential prognostic factors are included for correction. Furthermore, two levels are marked down for very severe imprecision: compare the wide confidence interval of the odds ratios (Table 6-3) and of the risk difference ('risk difference' in Figure 6-1).

For the factors for which a statistically significant effect was found, namely the irrigation protocol and whether or not EDTA was applied, the same assessment of the quality of evidence applies as for the prognostic significance of the cause of pulpal necrosis.

Conclusions

Very low GRADE	<i>Prognostic significance of cause of pulpal necrosis</i>
	Trauma or dens evaginatus as a cause of pulpal necrosis appears to increase the likelihood of regenerative procedure failure compared to caries, but the evidence is very uncertain. Koc and Del Fabbro, 2020 [Alagl et al., 2017; Linsuwanont et al., 2017; Silujjai & Linsuwanont, 2017; Bezgin et al., 2015]
Very low GRADE	<i>Prognostic significance of irrigation protocol and application of EDTA irrigation</i>
	NaOCl+EDTA as a combination in the irrigation protocol appears to increase the risk of regenerative procedure failure compared to NaOCl alone or in combination with chlorhexidine and EDTA, but the evidence is very uncertain. Applying EDTA irrigation appears to increase the risk of regenerative procedure failure compared to not applying it, but the evidence is very uncertain. Koc and Del Fabbro, 2020

In patients with permanent, immature teeth with pulpal necrosis, what is the clinical and/or radiographic success of regenerative endodontic treatment in one session compared with regenerative endodontic treatment in a second session?

Rossi-Fedele et al. (2019) included studies that included at least one session of regenerative endodontic treatment. They found five case reports, one animal study and one randomized trial. In accordance

with the inclusion and exclusion criteria used in this guideline, only the design and results of the randomized trial (Botero et al., 2017) are presented and analyzed.

Botero et al. (2017) included 25 patients (28 teeth), 17 boys and 8 girls, with a mean age of 10.5 years. In 22 of the 25 patients, trauma was the cause of pulpal necrosis, in three of the 25 patients caries or a dental anomaly. Of the teeth involved, 79% were anterior teeth, 19% were premolar, and 2% were molar. Thirteen patients were randomized to the experimental group (regeneration in one session) and 15 patients to the control group (regeneration in second sessions).

The experimental group received the following treatment:

'A 20 k file with a curved tip was placed 2-3 mm beyond the apex to induce bleeding in the canal. Fifteen minutes were allotted for it to obtain a blood clot that would reach the coronal third of the canal. If no bleeding occurred, patients were transferred to the "Rescue Protocol Group." This group received the same treatment as the control group. After the formation of the blood clot, a small Collacote piece was placed on the blood clot, followed by 2-3 mm of white MTA. An X-ray was taken and a sponge was placed before temporization with glass ionomer. The occlusion was evaluated and adjusted. If a sinus tract was present, 0.12% chlorhexidine was used to irrigate the sinus tract before the patient was discharged'.

The control group - as well as the "Rescue Protocol Group" - received the following treatment:

'Calcium hydroxide was used as an intracanal drug to fill the entire canal, and access to the pulp chamber was closed with glass ionomer. Occlusion was evaluated and adjusted. If a sinus tract was present, 0.12% chlorhexidine was used to irrigate. At the next appointment, patients were examined. If signs and symptoms had disappeared, access to the dentition was again obtained and a blood clot was induced as described in the experimental protocol. If signs and symptoms of disease persisted or if bleeding was not induced, calcium hydroxide was replaced in the canal. A maximum of two visits involving further irrigation and placement of calcium hydroxide in the canal was allowed before cases were categorized as failure and "Rescue Protocol Treatment" was offered'.

After inducing the blood clot, patients were examined for the presence of symptoms, but no radiograph was taken. Patients were advised to return at 3, 12, and 24 months for clinical and radiographic follow-up. Financial reimbursement was given at each follow-up visit. The radiographs were reviewed "blind" by four investigators. The reviewers evaluated and classified the difference in periapical radiolucency (before and after treatment) as decreased, unchanged, or increased. Decreased lesions combined with absence of signs or symptoms were considered *success*. Cases with increased or indistinct/unchanged periapical lesion combined with signs or symptoms were classified as *failure*.

After 12 months of follow-up, the success rate in the group in whom the regeneration procedure was applied in one session was 33 (4/12). In the group in whom the regeneration procedure was applied only in a second session, the success rate was 71 (5/7). Thus, the difference in success was -38% (95% BI: -58%; 13%) to the detriment of the group in whom regeneration was applied in one session. The percentages 71 and 33 in the control and experimental groups, respectively, are definitely distorted by:

- 1) the percentage of patients in whom failure to induce a blood clot differed between the two groups: 31% (4/13) versus 53% (8/15) in the experimental and control groups, respectively, and
- 2) there were eight dropouts in the control group and one dropout in the experimental group.

Quality of evidence clinical and radiographic success

One level is downgraded for risk of bias because of ambiguity about the randomization procedure and because of the many dropouts. In addition, two levels are marked down for very severe imprecision: the upper limit indicates a significant benefit for the experimental group ("one session") while the lower limit indicates a very significant benefit for the control group (regeneration in second session).

Conclusion

Very low GRADE	<i>Clinical and radiographic success of regeneration procedure in one session or in a second session</i>
	Success of regeneration of permanent immature anterior teeth appears to be lower when done during one session rather than a second session, but the evidence is very uncertain.
	Rossi-Fedele et al., 2019 [Botero et al., 2017]

In patients with permanent, immature teeth with pulpal necrosis receiving regenerative endodontic treatment, what is the effect of using calcium hydroxide versus antibiotics as an intra-canal medication on root canal calcification?

Almutairi et al. (2022) conducted a review of studies examining whether there was an association between use of calcium hydroxide or antibiotics as a medication and root canal calcification. Inclusion criteria included adolescents < 14 years old, and follow-up duration of at least 12 months. Eight studies (300 teeth) met the inclusion criteria: three randomized and five non-comparative observational studies. None of the randomized studies involved a direct comparison of the two drugs! The mean age of study participants was 11 years. Antibiotics had been applied in 76% of the teeth, and calcium hydroxide in 24%.

When complete and partial calcification are taken together, the odds ratio of calcium hydroxide versus antibiotics is: 2.50 (95% BI: 1.440-4.348). In other words, in case of calcium hydroxide, approximately 2.5 times more (partial and/or complete) calcification of the root canal occurs. For complete calcification, the ratio is even more unfavorable for calcium hydroxide, odds ratio: 6.21 (95% BI: 3.293-11.695).

Quality of evidence calcification root canal

There is no downgrading for risk of bias, inconsistency or publication bias because two levels could already be downgraded for indirect evidence and two levels for imprecision. Note: No *direct* comparison of the two intra-channel drugs took place. In addition, the confidence intervals are wide (upper limit at least 2.5x larger than the lower limit). Thus, the quality of evidence is very low.

Conclusion

Very low GRADE	<i>Calcification of the root canal</i>
	Calcium hydroxide appears to increase the prevalence of root canal calcification compared with antibiotics as an intracanal medication, but the evidence is very uncertain.
	Almutairi et al., 2022

Considerations

Quality of evidence

For most outcome measures, the quality of evidence is (very) low. In a single case, namely the outcome measure discoloration and calcification, the quality of evidence is high.

Values and preferences

Dental retention and absence of discoloration are crucial outcome measures for patients.

Balance of desired and undesired effects

Re recommendation 2. A clinically relevant difference in success or survival between regenerative therapy and apexification has not been demonstrated. The study group assumes that the costs for both options are reimbursed and therefore not a reason to prefer one or the other. The cause of pulpal ne-

crisis (trauma, dens evaginatus or caries) is not an indication for one or the other treatment, the working group believes based on the literature.

Re recommendation 3.

- NaOCl + EDTA as a combination in the irrigation protocol, compared to NaOCl alone or in combination with chlorhexidine and EDTA, seems to increase the risk of regenerative procedure failure. According to the working group, sodium hypochlorite is therefore sufficient.
- Use of antibiotics should be avoided whenever possible. While the discussed literature provides evidence that calcium hydroxide compared with antibiotics increases the risk of root canal calcification, the study group believes that calcification should not be considered as a failure of regenerative therapy nor an obvious risk factor for root canal treatment.
- The evidence seems to indicate that a better result is achieved with a second session.

Re recommendation 4.

There are alternatives to TAP and gray MTA that reduce the risk of discoloration.

Re recommendation 5. This is taken from European Society of Endodontists position statement (Galler et al., 2016).

Recommendations

1. Consider preservation of an immature tooth with pulpal necrosis by regenerative therapy or apexification. The cause of pulpal necrosis (trauma, dens evaginatus or caries) *does not play a* role in choosing between the two options.
2. If regenerative therapy is chosen, consider
 - not apply EDTA irrigation, but only sodium hypochlorite,
 - avoid use of antibiotics as an intracanal medication (in favor of calcium hydroxide)
 - perform regeneration (induction of bleeding, formation of a blood clot) in a second session.
3. Consider using a non discoloring material and inform patient and/or parents or guardians of the possibility of discoloration of the element.
4. Regenerative therapy is contraindicated in case of:
 - replantation of teeth because revitalization can occur naturally,
 - Insufficient ability to isolate the dentition,
 - dentition with extensive loss of coronal tissue requiring repair with a post buildup that occupies the space required for blood clot formation.
5. The study group did not formulate a recommendation regarding regenerative therapy in the case of mature teeth. In the study group's opinion, insufficient research has been conducted to base a recommendation on this.

Rational

A clinically relevant difference in success or survival between regenerative therapy and apexification has not been demonstrated. The cause of pulpal necrosis (trauma, dens evaginatus or caries) is not an indication for one or the other treatment, the study group believes. There is evidence from the discussed literature to avoid EDTA as an irrigant and make do with sodium hypochlorite. There are also indications from the discussed literature that it is better to perform the entire regeneration procedure in two sessions *rather than* one. Regarding the avoidance of antibiotics as intra-channel medications, the study group believes that due to the risk of antibiotic resistance, it is desirable to use them as little as possible. According to Kharchi et al. (2020), their review shows that the combination of sodium hypochlorite with calcium hydroxide may provide a sufficiently disinfected environment. They acknowledged that although the evidence is weak, they note: '(...) it can be argued that when evidence is questi-

onable but calcium hydroxide does not have the disadvantages of TAP [in addition to risk for antibiotic resistance a lesser control of discoloration], it is practical to use calcium hydroxide as a non-antibiotic intra-channel medication'. While the discussed literature provides evidence that calcium hydroxide increases the risk of calcification of the root canal compared to antibiotics, calcification, according to the working group, should not be considered as a failure of regenerative therapy nor an obvious risk factor for root canal treatment.

The study group assumes that the costs for both options will be reimbursed and thus not a reason to prefer one or the other. The recommendations on contraindications were taken from European Society of Endodontists position statement (Galler et al., 2016).

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7. Treatment of a necrotic pulp

Introduction³⁰

The purpose of root canal treatment of a tooth with a necrotic and/or infected pulp is to prevent peri-odontitis apicalis or restore the normal structure of the periapical tissues. Usually, the teeth become asymptomatic immediately or a few days later after treatment.

The persistence of symptoms may indicate that removal of the bacterial infection has not been successful. Incidentally, the restoration of the normal structure of the periapical tissues is a relatively slow process. It may take six to 12 months before there are signs of full recovery, and sometimes it may even take several years.

Therefore, it can be difficult to use imaging diagnostics to determine whether the jawbone is fully recovering or not.

The essential steps in root canal treatment include: instrumentation (shaping), irrigation and disinfection, followed by filling the root canal. Instrumentation and irrigation together are called chemo-mechanical cleaning. The goal of chemo-mechanical cleaning is to remove the infected hard and soft tissue so that the root canal can be effectively disinfected and closed with a root canal filling.

Instrumentation and preparation of root canals can be done with regular hand instruments or with machine-driven instruments.

Various irrigants with disinfectant properties have been tested over the years. It is desirable that the irrigant help dissolve necrotic tissue and kill bacteria in areas inaccessible to the instruments used.

To enhance the effect of treatment, medications are often inserted for some time. Techniques and materials vary. There is uncertainty as to which produce the best results. Root canal filling is intended to prevent reinfection and regrowth of retained bacteria.

NaOCl is generally recommended as the main irrigant for the root canal because of broad antimicrobial spectrum, effective organic agent for dissolving necrotic tissue, low cost, despite concerns about chemical and cytotoxic effects. CHX is also widely used because of broad antimicrobial spectrum and low risk of side effects. Can CHX be recommended to replace NaOCl or as additional irrigation *after* NaOCl and EDTA? What does the recent literature say about this?

[Update 2022/3] During endodontic treatment, residual soft tissue or debris in the apical region of the root canal can cause blockage of the third apical portion. This can be avoided if the *permeability of the apical foramen is maintained during canal shaping*. To this end, a "patency" file (a small flexible #08 or #10 K file) can be used during instrumentation. Although this technique facilitates intracanal irrigation as well as access of medication to the foramen apical and periapical tissues, there is a potential risk of apical extrusion of infected debris, secondary to mechanical instrumentation, beyond the foramen apical. This could cause postoperative pain. To what extent does recent research demonstrate this?

Also related to reducing the risk of postoperative pain, *ultrasonic (activated) irrigation* has been investigated. Conventional irrigation with syringe and endodontic suction cannula has limitations, partly because it is usually limited to the main canal and, for example, lateral canals do not benefit from it, and fails in removing debris. It is therefore unlikely to remove all pathogenic microorganisms. Against this background, alternative techniques, such as ultrasound-activated irrigation, have been developed for better diffusion of chemical fluids into the complex anatomical structures of the root canal. To what extent is this successful according to recent literature?

Reciproke systems offer slightly more comfort for both patient and professional because it shortens working time somewhat. It is still up for debate whether an instrumentation technique with a single file can shape and clean the canal in a shorter time and with a smaller amount of antimicrobial agent as well as a rotary system with multiple files. What does the recent literature say about the degree of bacterial reduction of both systems?

³⁰ This introduction is based in part on *Methods of Diagnosis and Treatment in Endodontics. A systematic review (2012)* and supplemented where necessary.

An effective sealer prevents future pathology by preventing bacterial proliferation. There are several types of sealers. Important types are *resin-based sealers* and *"bioceramic" sealers*. According to recent literature, to what extent do both types yield corresponding results with respect to an important outcome measure such as periapical healing?

Two approaches exist for root canal treatment: *treating in one session or in two (or more) sessions*. The advantage of endodontic treatment in one session is that it saves both practitioners and patients time "in the chair. In addition, it is cheaper, and it may also be more comfortable for patients with temporomandibular disorders who cannot tolerate lengthy treatment. However, treatment in multiple sessions may be indicated if the patient can tolerate extended time in the chair, if there is insufficient time available for the dentist to complete treatment to the required standard of quality, or if the canal continues to fill with fluid and/or blood and cannot be dried. Well, what are the clinical and patient-relevant outcomes of both approaches according to the recent literature? In the case of multiple sessions, there is also the question of the importance of an *intracanal medication*, for which calcium hydroxide is generally used. What does the recent literature say about this?

An important question is to what extent the *quality of root canal filling and coronal restoration procedure* has an effect on periodontitis apicalis. What does recent literature reveal about this?

For *medicinal analgesia*, refer to Chapter 9. Acute symptoms and pain management.

Specific questions related to effect of different methods and materials for instrumentation, filling materials and disinfection (irrigation and medication) on outcomes of root canal treatment:

1. Is there any difference in effect of irrigating with sodium hypochlorite (different concentrations) *versus* chlorhexidine (different concentrations)?
2. Is there any difference in effect of irrigating with 0.2% chlorhexidine *versus* saline?
3. Is there a difference in effect of irrigating with 1% sodium hypochlorite with additional irrigation of chlorhexidine 2% *versus* saline?
4. Does the use of lasers in combination with chemo-mechanical cleaning of infected root canals add value?
5. Is there any difference in effect of irrigating with negative pressure *versus* irrigating with positive pressure?
6. Is there any difference in effect of irrigating with 1% sodium hypochlorite *versus* a passive ultrasound protocol prescribing 1% sodium hypochlorite, 17% EDTA, and 2% chlorhexidine?
7. Is there any difference in effect of irrigating with Er,Cr:YSGG *versus* 3% sodium hypochlorite?
8. Is there a difference in effect of conventional irrigation and ultrasonic (activated) irrigation?
9. [update 2022/3] Is there difference in effect of reciprocal *versus* rotational motion?
10. [update 2022/3] Is there a difference in effect of "bioceramic" and epoxy resin-based sealers?

Any specific questions regarding effect of other factors (number of treatment sessions, preoperative periapical status, microbiological status, root canal filling quality) that may affect the outcome of root canal treatment?

1. Is there a difference in the effect of treating in one session *versus* treating in two sessions?
2. [update 2022/3] Is there a difference in endotoxin levels in infected root canals before and after application of calcium hydroxide medication?
3. Does the preoperative status of dentition with necrotic pulp, with or without periodontitis apicalis, have a significant effect on periapical healing ?
4. Is there difference in effect of adequate *versus* inadequate root canal filling and coronal restoration procedures?

Specific questions regarding effect of methods for prevention or treatment of postoperative complications after treatment of a necrotic pulp?

1. Is there a difference in effect of administration of systemic antibiotics versus no antibiotics/placebo?
2. Is there difference in effect of calcium hydroxide paste with 2% chlorhexidine gel versus 2% chlorhexidine gel versus calcium hydroxide paste versus no disinfectant as intracranial medicament ?
3. Is there a difference in effect of 5.25% sodium hypochlorite versus 2% chlorhexidine gel as an intracanal medication?
4. [update 2022/3] Is there difference in effect of retained versus nonretained apical patency? ("apical patency")?

Search and selection

As a starting point for the literature search, the systematic review *Methods of Diagnosis and Treatment in Endodontics* (2012) was taken as an update. The search strategy contained therein was used for this update. The criteria for selecting found studies were created by the working group itself and do not entirely match the criteria used in *Methods of Diagnosis and Treatment in Endodontics* (2012).³¹ The search strategy (see Appendix 7.1) was conducted in September 2015 through a search in PubMed. A total of 228 articles were found, of which 20 were included. These included 4 systematic reviews and 16 original studies. These systematic reviews included a total of 14 original studies that met the selection criteria. This brings the total to 30 original studies. *Methods of Diagnosis and Treatment in Endodontics* (2012) provided 5 additional studies.

[update 2022/3] For the starting question on *sodium hypochlorite versus chlorhexidine*, a systematic review of good methodological quality (Ruksakiet et al., 2020) was selected. For the starting question on *ultrasonic versus conventional irrigation*, two systematic reviews of good methodological quality (Chalub et al., 2022; Căpută et al., 2019) were selected. For the output question on *reciprocal versus rotary motion*, one systematic review of reasonable methodological quality (Siddique et al., 2019) and one review of good methodological quality (Martins et al., 2019) were selected. For the baseline question on *single versus multiple sessions*, a systematic review of good methodological quality (Mergoni et al., 2022) was selected. A systematic review of good methodological quality (Mekhdieva et al., 2021) and one of moderate methodological quality (Khandelwal et al., 2022) were selected for the output question on *"bioceramic" versus resin-based sealers*. These reviews reported on different outcome measures (postoperative pain and periapical healing, respectively). For the baseline question on *adequate versus non-adequate filling*, a systematic review of good methodological quality (Jakovljevic et al., 2020) was selected. For the baseline question on *antibiotics and pain/swelling*, a systematic review of good quality was selected (Shamszadeh et al., 2021). A systematic review of reasonable methodological quality was selected for the output question on *maintaining apical clearance* (Abudulrab et al., 2018).

Selection Criteria

Type of patients	- patients with permanent teeth with necrotic pulp, with or without periodontitis apicalis
Type of Intervention	- root canal instrumentation - root canal disinfection - filling materials
Type of outcome measures	- clinical cure - X-ray-based healing (PAI) - extraction - quality of life - number of sessions - cost

³¹ For example, a minimum of 15 dentures per group in controlled trials, or 30 dentures in cohort studies was not applied. Nor was a maximum dropout rate of 30 applied. Regarding follow-up duration, a minimum of 1 year was not used. The study group believes that applying the GRADE criteria of 'imprecision' and 'indirectness' can sufficiently take into account limited study size and short follow-up duration, respectively.

	<ul style="list-style-type: none"> - postoperative pain - positive or negative bacterial culture
Type of setting	<ul style="list-style-type: none"> - general practitioners - dental endodontists
Inclusion and exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - human <i>in vivo</i> studies - comparative observational studies - (quasi-) randomized) or controlled experimental studies - systematic reviews (with or without meta-analyses) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - case reports - patient series - <i>in vitro</i>, <i>ex vivo</i> (human) studies

Summary of literature

Effect of different methods and materials for disinfection (irrigation and medication), instrumentation, and filling materials on outcomes of root canal treatment

Disinfection

The well-conducted Cochrane review by Fedorowicz et al. (2012) included four randomized studies (Bebek et al., 2009; Zamany et al., 2003; Ercan et al., 2004; Vianna et al., 2006) that involved patients with necrotic pulpitis/irreversible pulpitis/parodontitis apicalis, and contained sufficient data for quantitative analysis. These four randomized studies evaluated the following comparisons:

- sodium hypochlorite versus chlorhexidine
- chlorhexidine versus saline and
- chlorhexidine versus saline after initial chemo-mechanical cleaning with 1% sodium hypochlorite.

In addition to this review, the literature search yielded 1 observational study (Rôças & Siqueira, 2011) evaluating sodium hypochlorite and chlorhexidine.

Is there any difference in effect of irrigating with sodium hypochlorite (different concentrations) versus chlorhexidine (different concentrations)?

The RCTs by Ercan et al. and Vianna et al. and the comparative study by Rôças & Siqueira involved a total of 109 teeth. Evaluated were 5.25% sodium hypochlorite versus 2% chlorhexidine, 2.5% sodium hypochlorite versus 2% chlorhexidine, and 2.5% sodium hypochlorite versus 0.12% chlorhexidine. For the outcome measure "percentage of positive bacterial culture," the results of these 3 studies can be combined. The relative risk of a positive bacterial culture is 0.955 (95% BI: 0.58 - 1.59) of sodium hypochlorite compared with chlorhexidine. This may not indicate a clinically relevant difference. [update 2022/3] The review by Ruksakiet et al. (2020) shows -despite some more recent studies (Rôças et al., 2016; Zandi et al., 2016, 2019; Xavier et al., 2013;)- almost the same effect size, namely, instead of a relative risk of 0.955, a relative risk of 1.003 (95% BI: 0.729; 1.380).

Quality of evidence percentage of positive bacterial culture

The quality of evidence is very low. It was downgraded by one level for risk of bias (2 of 3 studies have severe bias because of inadequate randomization and no blinding of practitioner and outcome assessor), by one level for circumstantial evidence (bacterial culture is not a patient-relevant outcome measure), and by one level for imprecision (small study size). There was no downgrading for publication bias and inconsistency.

[update 2022/3] Ruksakiet et al. (2020; 'summary of findings table') rated the quality of evidence as low because most (new) studies did not have severe risk of bias. As a result, it was downgraded by one level.

Conclusion

Low	<i>Outcome measure bacterial culture</i>
GRADE	Sodium hypochlorite and chlorhexidine do not seem to differ in effect. Ruksakiet et al., 2020 (Ercan et al., 2004; Vianna et al., 2006; Rôças et al., 2011, 2016; Xavier et al., 2013; Zandi et al., 2016, 2019)

Is there any difference in effect of irrigating with 0.2% chlorhexidine versus saline?

Bebek et al. (2009) studied 44 subjects with necrotic pulp and periodontitis apicalis. Orthograde root canal treatment took place in one session. No intracanal medication was included. Bacterial samples were taken at the start of treatment. Irrigation of root canals occurred three times during instrumentation, with 0.2% chlorhexidine or saline. All canals were tolerated with paper pins and temporarily closed with zinc oxide sulfate. After 48 hours, bacterial samples were taken for the second time. In the chlorhexidine group (n=25), 65% of the samples were positive; in the group receiving saline (n=19), 89% of the samples were positive (RR: 0.72; 95% BI: 0.51 - 1.00).³² The relative risk seems to indicate that chlorhexidine is more effective than saline.

Quality of evidence percentage of positive bacterial culture

The quality of evidence is very low. It was downgraded by one level for risk of bias (2 of 3 studies have severe bias because of inadequate randomization and no blinding of practitioner and outcome assessor), by one level for circumstantial evidence (bacterial culture is not a patient-relevant outcome measure), and by one level for imprecision (small study size). There was no downgrading for publication bias and inconsistency.

Conclusion

Very low	<i>Bacteria Culture</i>
GRADE	0.2% Chlorhexidine seems to have better results than saline. Bebek et al., 2009

Is there a difference in effect of irrigating with 1% sodium hypochlorite with additional irrigation of chlorhexidine 2% versus saline?

Zamany et al. (2003) investigated in 24 individuals with a necrotic pulp of a single-root dentition, whether chlorhexidine and saline after initial biomechanical preparation with sodium hypochlorite as irrigant differed in their effect on the percentage of positive cultures. Samples taken after the first appointment revealed that in the chlorhexidine group 1 out of 12 had a positive culture, in the group using physiological saline it was 7 out of 12 (RR 0.14; 95% BI: 0.02 - 0.99). The relative risk seems to indicate that sodium hypochlorite is more effective than saline.

Quality of evidence percentage of positive bacterial culture

The quality of evidence is very low. It was downgraded by one level for risk of bias (2 of 3 studies have severe bias because of inadequate randomization and no blinding of practitioner and outcome assessor), by one level for circumstantial evidence (bacterial culture is not a patient-relevant outcome measure), and by one level for imprecision (small study size). There was no downgrading for publication bias and inconsistency.

Conclusion

³² Calculation by guideline working group (2015-2017)

Very low	<i>Bacteria Culture</i>
	Chlorhexidine with sodium hypochlorite seems to have better results than saline. Zamany et al., 2003
GRADE	

Does the use of lasers in combination with chemo-mechanical cleaning of infected root canals add value?

Fransson et al. (2013) conducted a systematic review of studies on the efficacy of different types of laser techniques as an adjunct to chemo-mechanical cleaning of infected root canals with 'reduction of bacteria' or 'normal periapical condition' as outcome measures. They found 5 studies of which 4 were non-randomized, experimental studies (Dostálová et al., 2002; Bonsor et al., 2006; Garcez et al., 2007 and 2008), and 1 RCT (Koba et al., 1999). These studies involved irreversible pulpitis, necrotic pulp, or periodontitis apicalis. In the RCT of Koba et al. (1999), 44 teeth were examined. 5% sodium hypochlorite and 2% hydrogen peroxide were used as disinfectants. Between the group with chemo-mechanical cleaning alone and the group with chemo-mechanical cleaning plus laser treatment, there was no statistically significant difference *in periapical recovery* based on radiographic examination. In the other 4 studies, the outcome measure was *reduction of microorganisms*. All 4 non-randomized studies - totaling more than 100 teeth - indicated reduction of bacterial "load" in different terms: "3 of 4 canals that remained infected after conventional treatment were negative after laser treatment"; "combining with photodynamic therapy promoted reduction of bacterial load significantly"). Because of the lack of quantitative information in several cases, a meta-analysis was impossible. Most studies were seriously deficient in reporting essential characteristics of the studies, such as information on buffering a sodium hypochlorite solution, or the distance between topical working length and foramen apicale.

Quality of evidence reduction bacterial load and periapical recovery based on radiological examination

The quality of evidence for bacterial load reduction is very low. It was downgraded by two levels for risk of bias because it was not a comparative study, by one level for circumstantial evidence (bacterial load is not a patient-relevant outcome measure), and by one level for imprecision (small study size). There was no downgrading for publication bias and inconsistency.

The quality of evidence for periapical repair based on radiological examination is very low.

It was downgraded by one level for risk of bias (incomplete description of laser treatment; criteria for evaluation periapical recovery ('good', 'poor' or 'unchanged') were not stated; blinding practitioner and outcomes practitioner not reported), and by two levels for imprecision (precision of outcome could not be ascertained)).

Conclusion

Very low	<i>Periapical repair and bacterial culture</i>
	Several studies indicate a beneficial effect of laser exposure in terms of more extensive bacterial reduction, but this does not seem to have an effect on periapical repair.
GRADE	Dostá-Lová et al., 2002; Bonsor et al., 2006; Garcez et al., 2008 and 2010; Koba et al., 1999.

Is there any difference in effect of irrigating with negative pressure versus irrigating with positive pressure?

The literature search yielded 2 studies (Cohenca et al., 2013; Pawar et al., 2012) comparing irrigating with negative pressure to irrigating with positive pressure. A total of 72 teeth with necrotic pulp and periodontitis apicalis were evaluated. Parwar et al. irrigated with buffered 0.5% sodium hypochlorite

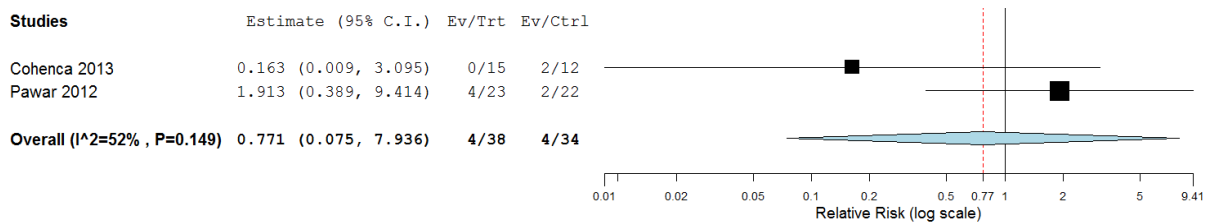
and 17% EDTA. After complete chemo-mechanical cleaning, the root canal was rinsed with 5% sodium thiosulfate, and filled with sterile saline, after which a final microbiological sample was taken before filling the root canal. Cohenca et al. irrigated with 6% sodium hypochlorite (2 minutes) followed by 17% EDTA (1 minute) and then 6% sodium hypochlorite again (2 minutes). Rinsing of the root canal was done with 5% sodium thiosulfate, after which the canal was filled with sterile saline. Cohenca et al. compared a tapered with a non-tapered preparation of the root canal in addition to positive and negative pressure.³³

Both studies applied root canal treatment in two sessions, and had bacterial load as the outcome measure. Sample collection occurred at different times. Pawar et al. considered the samples taken after complete preparation of the root canal, i.e. before temporary filling with calcium hydroxide, as the essential samples. Cohenca et al. however, considered the samples taken after temporary filling with calcium hydroxide (i.e., one week later, i.e., at the second appointment) as the essential samples for comparing antimicrobial efficacy of irrigating with negative versus positive pressure.

Pawar et al. also examined the extent to which outcomes were affected by difference in preoperative status and lesion size, among other factors. They found no significant effect of this on the risk of a positive culture.

Combining the results of the two studies yields an RR of 0.77 (95% BI: 0.075 - 7.936) (Figure 7-1). Ostensibly, irrigating with negative pressure reduces the risk of positive culture by over 20%, but given the wide confidence interval, this effect is uncertain.

Figure 7-1 Relative risk of irrigating with negative pressure versus irrigating with positive pressure on a positive culture after complete chemo-mechanical preparation of the root canal or after temporary filling with calcium hydroxide



Source: guideline working group (2015-2017)

Quality of evidence percentage of positive bacterial culture

The quality of evidence is very low. It was downgraded by one level for risk of bias (blinding of allocation to experimental and control groups is unclear in both studies; in 1 of the 2 studies, blinding of the outcome assessor is unclear), by one level for circumstantial evidence (bacterial culture is not a patient-relevant outcome measure), and by two levels for imprecision (very small study size). There was no downgrading for publication bias and inconsistency.

Conclusion

³³ Therefore, there were four study groups: negative or positive pressure with non-taped or taped preparation.

	<i>Bacteria Culture</i>
Very low	Whether negative pressure has a beneficial effect on bacterial status is uncertain.
GRADE	Cohenca et al., 2013; Pawar et al., 2012

Is there any difference in effect of irrigating with 1% sodium hypochlorite versus a passive ultrasound protocol prescribing 1% sodium hypochlorite, 17% EDTA, and 2% chlorhexidine?

The literature search yielded 1 study comparing 1% sodium hypochlorite with a passive ultrasound protocol (PUI). Beus et al. (2012) investigated in a group of 50 patients with periodontitis apicalis (verified by radiograph and cold test) whether an irrigation protocol with sodium hypochlorite alone made more or fewer root canals free of bacteria than an irrigation protocol with 1% sodium hypochlorite, 17% EDTA, and 2% chlorhexidine. The PUI protocol required that the canals be filled with 1 ml of 1% sodium hypochlorite. PUI was performed with an ultrasonic file number 15 for 30 seconds. The channels were then refilled with 1 ml of 1% sodium hypochlorite. PUI was resumed after 30 seconds. After irrigation with 1% sodium hypochlorite, the channels were dried with paper sticks and filled with 1 ml 17% EDTA and activated with PUI for 30 seconds. The channels were again filled with 1 ml 17% EDTA, and PUI protocol was again applied for 30 seconds. After irrigation with 17% EDTA, the channels were dried with paper sticks, filled with 1 ml 2% chlorhexidine, and activated with PUI for 30 seconds. The channels were again filled with 1 ml of 2% chlorhexidine, and PUI was again applied for 30 seconds. After 2% chlorhexidine activation, the channels were rinsed with sterile saline and dried with paper towels. Prior to bacterial culture, the channels were filled with a mixture of 0.3% L-a-lecithin to negate any antimicrobial effect of chlorhexidine, and then rinsed with sterile saline. After inactivation, a bacterial sample was taken using the "pumping maximal recovery" method, as described by Möller.

The other protocol prescribed that the channels were filled with 1% sodium hypochlorite. Irrigation took place for 3 minutes. This involved using 2 ml of 1% sodium hypochlorite per minute. After irrigation, the channels were dried with paper pens. Prior to bacterial culture, the channels were filled with 5% sodium thiosulfate to deactivate sodium hypochlorite, and then rinsed with sterile saline. A hand file was used to access the canals and remove any debris/bacteria from the dentin wall. A bacterial sample was then taken. Finally, the canals were temporarily filled with calcium hydroxide. A second appointment was scheduled after at least 7 days.

Unfortunately, the researchers report the rates of negative bacterial cultures graphically, with the exception of the rates of negative bacterial cultures after irrigation during the first appointment.³⁴ The sodium hypochlorite-only protocol resulted in a negative culture in 80% (20/25) of teeth. In case of the PUI protocol, 84% (21/25) of bacterial cultures were negative. This gives a relative risk of a negative bacterial culture when applying sodium hypochlorite alone of 0.95 (95% BI: 0.73 - 1.24) compared to a PUI protocol with sodium hypochlorite 1%, 17% EDTA and 2% chlorhexidine.³⁵

Using multiple regression analysis, the researchers examined whether age, gender, type of protocol followed, size of apical head file, preoperative pain, postoperative pain, and presence or absence of a fistula had an effect on bacterial status. The researchers do not provide quantitative information, but conclude that none of these independent variables had a significant effect.³⁶

Quality of evidence percentage of negative bacterial culture

The quality of evidence is very low. It was downgraded by one level for risk of bias (no blinding clinician and unclear as to the blinding of the outcome assessor), by one level for circumstantial evidence (bacterial culture is not a patient-relevant outcome measure), and by one level for imprecision (small study size). There was no downgrading for publication bias and inconsistency.

Conclusion

³⁴ The scale of the Y-axis showing the percentages of negative bacterial cultures is so coarse that accurate interpolation is not possible.

³⁵ Calculation guideline working group (2015-2017).

³⁶ Usual regression coefficients and p-values are reported. The analysis was performed for the sample as a whole.

Very low GRADE	<i>Bacteria Culture</i>
	There appears to be no difference between 1% sodium hypochlorite <i>versus</i> a passive ultrasound protocol in which 1% sodium hypochlorite, 17% EDTA, and 2% chlorhexidine were prescribed. Beus et al., 2012

Is there a difference in effect of irrigating with Erbium, chromium:yttrium-scandium-gallium-garnet (Er,Cr:YSGG) laser radial firing tips (rft) versus 3% sodium hypochlorite with intermediate calcium hydroxide?

The literature search yielded 1 study (Martins et al., 2013) comparing Er,Cr:YSGG with 3% sodium hypochlorite . Martins et al. (2013) examined 29 patients with 36 necrotic teeth with chronic periodontitis apicalis. The mean age was 45 years. 62.5 percent were women.

Irrigation in the control group was done with 5 ml of 3% sodium hypochlorite. Root canals were dried with sterile paper sticks and temporarily filled with calcium hydroxide paste. At the second appointment, abundant irrigation with 3 % sodium hypochlorite was done after removal of calcium hydroxide paste. Visual inspection verified that all paste was removed. Final irrigation was done with 5 ml of 3% sodium hypochlorite. Root canals were filled with gutta-percha using the cold lateral condensation technique. The cavity was sealed with zinc oxide eugenol cement followed by X-ray.

In the test group, irrigation was done with 2 ml of saline solution. The root canal was filled with distilled water, followed by laser irradiation. The tip was placed at working length and irradiation took place at a rate of 2 mm s⁻¹ , until the most coronary part of the canal was reached. Irradiation was repeated four times at 15-second intervals.

At the second appointment, canal preparation was completed with saline. The main canal was filled with distilled water, followed by laser irradiation. Canal was then irrigated with 5 ml of saline solution. Filling of the root canal was otherwise identical to how it was done in the control group.

In the control group (n=12), 66.67% (n=8/12) of teeth were considered healed (PAI ≤2) after 6 months, and 83.33% (n=10/12) were considered improved (i.e., lower PAI score).

In the test group (n=17), 58.82% (n=10/17) of teeth were considered healed after 6 months, and 82.35% (n=14/17) were considered improved. The corresponding relative risks - test group versus control group - are: RR (PAI≤2): 0.88 (95% BI: 0.50 - 1.55), and RR (improvement): 0.99 (95% BI: 0.71 - 1.38). There was no statistically significant difference for either outcome measure.

Quality of evidence PAI≤2 and improvement in PAI score, both after 6 months of follow-up

The quality of evidence is very low. It was downgraded by two levels for imprecision (very small study size). There was no downgrading for risk of bias, indirect evidence, publication bias and inconsistency.

Conclusion

Very low GRADE	<i>Periapical status</i>
	There appears to be no difference in the degree of recovery or improvement between applying laser exposure and sodium hypochlorite. Martins et al., 2013

Instrumentation

Is there a difference in effect of conventional irrigation and ultrasonic (activated) irrigation on post-operative pain intensity and/or pain incidence?

[update 2022/3] Chalub et al. (2022) included three randomized studies (Middha, et al., 2017; Chen et al., 2016; Tang et al., 2015) with a total of 430 patients (491 dentitions) with non-vital pulp / periodontitis apicalis in their systematic review related to the above question. The mean ages in these three

studies were: 27.2, 40.2 and 61.3 years. These studies were conducted in India (n=1) and China (n=2). Dental elements were premolars (n=105), molars (n=238) and anterior elements (n=147). The concentrations of irrigant (sodium hypochlorite) used were: 2.5% (n=2) and 5.25% (n=1).

Two studies measured pain intensity and all three measured the incidence of pain during the first 24 hours. However, pain intensity was measured in different ways, namely on a 0-100 VAS scale and as no, mild, moderate and severe pain. In addition, also at different times: one study looked only at the first 24 hours, the other study up to day 7. Therefore, a meta-analysis of pain intensity as opposed to incidence of pain is not possible.

Outcome measure postoperative pain intensity

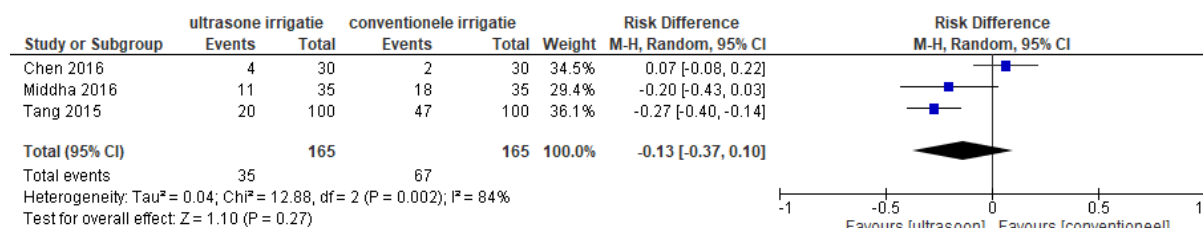
Regarding *pain intensity*, both studies showed lower pain intensity *after the first 24 hours*:

- 5.5% (11/200) in the ultrasound group and 21% (21/100) in the conventional group had moderate - severe pain in the study by Tang et al. (2015). The difference of 15.5% was statistically significant (95% BI: 7.5; 24.8%);
- on a 0-100 VAS scale, pain intensity was 5.82 ± 9.4 in the ultrasound group and 13.40 ± 15.5 in the conventional group in the study by Middha et al. (2016). While the difference between 5.82 and 13.40 (-7.58) is statistically significant (95% BI: -13.69; -1.47), it is not clinically relevant: in general, for a 0-100 pain scale, values greater than 10 to 11 are considered an observable reduction in pain intensity by the patient.³⁷

Outcome measure postoperative incidence of pain

As for the postoperative *pain incidence*, it shows Figure 7-2 does not show unambiguous outcomes: two studies showed a reduction in pain incidence of about 20% but the third study showed an increase of 7%.

Figure 7-2 Incidence of postoperative pain after 24 hours with ultrasound activated versus conventional irrigation



Quality of evidence incidence of postoperative pain

The quality of evidence is very low for incidence of *postoperative pain* and low for postoperative pain intensity. It was downgraded by one level because of severe risk of bias for most studies related to possible selection bias. For the outcome measure incidence of postoperative pain was downgraded by one level because of severe inconsistency (I² : 84%) and by one level for severe imprecision (confidence interval crosses risk difference of 0). Publication bias was not detected.

³⁷ After 48, 72 etc. hours postoperatively, the differences in pain intensity between the two groups became progressively smaller: 4.9; 1.34 etc.

Conclusions

Very low GRADE	<i>Incidence of postoperative pain after 24 hours</i>
	Ultrasound-activated irrigation appears to reduce the incidence of postoperative pain compared with conventional irrigation but its relevance and evidence are highly uncertain.
	Chalub et al, 2022 (Middha, et al, 2017; Chen et al, 2016; Tang et al, 2015)

Low GRADE	<i>Postoperative pain intensity after 24 hours</i>
	Ultrasound-activated irrigation appears to reduce <i>pain intensity</i> little or not at all compared to conventional irrigation.
	Chalub et al., 2022 (Middha, et al., 2017; Tang et al., 2015)

Outcome measure periodontitis apicalis with respect to conventional irrigation and ultrasonic (activated) irrigation

Căpută et al. (2019) included one randomized study (Liang et al, 2013; 105 patients aged approximately 37 years and a sex ratio of one) that evaluated the aforementioned outcome measure (follow-up after 10-19 months). Dental elements were incisors, cuspids and premolars with a single radix in maxilla and mandible. 5.25% NaOCl and 15% EDTA were used as irrigants. Ultrasonic activation was also applied during instrumentation. An endodontologist and a radiologist, assessed the periapical and CBCT recordings independently and "blind." A periapical lesion was diagnosed if lamina dura disruption was noted AND a radiolucency associated with the radiographic apex had at least twice the width of the periodontal ligament for both periapical radiography and CBCT.

Absence and reduction of radiolucency was observed in 95.1% in the ultrasound group and 88.4% in the conventional group: a difference of 6.7% (95% BI: -6%; 20%).

Quality of evidence periodontitis apicalis

The quality of evidence is low for *periodontitis apicalis*. It was downgraded by one level for severe risk of bias related to possible selection bias. There has been downgraded by one level for severe imprecision (confidence interval crosses risk difference of 0). Thus, the quality of evidence is low. Publication bias was not detected.

Conclusion

Low GRADE	<i>Periodontitis apicalis</i>
	Ultrasonic irrigation, compared with conventional irrigation, does not seem to cure <i>periodontitis apicalis</i> much, if at all.
	Căpută et al., 2019 (Liang et al., 2013)

[update 2022/3] Is there difference in effect of reciprocal versus rotary motion on bacterial reduction and on postoperative pain?

Siddique et al. (2019) included three randomized studies (Neves et al. 2016, Cavalli et al. 2017, Martinho et al., 2014) in their systematic review related to the above question. A total of 137 patients with periodontitis apicalis were included. In 73 of them, reciprocal instrumentation was used in 64 rotary instrumentation. Their ages ranged from 16 to 85 years. The entire treatment took place in one session. Bacterial reduction in samples from the root canal were monitored before (S1) and after (S2) chemo-mechanical instrumentation using a single reciprocating instrument or a continuously rotating multi-instruments series.

The only outcome measure the reviewers examined was bacterial reduction.

Outcome measure bacterial reduction

The reviewers refrained from combining the outcomes of these studies because of the heterogeneity they identified, such as different types of composite and duration of follow-up. Table 7-1 summarizes the outcomes in the three studies. Differences between the two systems, reciprocal and rotational, seem to be few if any.

Table 7-1 Differences in bacterial load between reciprocal and rotary motion after chemo-mechanical cleaning

Study	Number of study participants	Outcome measure	Reciprook	Rotating
Neves 2016	59	Presence of bacteria	55,2%	50%
Cavalli 2017	30	Reduction of endotoxin	65%	95%
Martinho 2014	48	Reduction of endotoxin	95/96%*	98%/96%*

*two rotary and two reciprocating applications were evaluated

Quality of evidence reduction endotoxin

The quality of evidence is very low. It was downgraded by one level for severe risk of bias (inadequate randomization and blinding), by one level for severe imprecision (very small study size), and by one level for severe inconsistency (study by Cavalli 2017) gives strongly different results). No downgrading was done for other GRADE criteria.

Conclusion

Very low GRADE	<p><i>Presence of bacteria/reduction of endotoxin after chemo-mechanical cleaning</i></p> <p>Reciprooke motion seems to be little or no different from rotary motion in terms of endotoxin reduction, but the evidence is very uncertain.</p> <p>Siddique et al., 2019 (Cavalli et al. 2017; Neves et al. 2016; Martinho et al., 2014)</p>
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Martins et al. (2019) included in their systematic review four randomized studies (Çiçek et al., 2017; Relvas et al., 2016; Shokraneh et al., 2016; Sand et al., 2016) investigating the effect on postoperative pain of reciprocal versus rotary motion. A total of 374 teeth with necrotic pulp were involved, Endodontic treatment took place in one sitting in all studies. Sodium hypochlorite was used as irrigant in three studies, 17% EDTA, as gel, with saline in one study. The final rinse was done in three studies with EDTA, in one study with sodium hypochlorite. None of the studies used ultrasonically activated irrigation. For obturation, AH 26 Sealer or AH Plus Sealer was used. The most common method for obturation was lateral condensation.

Outcome measures: occurrence of postoperative pain, moderate and severe pain after 12, 24 and 48 hours

Table 7-2 shows that there seems to be little or no difference in postoperative to 48 hours.

Table 7-2. Postoperative pain after applying reciprocal motion versus rotational motion

Outcome measure		Risk difference (reciprocal - rotational)
Incidence of postoperative pain		-3% (-15%, 9%)
Moderate pain	after 12 hours	0% (-14%, 14%)
	after 24 hours	1% (-6%, 9%)
	after 48 hours	-8% (-29%, 14%)
Severe pain	after 12 hours	-3% (-10%, 5%)
	after 24 hours	-1% (-4%, 3%)
	after 48 hours	-1% (-6%, 4%)

Quality of evidence postoperative pain, moderate or severe pain after 12, 24, 48 hours

Incidence of postoperative pain: quality of evidence is low. It was downgraded by one level for severe risk of bias (potential selection bias). One level was downgraded for severe imprecision (confidence interval crosses 10% [threshold for relevant difference]). No downscaling was done for other factors.

Moderate pain after 12 hours and 48 hours: the quality of evidence is very low. It was downgraded by two levels for very severe imprecision (confidence interval crosses -10% and +10% [threshold values for relevant difference]). One level was downgraded for severe inconsistency (estimates of individual studies vary widely). No downscaling was done for other factors.

Moderate pain after 24 hours: the quality of evidence is reasonable. One level was downgraded for severe inconsistency (one study showed a strong opposite effect). No downgrading was done for other factors.

Severe pain after 12 hours and 24 hours: the quality of evidence is reasonable. One level was downgraded for severe risk of bias (potential selection bias). No downgrading was done for other factors.

Severe pain after 48 hours: the quality of evidence is high. No downgrading was done for any of the GRADE factors.

Conclusions

Low GRADE	<p><i>Incidence of postoperative pain</i></p> <p>There appears to be little or no difference in the incidence of postoperative pain between reciprocal and rotational systems.</p> <p>Çiçek et al., 2017; Relvas et al., 2016; Shokraneh et al., 2016; Sand et al., 2016</p>
Very low GRADE	<p><i>Moderate pain after 12 and 48 hours</i></p> <p>There appears to be little or no difference in moderate postoperative pain between reciprocal and rotational systems, but the evidence is very uncertain.</p> <p>Çiçek et al., 2017; Shokraneh et al., 2016; Sand et al., 2016</p>
Fair GRADE	<p><i>Moderate pain after 24 hours</i></p> <p>There is probably little or no difference in moderate postoperative pain between reciprocal and rotary systems.</p> <p>Çiçek et al., 2017; Relvas et al., 2016; Shokraneh et al., 2016; Sand et al., 2016</p>

Fair GRADE	<p><i>Severe pain after 12 and 24 hours</i></p> <p>There is probably little or no difference in severe postoperative pain between reciprocal and rotational systems.</p> <p>Çiçek et al., 2017; Relvas et al., 2016; Shokraneh et al., 2016; Sand et al., 2016</p>
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High GRADE	<p><i>Severe pain after 48 hours</i></p> <p>There is little or no difference in severe postoperative pain between reciprocal and rotational systems.</p> <p>Çiçek et al., 2017; Sand et al., 2016</p>
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Fill materials

[update 2022/3] Is there a difference in effect of "bioceramic" or calcium silicate-based and resin-based sealers?

Mekhdieva et al. (2021) examined in a systematic review whether there are differences between the two types of sealers in terms of their possible effect on postoperative pain. Other outcome measures such as *element survival or healing* were not examined. Khandelwal et al. (2022) paid attention to peri-apical healing but not to element survival in their systematic review.

Postoperative pain

Mekhdieva et al. (2021) included five randomized studies regarding nonvital teeth that reported on postoperative pain. In most studies, patients were asymptomatic. Instrumentation and irrigation protocols were identical in the studies but filling techniques varied (including vertical condensation, lateral condensation). All studies involved single-session treatment. Postoperative pain was reported as pain intensity and whether or not postoperative pain occurred. See Table 7-3.

The standardized mean difference of -0.24 (pain intensity after 24 hours) or more indicates a small but patient-relevant reduction in pain after 24 hours in favor of "bioceramic" sealers. The difference after 48 hours (-0.35 on a scale of 0-10) indicates a non-relevant difference; a relevant difference would be at least one or more. The numbers for whether or not postoperative pain occurred, 6.5% and 0.9% less in the case of "bioceramic" sealers, do not directly indicate a relevant difference between the two types of sealers.

Table 7-3 Postoperative pain after 24-48 h: "bioceramic" versus resin-based sealers

	Standardized mean difference (95% BI)*	Mean difference (95% BI)	Odds ratio** (95%BI) [absolute reduction; 95% BI]
Postoperative pain intensity after 24 hours (n=142)	-0.24 (-0.57; 0.09)	-	-
Postoperative pain intensity after 48 hours (n=64)	-	-0.35 (-0.58; -0.02)	-
Occurrence of postoperative pain after 24 hours (n=345)	-	-	0,68 (0,40; 1,16) [-6,5%; -13,2%, 2,9%]
Occurrence of postopera-	-	-	0.92

tive pain after 48 hours
(n=222)

(0.41; 2.05)
[-0,9%; -7%, 10,2%]

* a negative number indicates a favorable effect of "bioceramic" sealers; ** a number less than 1 indicates a favorable effect of "bioceramic" sealers.

Periapical healing

Khandelwal et al. (2022) included two studies (n= 103 patients) with non-vital pulp comparing "bioceramic" sealers to resin-based sealers. The teeth were anterior teeth in the maxilla. In one study, rotary instrumentation was used. The other study did not mention this. Both used sodium hypochlorite. One study involved a one-session treatment, the other a two-session treatment, using calcium hydroxide as an intracanal medication. One study reported (n=40) only that there was a significant (p<0.05) difference in radiographic healing in favor of a "bioceramic" sealer. The other study (n=63) mentioned that digital periapical radiographic evaluation was done to determine the extent of periapical healing 1, 3 and 6 months after treatment. With a "bioceramic" sealer, radiographic healing involved a reduction in lesion size of 12.8 mm², with a resin-based sealer, the reduction was 11.7 mm². Thus, the "bioceramic" sealer shows more healing than the resin-based sealer.

Quality of evidence postoperative pain after 24 - 48 hours, radiographic healing

Postoperative pain: the quality of evidence is low for *postoperative pain intensity after 24 hours*. There was downgraded by two levels for very severe imprecision (confidence interval crossed value for small [0.2] and medium effect [0.5]). There was no downgrading for other factors. The quality of evidence is high for *postoperative pain intensity at 48 hours*. There was no downgrading for any of the GRADE factors. The quality of evidence is reasonable for the *occurrence of postoperative pain at 24 and 48 hours*. There was downgraded by one level for severe imprecision (confidence interval crossed 10% which was retained as a small but relevant difference).

Radiographic healing: the quality of evidence is very low. It has been downgraded by one level for severe risk of bias (one study was not randomized). Downgraded by two levels for very serious imprecision because the degree of accuracy cannot be determined: one study does not report outcomes but only a p-value; the other study does not provide a confidence interval of the change in lesion size.

Conclusions

Low GRADE	<p><i>Postoperative pain intensity after 24 hours.</i></p> <p>"Bioceramic" sealers seem to slightly reduce postoperative pain after 24 hours compared with epoxy resin-based sealers.</p> <p>Mekhdieva et al., 2021 (Ates et al., 2019; Fonseca et al., 2019)</p>
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High GRADE	<p><i>Postoperative pain intensity after 48 hours.</i></p> <p>"Bioceramic" sealers have similar effects on postoperative pain after 48 hours as epoxy resin-based sealers.</p> <p>Mekhdieva et al., 2021 (Fonseca et al., 2019).</p>
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Fair GRADE	<p><i>Occurrence of postoperative pain after 24-48 hours</i></p> <p>"Bioceramic" sealers are likely to have a similar effect on the occurrence of post-operative pain after 24-48 hours as epoxy resin-based sealers....</p> <p>Mekhdieva et al., 2021 (Ferreira et al., 2020; Tan et al., 2020; Ates et al., 2019; Fonseca et al., 2019; Paz & Ginjeira, 2018)</p>
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Very low GRADE	<p><i>Radiographic healing</i></p> <p>"Bioceramic" sealers seem to promote radiographic healing up to 6 months slightly more than resin-based sealers.</p> <p>Khandelwal et al., 2022 (Khandelwal et al., 2022; Nagar & Kumar, 2018)</p>
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Considerations

Regarding sodium hypochlorite versus chlorhexidine

Quality of evidence

There is low quality of evidence for the outcome measure positive bacterial culture.

Patient values and preferences: not applicable

Balance of desired effects versus undesired effects and costs

Sodium hypochlorite and chlorhexidine seem equally effective in terms of bacterial reduction.

However, the combination sodium hypochlorite + EDTA (and again sodium hypochlorite) is preferable because of the simplicity of the procedure as well as the dissolution capacity of organic tissue and low cost.

Regarding laser technology as an addition to chemo-mechanical cleaning

Quality of evidence

The quality of evidence is very low for the outcome measures bacterial reduction and periapical recovery. Thus, the overall quality of evidence is very low.

Patient values and preferences: not applicable

Balance of desired effects versus undesired effects and costs

Adding laser techniques to chemo-mechanical cleaning has no additional effect on periapical repair but requires additional costs. Thus, the balance falls negatively for adding laser techniques.

[update 2022/3] Regarding reciprocal versus rotary systems

Quality of evidence

The quality of evidence ranges from very low to high for (moderate and severe) pain and is very low for endotoxin reduction. Thus, the *overall* quality of evidence is very low.

Patient Values and Preferences

Less pain is an important outcome measure

for patients. Endotoxin reduction is a less important outcome measure for patients.

Balance of desired effects versus undesired effects and costs

In terms of endotoxin reduction and pain, there seems to be little or no difference between reciprocal and rotary systems. In addition, reciprocal systems require somewhat less working time, *providing* slightly more comfort for the patient, Use of rotary systems leads to more costs for the patient than reciprocal systems. Thus, the balance seems slightly in favor of using reciprocal systems.

Applicability

Treatment outcomes will also depend on the more or less familiarity of the practitioner reciprocal and rotary systems. Most dentists/endodontologists are probably familiar with rotary systems, especially since students are only taught this way in faculties.

Therefore, the preference of the practitioner should be taken into account, especially since this is the only way students still learn this on the faculties.

[update 2022/3] Regarding ultrasound-activated irrigation

Quality of evidence

The quality of evidence for the outcome measures occurrence of pain/pain intensity and recovery of periodontitis apicalis is (very) low and low, respectively. Thus, the *overall* quality of evidence is very low.

Patient values and preferences

Recovery from periodontitis apicalis and less pain are important outcome measures for patients.

Balance of desired effects versus undesired effects and costs

Ultrasonic activated cleaning seems to lead to slightly less short-term pain and slightly more healing/reduction of periodontitis apicalis. To that extent, the balance is positive. As for costs, these are variable and need not be an impediment to applying ultrasonic activated cleaning.

Regarding removal of smear layer

After instrumentation, a smear layer forms on the canal wall. There is much debate in the literature about whether or not to remove this smear layer. In practice, it is generally chosen to remove the smear layer with an irrigation with 17% EDTA. This liquid is left in the canal for one to five minutes and then removed with a "final flush" of 12 ml of sodium hypochlorite (Van der Sluis, 2015).

[Update 2022/3] Regarding "bioceramic" or calcium silicate-based versus resin-based sealers

Quality of evidence

The quality of evidence for the outcome measures occurrence of pain/pain intensity ranges from low to high, and is very low for the outcome measure radiographic healing. Thus, the *overall* quality of evidence is very low.

Patient values and preferences

Radiographic healing and less pain are important outcome measures

for patients

Balance of desired effects versus undesired effects and costs

Regarding their effect on pain, "bioceramic" and epoxy resin-based sealers differ little or not at all. Regarding their effect on radiographic healing, *for the short term* (<6 months) there is a slight advantage for "bioceramic" sealers. Bioceramic sealers are considerably more expensive than epoxy resin-based sealers (factor 5-10 times as expensive!). Therefore, the balance of desired and undesired effects (including costs) goes toward epoxy resin-based sealers.

Applicability Although "bioceramic" sealers seem to show slightly more radiographic healing in the short term than epoxy resin-based sealers, studies involving teeth with a necrotic pulp / periodontitis apicalis with a follow-up duration of at least 24 months are needed to be more certain about their long-term effect.

Recommendations

It is recommended to use hand irrigation with sodium hypochlorite during chemo-mechanical cleaning, preferably after each instrument.

[unchanged after update 2022/3]

Rationale The combination sodium hypochlorite + EDTA (and again sodium hypochlorite) is a simple procedure, has good dissolution capacity of organic tissue and is associated with low cost.

Do not consider adding laser techniques to chemo-mechanical cleaning.

[update 2022/3: new recommendation]

Rationale

Adding laser techniques to chemo-mechanical cleaning has no additional effect on periapical repair but requires additional costs.

Consider a reciprocating or rotary system

[update 2022/3: new recommendation]

Rationale

The two systems differ little or not at all in terms of bacterial reduction and effect on postoperative pain. Reciproke systems require a little less operating time, providing a little more comfort for the patient, and give a little less cost to the patient. Given the possibly minor or even absent differences, familiarity and experience of practitioners with these systems will play an important role.

At the end of chemo-mechanical cleaning, ultrasonic activated irrigation can be considered.

[unchanged after update 2022/3]

Rational

Ultrasonic activated cleaning seems to lead to slightly less short-term pain and slightly more healing/reduction of periodontitis apicalis. As for cost, it is variable and need not be an impediment to applying ultrasonic activated cleaning.

Removal of the resulting smear layer with EDTA may also be considered.

[unchanged after update 2022/3]

Rationale

According to the working group, removing the smear layer provides more cleaning and disinfection of the root canal walls and better adaptation of filling materials to the cavity wall.

Consider use of epoxy resin-based sealers

[update 2022/3: new recommendation]

Rational

Although "bioceramic" sealers seem to show slightly more radiographic healing in the short term than epoxy resin-based sealers, nevertheless, more studies are needed to be more certain about their long-term effect before a recommendation can be given, also considering the additional cost of "bioceramic" sealers.

Knowledge gaps

There are insufficient large, randomized and non-randomized studies with metaregressions in which different methods of disinfection and filling of the root canal of teeth with necrotic pulp have been

evaluated for their effect on relief of symptoms, prevention of reinfection, and preservation of the tooth.

Effect of other factors (number of treatment sessions, preoperative periapical status, microbiological status, root canal filling quality) that may affect the outcome of root canal treatment

Is there a difference in the effect of treating in one session versus treating in two sessions?

[update 2022/3] Mergoni et al. (2022) included 22 studies with necrotic teeth. They examined the following primary outcome measures:

- extraction of teeth due to endodontic problems
- radiological failure,

and the following secondary outcome measures:

- after pain within one week
- postobturation pain after one week
- pain up to 72 hours after obturation
- swelling/flare-up
- use of pain relief
- Presence of a fistula.

For the outcome measure extraction, they found *no* studies with necrotic teeth.

In five of the 22 studies with necrotic teeth in which treatment was performed in multiple sessions, no intracanal medication was used for the intervening period. In most studies, calcium hydroxide was used as an intracanal medication. A magnifying glass was used for magnification in three of the 22 studies. For shaping the root canal, conventional hand instruments were used in nine of 22 studies, in seven studies a combination of hand files and NiTi rotary files, in two studies only a rotary file, Sometimes this was not adequately described. Obturation of the canal was done with guttapercha in 21 of 22 studies. In one study with a vertical condensation technique. All studies used sodium hypochlorite with concentrations ranging from 0.5 to 5.25%.

Table 7-4 summarizes the outcomes for the listed outcome measures. For the primary outcome measure radiological failure, the studies show a difference of 3.2% less radiological failure in favor of treating in one sitting. However, this does not seem to be a relevant difference. For all secondary outcome measures, the studies also do not show relevant differences when we would judge a 5-10% difference to be a significant difference for the patient.

Table 7-4 Outcomes of treating in one session versus multiple sessions

Outcome measure	Number of studies	Number of elements	Relative risk	Risk difference	Risk in multi-session group
radiological failure	10	924	0,83 (0,61; 1,14)	-3,2% (-7,3; 2,6%)	18,8%
after pain within one week	2	104	1,01 (0,55; 1,84)	+0,3% (-13,0; 24,2%)	029%
pain up to 72 hours after obturation	6	569	0,97 (0,81; 1,16)	-0,2% (-1,3; 1,1%)	007%
postobturation pain after one week	4	445	1,52 (0,24; 9,41)	+5,7% (-8,4; 92,7)	011%
swelling/flare-up	2	142	5,00 (0,25; 99,95)	+0,4% (-0,1; 9,9%)	0%
use of pain relief	2	104	1,29 (0,52; 3,19)	+3,9% (-6,5; 29,5%)	013%
presence of fistula	4	468	1,35 (0,26; 6,84)	+0,3% (-0,6; 5,1%)	001%

Quality of evidence radiological failure, follow-up pain <1 week, postobturation pain <72 hours and <1 week, swelling and flare-up and use of analgesia

Radiological failure: the quality of evidence is reasonable. There is downgrading only for severe imprecision: the confidence interval crosses the value of 5% held as a relevant difference.

Nap pain within one week: the quality of evidence is very low. It was downgraded for severe risk of bias (potential selection bias) by one level, for very severe imprecision by two levels, not for other GRADE criteria.

Pain up to 72 hours after obturation: the quality of evidence is reasonable. It was downgraded only for severe risk of bias (potential selection bias) by one level, not for other GRADE criteria.

Postobturation pain after one week: the quality of evidence is very low. It was downgraded for severe risk of bias (potential selection bias) by one level, for very severe imprecision by two levels (very wide confidence interval), for severe inconsistency by one level (large differences in effect estimates), and not for other GRADE criteria.

Swelling/flare-up: the quality of evidence is very low. It was downgraded for severe risk of bias (potential selection bias) by one level, for severe imprecision by one level (confidence interval crosses threshold for relevant difference [5-10%]) and not for other GRADE criteria.

Use of analgesia: the quality of evidence is very low. It was downgraded for severe risk of bias (potential selection bias) by one level, for very severe imprecision by two levels (very wide confidence interval) and not for other GRADE criteria.

Presence of fistula: the quality of evidence is low. It was downgraded for severe risk of bias (potential selection bias) by one level, and by one for severe imprecision of baseline risk (0.87%) and not for other GRADE criteria.

Conclusions³⁸

Fair	<i>Radiological failure at follow-up 1-3 years</i>
GRADE	Treating in one session probably does not differ much, if at all, from treating in multiple sessions in terms of effect on radiological failure. Mergoni et al., 2022 (Paredes-Vieyra et al., 2018; Micoogullari Kurt & Çalışkan , 2018; Gill 2016 et al., Dorasani et al., 2013; Paredes-Vieyra et al., 2012; Penenis et al., 2008; Molander et al., 2007; Peters et al., 2002; Trope et al., 1999; Weiger 2000)
Very low	<i>Nap pain within one week</i>
GRADE	Treatment in one session may be little or no different from treatment in multiple sessions in terms of effect on post-pain within one week, but the evidence is very uncertain. Mergoni et al., 2022 (Abdurrahman et al., 2019; Mulhern et al., 1982)
Fair	<i>Pain up to 72 hours after obturation</i>
GRADE	Treatment in one session probably does not differ much, if at all, from treatment in multiple sessions in terms of effect on pain up to 72 hours after obturation.

³⁸ The Cochrane reviewers included studies on dentures with vital and necrotic pulp. In this chapter only the studies on a necrotic pulp, in chapter 5 only the studies on a nonnecrotic pulp are described in which the effects of treating in one session versus in multiple sessions were examined. The reviewers named the interventions for a necrotic or a nonnecrotic pulp, as root canal treatment or endodontic treatment. Extraction was also an outcome measure but there were no studies reporting on this separately for pulpitis and pulpal necrosis....

	Mergoni et al, 2022 (Abdurrahman et al, 2019; Micoogullari Kurt & Çalışkan , 2018; Ince 2009; Risso et al, 2008; Mulhern et al, 1982)
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Very low GRADE	<i>Postobturation pain after one week</i>
	Treatment in one session may not differ much, if at all, from treatment in multiple sessions in terms of effect on postobturation pain after one week, but the evidence is very uncertain. Mergoni et al., 2022 (Abdurrahman et al., 2019; Gesi et al., 2006; Al-Negrish et al., 2006; Mulhern et al., 1982)

Very low GRADE	<i>Swelling/flare-up</i>
	Treatment in one session may not differ much, if at all, from treatment in multiple sessions in terms of effect on swelling/flare-up, but the evidence is very uncertain. Mergoni et al., 2022 (Micoogullari Kurt & Çalışkan , 2018; Mulhern et al., 1982)

Very low GRADE	<i>Use of pain relief</i>
	Treatment in one session may be little or no different from treatment in multiple sessions in terms of effect on use of analgesia, but the evidence is very uncertain. Mergoni et al., 2022 (Abdurrahman et al., 2019; Mulhern et al., 1982)

Low GRADE	<i>Presence of fistula</i>
	Treatment in one session may be little or no different from treatment in multiple sessions in terms of effect on the presence of a fistula. Mergoni et al., 2022 (Paredes-Vieyra et al., 2018; de Castro Rizzi-Maia 2016; Paredes-Vieyra et al., 2012; Penis et al., 2008)

[update 2022/3] Is there a difference in endotoxin levels in infected root canals before and after application of calcium hydroxide medication?³⁹

The purpose of the systematic review by Bedran et al. (2020) was to evaluate the efficacy of calcium hydroxide as an intracanal medication in terms of endotoxin levels in infected root canals. Intracanal medication refers to antibacterial agents placed in the root canal between sessions to clear residual microorganisms.

Various forms of calcium hydroxide such as a powder mixed with saline, or as a paste form or in combination with 2% chlorhexidine (CHX) gel were used in the studies included in this systematic review. Primary outcomes were the level of endotoxins, i.e., lipopolysaccharides (LPS), before and after the use of calcium hydroxide as an intracanal medication in infected teeth. Outcome measures were reported in the form of standardized mean difference (SMD) and total percent reduction in endotoxin level. Evaluation of the level of endotoxins and bacteria in infected root canals is the most relevant surrogate outcome because of their primary role in the development of periradicular disease.

Seven studies lent themselves to meta-analysis. All studies involved patients with necrotic pulp and apical periodontitis.

³⁹ For this literature review, Sadaf & Ahmad (2021) were used in part

Teeth showed a reduction in LPS after using calcium hydroxide as an intracanal medication (number of studies: 5; 266 patients) equivalent to an SMD of -1.036 (95% BI, -2.053; -0.020). The overall percentage reduction of LPS with calcium hydroxide alone was 61.7% (number of studies: 3 with a total of 156 patients [95% BI: 37.7% - 82.9%]) compared with 98.9% with calcium hydroxide in combination with antimicrobials (number of studies: 3 with a total of 156 patients [95% BI: 97.4%-99.8%]). An SMD of more than 0.8 is considered a large effect. In other words, the meta-analysis shows a large effect of calcium hydroxide on endotoxin levels. Application of the intracanal drug was done for 7, 14 and 30 days and endotoxin levels were significantly reduced for each period. However, 30 days gave significantly more reduction than 7 or 14 days witnessed an SMD of -1.886 (95% BI: -2.919, -0.853) and -1.142 (95% BI: -1.427; -0.857), respectively. At the same time, it is clear that calcium hydroxide does not provide 100 percent endotoxin reduction.

Quality of evidence reduction of lipopolysaccharides and total percent reduction of LPS

The quality of evidence for the outcome measures *reduction of LPS and total percent reduction of LPS* is very low. Indirect evidence was downgraded by one level because LPS is a surrogate parameter for complete disappearance of apical radiolucency as well as absence of signs and symptoms. Furthermore, we downgraded by two levels for very severe imprecision (confidence interval crosses values for small [0.2], medium [0.5] and large effect [0.8] respectively) and the number of study participants is significantly less than the 30-50% of the optimal number, namely 800).

Conclusion

Very low GRADE	<p><i>Reduction of lipopolysaccharides and total percent reduction of LPS with calcium hydroxide</i></p> <p>Calcium hydroxide appears to reduce endotoxin levels, but the evidence is very uncertain.</p> <p>Bedran et al., 2020 (Alarbeed et al., 2019; Carvalho et al., 2016; Adl et al., 2015; Sousa et al., 2014; Oliveira et al., 2012)</p>
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Does preoperative status have a significant effect on periapical healing?

The literature search yielded no study evaluating the effect of preoperative periapical status on treatment outcome (retention of dentition). *Methods of Diagnosis and Treatment in Endodontics* (2012) cited 2 studies that did make a statement on this.

Weiger et al. (2000) found an increased risk of failure if an apical lucency was greater than 5 mm (odds ratio: 2.45; 95% BI: 1.21 -4.58) compared to an apical lucency less than or equal to 2 mm. While Sjögren et al. (1990) also found an increased risk (odds ratio: 1.42; 95% BI: 0.60 - 3.37) for lesions larger than 5 mm compared with lesions smaller than or equal to 5 mm, this was not statistically significant.⁴⁰

Quality of evidence prognostic value of preoperative status

The quality of evidence is reasonable. There was no downgrading for risk of bias, publication bias, circumstantial evidence, and inconsistency. One level was downgraded for imprecision: the lower limits of the confidence interval for both odds ratios do not indicate a relevant effect (odds ratio > 2.0).

⁴⁰ Calculated by the working group based on Table 4 in Sjögren et al. (1990).

Conclusion

Fair	<i>Prognostic value of preoperative status</i>
GRADE	Teeth with periapical lucency greater than 5 mm may have a worse prognosis for denture retention than lesions less than or equal to 5 mm. Weiger et al., 2000; Sjögren et al., 1990

[update 2022/3] Is there a difference in effect of adequate versus inadequate root canal filling and coronal restoration procedures?

Jakovljevic et al. (2020) examined in a systematic review whether inadequate root canal filling and inadequate coronal restoration procedures were associated with a greater risk of *periodontitis apicalis*. Other outcome measures such as denture survival were not examined. They included eight cross-sectional studies (Meirinhos et al., 2020; Kielbassa et al., 2017; Archana et al., 2015; Oginni et al., 2015; Di Filippo et al., 2014; Ureyen Kaya et al., 2013; Jersa & Kundzina, 2012; Mukhaimer et al., 2012) in which this was examined. Most studies used the following criteria for inadequate:

- radiopaque materials in the pulp chamber whose presence ends more than 2 mm from the radiographic apex, or if there is gross overfilling,
- the filling of the root canal can be considered non-homogeneous, voids can be seen,
- inadequate density, and/or insufficient condensation.

Periodontitis apicalis was defined as: a radiolucency involving the apical part of the root greater than at least twice the width of the lateral part of the periodontal ligament or a value of 3, 4 or 5 of the periapical index.

The combined estimates of the eight cross-sectional studies (N=11,293 dentitions) show an odds ratio of 4.65 (95% BI: 2.75; 7.84), or: inadequate root canal filling and coronal restoration procedures are associated with an almost five times higher probability of periodontitis apicalis. In absolute terms, this means 36.5% (95% BI: 23.9; 47.2%) more cases of periodontitis apicalis with inadequate root canal filling and coronal restoration procedures.

A caveat about these results is in order: the outcomes just described are based on cross-sectional studies; these studies are particularly well suited for calculating correlations. However, as is well known, a correlation does not directly imply a *causal relationship*, although here the magnitude of the effect - a 36.5% increase with the outcome periodontitis apicalis - suggests it.

In an implementation study by Koch (2013) that aimed to evaluate aspects of an educational intervention in clinical endodontic routines and new instrumentation techniques (rotary nickel-titanium instrumentation) at a 'Swedish County Public Dental Service'. One of the findings in this large-scale before-after study (850 root canal treatments, half of which took place before [in 2002] and half after the educational intervention [in 2005]) with long-term follow-up (≥ 4 years) was that, despite the improved quality of root canal filling, namely an increase from 33% to 48% adequate, there was little improvement in PAI 1 + 2 (normal periapical structures + small changes in bone structure). PAI 1+2 before the educational intervention was 58%; after this intervention 64%. The success rate (cure or prevention of periodontitis apicalis) was 68% and 67%, respectively, and the failure rate (PAI 4 + PAI 5; periodontitis with marked radiolucency, severe periodontitis with features of exacerbation) was 19% and 16%, respectively. Koch explained this as follows: "*One explanation for this finding is that the distribution of teeth with normal periapical status and teeth with AP was the same for the remaining teeth treated before and after the education. Factors that may influence the rate of remaining teeth, besides signs of disease, are individual treatment decisions and patients' preferences.*"

Quality of evidence periodontitis apicalis

[update 2022/3] The quality of evidence is very low. The initial quality is low because they were not randomized studies, in addition, one level was downgraded for severe risk of bias because the studies

did not have a direct comparative design. No downgrading was done for indirect evidence, inconsistency, imprecision and publication bias.

Conclusion

Very low	<i>Periodontitis apicalis associated with inadequate root canal filling and coronal restoration procedures</i>
GRADE	Inadequate filling of the root canal and coronal restoration procedures may be associated with a nearly five-fold increased risk of periodontitis apicalis, but the evidence is very uncertain. Jakovljevic et al., 2020 (Meirinhos et al., 2020; Kielbassa et al., 2017; Archana et al., 2015; Oginni et al., 2015; Di Filippo et al., 2014; Ureyen Kaya et al., 2013; Jersa & Kundzina, 2012; Mukhaimer et al., 2012); Koch, 2013

Effectiveness of methods for prevention or treatment of postoperative complications after treatment of a necrotic pulp

Is there a difference in effect of administration of oral antibiotics versus no antibiotics/placebo?

One study (Akbar et al., 2015) was found that examined the effect of antibiotics on flare-ups (pain, swelling or both) in cases of a necrotic pulp. In this RCT, 50 patients received 2 grams of amoxicillin one hour before the first visit for root canal treatment; the other 50 patients in whom root canal treatment was also performed in two sessions received neither an antibiotic nor a placebo. Pain and swelling were measured with a 0-10 VAS scale. No pain/swelling corresponded to score 0, mild pain/swelling to a score of 1-3, moderate pain/swelling to a score of 4-6 and severe pain/swelling to 7-10. Moderate or severe pain/swelling was interpreted as a flare-up. Pain and swelling were noted at 4, 12, 24, 48 and 72 hours after the first visit by the patient. The study involved 55 men and 45 women with a mean age of 34 years. In the group that received antibiotics, 8% (4/50) had a flare-up. In the group that did not receive antibiotics, 12% (6/50) had a flare, giving a relative risk of 0.67 (95% BI: 0.20-2.22). This difference was not statistically significant.

The Swedish report *Methods of Diagnosis and Treatment in Endodontics: A Systematic Review* (2012) cited 3 studies (total N=250; Mata et al., 1985; Walton & Chiappinelli, 1993; Pickenpaugh et al., 2001) in which penicillin or amoxicillin was used prophylactically in a necrotic pulp, and flare-up was an outcome measure. In the group receiving an antibiotic, the rate of flare-ups ranged from 3.8 to 6%, in the placebo group from 4 to 12%, with an outlier of 24%. This does not indicate an obvious effect of an antibiotic on postoperative pain.

[update 2022/3] Shamszadeh et al. (2021) included a total of eight studies of patients with a necrotic pulp as well as periodontitis apicalis (n=690) that studied either pain or swelling as outcome measures. Thus, not like Akbar et al. (2015) only the outcome pain combined with swelling. Table 7-5 shows the results for both outcome measures at different postoperative time points. A standardized mean difference (SMD) of at least +0.2 or -0.2 indicates a small unfavorable or favorable effect, respectively. The outcomes in Table 7-5 sometimes show no effect (pain after 24 hours; pain after 48 hours), sometimes a small unfavorable effect (swelling after 24 hours) and sometimes a small favorable effect (pain after 12 hours and swelling after 48 hours).

Table 7-5 Effect of antibiotics versus placebo on postoperative pain and swelling

Outcome measure	Standardized mean difference (95% BI).
Pain after 12 hours	-0,20 (-1,24; 0,83)
Pain after 24 hours	-0,04 (-0,29; 0,20)
Pain after 48 hours	0,18

Swelling after 24 hours	(-0,26; 0,62) 0,29
Swelling after 48 hours	(-0,72; 1,32) -0.23
Swelling after 72 hours	(-0.98; 0.51) 0.03 (-1.25; 1.31)

Quality of evidence pain and swelling after 12 to 72 hours after treatment

Pain after 12 and 48 hours and 48 hours; swelling after 24, 48 and 72 hours: the quality of evidence is very low. Downgraded for severe risk of bias (selection bias) and by three levels for extremely severe imprecision (95% confidence interval crosses values for small [+/-0.2], medium [+/-0.5] and large [+/-0.8] effect.

Pain after 24 hours: the quality of evidence is low. It was downgraded for severe risk of bias (selection bias) and by one level for severe imprecision (95% confidence interval crosses values for small [-0.2] effect.

Conclusions

Very low	<i>Outcome measure postoperative pain after 12 hours</i>
	Prophylactic administration of oral antibiotics may reduce postoperative pain after 12 hours, but the evidence is very uncertain.
GRADE	Shamszadeh et al., 2021 (Shah et al., 2011; Fouad et al., 1996)

Low to very low	<i>Outcome measure postoperative pain at 24 and 48 hours</i>
	Prophylactic administration of oral antibiotics may <i>not</i> reduce postoperative pain after 24, 48 hours, but the evidence is very uncertain.
GRADE	Shamszadeh et al., 2021 (Alsomadi et al., 2015; Shah et al., 2011; Henry et al., 2001; Fouad et al., 1996; Walton et al., 1992)

Very low	<i>Outcome measure postoperative swelling at 24, 48 and 72 hours</i>
	Prophylactic administration of oral antibiotics shows conflicting (none; minor favorable and minor unfavorable) effects on postoperative swelling, but the evidence is highly uncertain.
GRADE	Shamszadeh et al., 2021 (Henry et al., 2001; Fouad et al., 1996; Walton et al., 1992; Mata et al., 1985)

Is there a difference in effect (on postoperative pain) between 5.25% sodium hypochlorite versus 2% chlorhexidine gel as an intracanal medication?

Singh et al. (2013) in a randomized trial of 64 patients, in whom the 64 mandibular molars had a diagnosis of necrotic pulp and acute periodontitis apicalis, investigated the efficacy of calcium hydroxide paste as an intracanal medication.⁴¹ The diagnosis was made based on a negative response to a heat

⁴¹ Allowing for some dropout, the researchers had calculated that 18 subjects per group would be sufficient at an α of 0.05 and a β of 0.80. As in most studies, there was no mention of what difference should be detectable, or whether this difference was a clinically relevant difference. The reported standard deviations are exceptionally small. All pain measurements at 24 hours, expressed as coefficient of variation, are less than 20%. In the studies included in Zanjir et al. (2020), the coefficients of variation are around 100%.

test, confirmed in the absence of vital pulp/bleeding during opening. Clinical and radiographic evidence of periodontitis apicalis was confirmed by sensitivity on palpation and a disrupted periodontal ligament. Patients were between 20 and 40 years of age. After chemo-mechanical cleaning, patients were randomized to four groups: canals were filled with (1) calcium hydroxide paste with 2% chlorhexidine gel, (2) with 2% chlorhexidine gel only, or (3) with calcium hydroxide paste, or (4) without disinfectant. No antibiotics were prescribed. Patients were told to measure and record pain at 4 hours after treatment, and then at 24, 48, 72 and 96 hours. The pain measurement instrument was a 100 mm-VAS scale, where 0-25 mm corresponded to no or mild pain, 26-50 mm to moderate pain requiring analgesia, 51-75 mm to severe pain in which analgesics did not help, and ≥ 76 mm to extreme pain in which no medication relieved the pain. There was no statistically significant difference between the calcium hydroxide and control groups. Both the group receiving chlorhexidine and the group receiving calcium hydroxide + chlorhexidine had less pain than the other two groups on all days (5 to 10 mm on average), but did not differ between them. Therefore, calcium hydroxide does not seem to have any effect on the degree of postoperative pain.

Quality of evidence postoperative pain at 24, 48, 72 and 96 hours

The quality of evidence is reasonable. It was downgraded by one level for imprecision (because of uncertainty about the size of the standard deviation and thus the precision of the effect). There was no downgrading for risk of bias, inconsistency, publication bias and circumstantial evidence.

Conclusion

Fair	<i>Outcome measure postoperative pain</i>
GRADE	Calcium hydroxide paste, used as an intracanal medication, in combination with 2% chlorhexidine is unlikely to provide more pain relief than chlorhexidine alone. Calcium hydroxide paste alone provides as much pain reduction as the control group (no disinfectant).
	Singh et al., 2013

Is there any difference in effect of 5.25% sodium hypochlorite versus 2% chlorhexidine gel?

2 RCTs (Almeida et al., 2012; Bashetty et al., 2010) were found comparing the effect of chlorhexidine on postoperative pain with that of sodium hypochlorite. Almeida et al. included 126 patients, including 80 women, in whom treatment of apical periodontitis and pulpanecrosis was necessary. This was done in a single session. The median age was 38 years.

Postoperative pain was measured after 24, 48, and 72 hours, and after 7 days. A 4-point VAS scale was used for this purpose (0=no pain, 1=mild pain, 2=severe pain [analgesics help], 3=severe pain [analgesics do not help]). Bashetty et al. included 40 patients aged 21-40 years with nonvital teeth and necrosis of the pulp. Postoperative pain was measured after 6 and 24 hours, after 4 and after 7 days. Pain was measured with a 10-point VAS scale (0=no pain, 1 to 3=mild pain, 4 to 6=moderate pain, 7 to 9=severe pain).

Both studies allow combining outcomes after 24 hours and those after 7 days. Neither after 24 hours nor after 7 days was there a statistically significant difference in postoperative pain between chlorhexidine and sodium hypochlorite (SMD: 0.06, 95% BI: -0.245; 0.364; SMD: -0.04, 95% BI: -0.344; 0.265).⁴²

In the study by Bashetty et al. a statistically significant difference of 1.5 in pain was measured only after 6 hours to the detriment of sodium hypochlorite. In the study by Almeida et al. a statistically significant difference was not measured between chlorhexidine and sodium hypochlorite at any of the measurement times.

⁴² Because different VAS scales were used, the study group converted the data from both studies to standardized mean differences (SMD).

Quality of evidence postoperative pain after 6-96 hours and after 7 days

The quality of evidence is low. It was downgraded by one level for risk of bias (unclear randomization procedure and blinding of allocation to study and control group), and by one level for imprecision (small study size). No downgrading was done for inconsistency, publication bias and circumstantial evidence.

Conclusion

Low GRADE	<p><i>Outcome measure postoperative pain</i></p> <p>Between 5.25% sodium hypochlorite and 2% chlorhexidine gel, there may be no difference in the degree of postoperative analgesia.</p> <p>Almeida et al., 2012; Bshetty et al., 2010</p>
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[update 2022/3] Is there a difference in effect of retaining vs. not retaining apical patency? ("apical patency")?

Abdulrab et al. (2018) included five randomized studies (Yaylali et al., 2018; Garg et al., 2017; Arora et al., 2016; Sharaan et al., 2012; Arias et al., 2009) that reported on postoperative pain when retained versus nonretained apical clearance was compared. However, one of these studies (Sharaan et al., 2012) did not report separately on vital and non-vital teeth. Therefore, the study group leaves this study out of consideration. The study group reperformed the meta-analysis of Abdulrab et al. (2018), limiting itself to teeth with pulpal necrosis whether or not in combination with periodontitis apicalis. Between studies there are differences in the type of dentition examined. One study examined only first molars in the mandible, A second study looked at molars in lower and upper jaws, a third study also included premolars, and a fourth study examined all dentition but analyzed outcomes by type (anterior versus posterior) of dentition. The studies differed in other respects as well:

- three studies used rotary instruments for channel preparation, the fourth study used manual instrumentation only;
- Regarding the irrigation protocol, some studies combined NaOCl with EDTA, others combined with saline or NaOCl alone.

The aforementioned differences, in addition to the potential effect of "apical patency," may also affect the outcome postoperative pain. The type of file used was a 10 or 15 small flexible K-file .

Outcome measure incidence of postoperative pain

Arias et al. (2009) reported only the incidence of postoperative pain for several days after treatment. Odds ratio was 2.53 (95% BI: 1.03; 3.70). In other words, the incidence of postoperative pain when apical patency was not preserved was two and a half times greater than when apical patency was preserved. "Apical patency" thus appears to have an effect. However, whether this is a patient-important effect cannot be inferred from this.

Outcome measure postoperative pain intensity (molars and premolars)

Three studies (Yaylali et al., 2018; Garg et al., 2017; Arora et al., 2016) reported on pain intensity, with one study reporting only on the first two days. The results of the meta-analysis are listed in Table 7-6. To what extent do these indicate a patient-relevant pain reduction when applying "apical patency"? On a 0-10 VAS scale, a reduction in pain intensity by one is generally considered a significant reduction. Well, the results in the mentioned table suggest that applying "apical patency" leads to less pain in the first three days after treatment (pain reduction > 1) and thereafter no longer has a patient-relevant effect But the necessary comments are appropriate here. See quality of evidence.

Table 7-6 Mean difference in postoperative pain intensity (0-10 VAS scale) retained versus not retained apical translucency

Day 1 (after 24 hours)	-1.06 (-3.34; 1.22) [n=405; 3 studies].
Day 2	-0.74 (-2.01, 0.53) [n=405; 3 studies].

Day 3	-1.02 (-2.62; 0.58) [n=385; 2 studies].
Day 4	-0.61 (-1.68; 0.46) [n=385; 2 studies].
Day 5	-0.52 (-0.60; -0.44) [n=320; 1 study]
Day 6	-0.09 (-0.19; 0.01) [n=320; 1 study]

Quality of evidence incidence of postoperative pain, pain intensity <3 days, <6 days

Incidence of postoperative pain: the quality of evidence is very low. It is downgraded by one level for severe risk of bias (possible selection bias) and by two levels for very severe imprecision (ratio upper and lower limits of confidence interval is greater than 2.5). There is no downscaling for other factors.

Postoperative pain intensity (day 1 to day 3): quality of evidence is very low. It is downgraded by one level for severe imprecision (confidence interval crosses threshold -1) and by two levels for very severe inconsistency: one study shows a very strong effect, two other studies small, patient-insignificant effects. No downgrading is done for other factors.

Postoperative pain intensity (day 4 to day 6): the quality of evidence is high. There is no downgrading for any of the GRADE factors.

Conclusions

Very low GRADE	<p><i>Outcome measure incidence of postoperative pain</i></p> <p>Applying "apical patency" compared to not applying it seems to reduce the <i>occurrence</i> of postoperative pain, but the evidence is very uncertain.</p> <p>Abdulrab et al., 2018 (Arias et al., 2009)</p>
Very low GRADE	<p><i>Outcome measure postoperative pain intensity (day 1 to 3)</i></p> <p>Applying "apical patency" compared to not applying it seems to reduce the <i>degree</i> of postoperative pain, but the evidence is very uncertain.</p> <p>Abdulrab et al., 2018 (Yaylali et al., 2018; Garg et al., 2017; Arora et al., 2016)</p>
High GRADE	<p><i>Outcome measure postoperative pain intensity (from day 4)</i></p> <p>Applying "apical patency" compared to not applying it <i>does not</i> seem to significantly reduce the <i>degree</i> of postoperative pain.</p> <p>Abdulrab et al., 2018 (Yaylali et al., 2018; Arora et al., 2016)</p>

Considerations

Regarding treating in one session versus multiple sessions

Quality of evidence

[update 2022/3] For the crucial outcome measures radiological failure and pain up to 72 hours after obturation, there is reasonable quality of evidence. For the other crucial outcome measures post-obturation pain within one week, post-obturation pain after one week, presence of fistula, swelling/flare-up, the quality of evidence is very low. Thus, the *overall* quality of evidence is very low because the lowest level of a crucial outcome measure determines the *overall* quality of evidence.

Patient values and preferences

It is important to inform patients about the effect of the number of sessions and preoperative status (apical lesions > 5 mm may have a worse prognosis) on tooth preservation or quality of life. According to Vela et al. (2012), most patients prefer to be treated in one session, unless it would appear that treatment in two sessions would be more likely to be successful. Azarpazhoh et al. (2014) confirm that most patients want to be informed about the chances of treatment success and value shared decision-making.

Balance of desired effects versus undesired effects and costs

[update 2022/3] For some key critical outcome measures, namely radiological failure and postobturation pain, there is probably little or no difference in effect between one or more sessions. Thus, the balance for these effects is the same for one or more sessions. For other critical outcomes, the quality of evidence is very low, making the balance of desired and undesired effects more difficult to determine. According to the guideline working group, there are several reasons to balance in favor of one session:

- most patients prefer this because of time savings
- costs can be saved.

Applicability

To assess the degree of complexity of root canal treatment, the Dutch Endodontic Treatment Index (DETI) and Classification of Endodontic Treatment (CEB) are used (Ree, 2009). The DETI counts fourteen criteria that can lead to complications (Appendix 7.2). When one or more criteria apply, there is a risk of complications in root canal treatment. If so, the CEB is completed to determine the degree of difficulty (Appendix 7.2).

In the case of an acute pain complaint, general practice often sees that an endodontic initial treatment takes place and treatment is completed at a later stage. In such a situation, there may be little or no choice between one or two sessions.

[update 2022/3] Regarding calcium hydroxide as an intracanal medication

Quality of evidence

The quality of evidence is very low regarding the reduction of endotoxin levels by calcium hydroxide. Nevertheless, it is clear that calcium hydroxide does not provide 100 percent endotoxin reduction.

Patient values and preferences: not applicable

Balance of desired and undesired effects and costs

Endotoxin reduction is a surrogate outcome. Looking at the outcomes of treating in one versus multiple sessions, the role of calcium hydroxide as an intra-channel drug appears to be of little or no significance. In addition, calcium hydroxide is difficult to remove when trapped. Retained calcium hydroxide can cause reduced adhesion of the canal filling or composite filling used. Therefore, undesirable effects outweigh desired effects.

[update 2022/3] Relating to apical translucency

Quality of evidence The quality of evidence for the various pain-related outcome measures ranges from high to very low. Thus, the *overall quality of evidence* is very low.

Patient values and preferences: not applicable

Balance of desired and undesired effects and costs

Achieving apical clearance seems to significantly reduce pain from day 1 to day 3, but there is no difference thereafter between achieving and not achieving apical clearance. Also, achieving apical translucency will (indirectly) cause the canal filling to end within 2 mm of the radiographic apex, which has a positive effect on the healing of periodontitis apicalis. Undesirable effect of achieving apical permeability is a potential risk of apical extrusion of infected débris after mechanical instrumentation outside

the apical foramen, which may cause postoperative pain. However, the likelihood of this seems small given the postoperative pain reduction effect the studies showed. Cost aspects of apical translucency are not available.

Applicability

Most endodontists apply achieving apical clearance. However, among the attending dentist, this seems to be a minority. Therefore, making the dentist consider this recommendation requires additional implementation effort.

Regarding administration of antibiotics

Quality of evidence

The quality of evidence for the outcomes on pain is very low. Thus, the *overall* quality of evidence is very low.

Patient values and preferences: not applicable

Balance of desired and undesired effects and costs

Antibiotics seem to have little or no effect on pain. In the absence of a beneficial effect in this regard, the negative consequences of antibiotic use, namely increasing resistance, weigh all the more heavily.

Recommendations

Consider performing root canal treatment of a necrotic pulp in one sitting. This may be deviated from when warranted by the presence of pain (emergency), the difficulty of the treatment and/or the patient's wishes.

[unchanged after update 2022/3]

Rationale

The outcomes of treating in one or more sessions seem to differ little or not at all. Most patients prefer treatment in one session.

*In root canal treatment of a necrotic pulp, consider **not using** calcium hydroxide as an intracanal medication.*

[update 2022/3: new recommendation]

Rationale

The endotoxin-reducing effect of calcium hydroxide as an intracanal medication seems to be of little importance for the final treatment outcomes. There are significant drawbacks to its use: it is difficult to remove and residual residue can cause reduced adhesion of the canal filling or composite filling used

During initial root canal treatment of a necrotic pulp or re-treatment with periodontitis apicalis, consider achieving apical clearance to prevent apical blockage.

[update 2022/3: new recommendation]

Rational

Achieving apical clearance (with a #08 or #10 K file) reduces postoperative pain and may indirectly have a beneficial effect on healing/reduction of apical periodontitis.

Antibiotics for the purpose of analgesia should not be administered.

[unchanged after update 2022/3]

Rationale

Use of an antibiotic as an ineffective form of analgesia should be avoided. This also contributes to limiting antimicrobial resistance.

Good practice statements

- Inform the patient prior to treatment about the prognosis of endodontic treatment and the possible effect of preoperative status on it.
- [update 2022/3] Please note that the following factors may have a negative effect on the healing of periodontitis apicalis:
filling of the root canal more than 2 mm from the radiographic apex endend;
 - gross overfilling;
 - voids.

Knowledge gaps

See above (page 131).

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Appendix 7.1 Search strategy

((("dental pulp cavity/pathology"[MeSH Terms] OR "dental pulp diseases"[MeSH Terms]. OR "Periapical Diseases"[Mesh] OR ("non-vital"[Title/Abstract] AND "pulp"[Title/Abstract])) AND ("root canal therapy"[MeSH Terms] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR "pulpectomy"[MeSH Terms] OR "pulpectomy"[Title/Abstract] OR "root canal obturation"[MeSH] OR "root canal obturation"[Title/Abstract]) AND ("episode of care"[MeSH Terms] OR "calcium hydroxide/therapeutic use"[MeSH Terms] OR "root canal irrigants/therapeutic use"[MeSH Terms] OR "sodium hypochlorite/therapeutic use"[MeSH Terms] OR "chlorhexidine/therapeutic use"[MeSH Terms] OR "lasers, semiconductor/therapeutic use"[MeSH Terms] OR "photochemotherapy/therapeutic use"[MeSH Terms] OR "photosensitizing agents/therapeutic use"[MeSH Terms] OR "sterilization"[MeSH Terms] OR *session[Title/Abstract] OR *sessions[Title/Abstract] OR *visit[Title/Abstract] OR *visits[Title/Abstract] OR *appointment[Title/Abstract] OR *appointments[Title/Abstract] OR "calcium hydroxide"[Title/Abstract] OR "sodium hypochlorite"[Title/Abstract] OR "chlorhexidine"[Title/Abstract] OR "laser"[Title/Abstract] OR "iodine potassium iodide"[Title/Abstract] OR "tincture iodine"[Title/Abstract] OR "ethyl alcohol"[Title/Abstract] OR "ethanol"[Title/Abstract] OR "edta"[Title/Abstract])) AND ("controlled clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "multicenter study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR allocat*[Title/Abstract] OR random *[Title/Abstract] OR systematic[sb]))

162 hits.

("dental pulp cavity/pathology"[MeSH Terms] OR "dental pulp diseases"[MeSH Terms]. OR "Periapical Diseases"[Mesh] OR ("non-vital"[Title/Abstract] AND "pulp"[Title/Abstract])) AND (("treatment outcome"[MeSH Terms] OR "prognosis"[MeSH Terms] OR "treatment outcome"[Title]) AND ("sensitivity and specificity"[MeSH Terms] OR "dental pulp cavity/microbiology"[MeSH Terms] OR "bacteria/isolation and purification"[MeSH Terms] OR "culturing"[Title] OR "Polymerase Chain Reaction"[Mesh] OR "real-time PCR"[Title/Abstract]))

84 hits.

((("root canal therapy"[MeSH Terms] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR "pulpectomy"[MeSH Terms] OR "pulpectomy"[Title/Abstract] OR "root canal obturation"[MeSH Terms] OR "root canal obturation"[Title/Abstract]) AND ("root canal therapy"[MeSH Terms] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR "pulpectomy"[MeSH Terms] OR "pulpectomy"[Title/Abstract] OR "root canal obturation"[MeSH Terms] OR "root canal obturation"[Title/Abstract] OR "dental pulp diseases/therapy"[MeSH Terms] OR "Periapical Diseases/therapy"[MeSH Terms] OR "pulpitis/therapy"[MeSH Terms] OR "endodontic treatment"[Title/Abstract] OR "endodontic therapy"[Title/Abstract] OR "endodontic"[Title] OR "root canal"[Title] OR "pulpless"[Title]) AND ("episode of care"[MeSH Terms] OR *session[Title/Abstract] OR *sessions[Title/Abstract] OR *visit[Title/Abstract] OR *visits[Title/Abstract] OR *appointment[Title/Abstract] OR *appointments[Title/Abstract]) AND ("controlled clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "multicenter study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR allocat*[Title/Abstract] OR random*[Title/Abstract] OR systematic[sb] OR control*[Title])) AND (has-abstract[text])

149 hits.

((("root canal therapy"[MeSH Terms] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR "pulpectomy"[MeSH Terms] OR "pulpectomy"[Title/Abstract] OR "root canal obturation"[MeSH Terms] OR "root canal obturation"[Title/Abstract] OR "dental pulp diseases/therapy"[MeSH Terms] OR "Periapical Diseases/therapy"[MeSH Terms] OR "pulpitis/therapy"[MeSH Terms] OR "endodontic treatment"[Title/Abstract] OR "endodontic therapy"[Title/Abstract] OR "endodontic"[Title] OR "root canal"[Title] OR "pulpless"[Title]) AND ("root canal obturation/instrumentation"[MeSH Major Topic] OR "root canal obturation/methods"[MeSH Major Topic] OR "root canal obturation/standards"[MeSH Major Topic] OR "root canal therapy/methods"[MeSH Major Topic] OR "root canal therapy/standards"[MeSH Major Topic]) AND ("controlled clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "multicenter study"[Publication Type]

OR "randomized controlled trial"[Publication Type] OR allocat*[Title/Abstract] OR random*[Title/Abstract] OR systematic[*sb*] OR control*[Title])) AND (hasabstract[*text*]) ("root canal obturation/instrumentation"[MeSH Major Topic] OR "root canal obturation/standards"[MeSH Major Topic] OR "root canal preparation/instrumentation"[MeSH Major Topic] OR "root canal preparation/standards"[MeSH Major Topic] OR "root canal therapy/instrumentation"[MeSH Major Topic] OR "root canal therapy/standards"[MeSH Major Topic]) NOT (hasabstract[*text*])

161 hits.

Necrotic pulp AND treatment AND (Randomized Clinical Trial[*ptyp*] OR systematic[*sb*] OR "review literature as topic"[MeSH Terms])

102 hits.

((("root canal therapy"[MeSH Terms] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR "pulpectomy"[MeSH Terms] OR "pulpectomy"[Title/Abstract] OR "root canal obturation"[MeSH Terms] OR "root canal obturation"[Title/Abstract] OR "dental pulp diseases/therapy"[MeSH Terms] OR "Periapical Diseases/therapy"[MeSH Terms] OR "pulpitis/therapy"[MeSH Terms] OR "endodontic treatment"[Title/Abstract] OR "endodontic therapy"[Title/Abstract] OR "endodontic"[Title] OR "root canal"[Title] OR "pulpless"[Title]) AND ("n2 dental cement"[Substance Name] OR "n2"[Title] OR "fr dental filling"[Substance Name] OR "root filling"[Title/Abstract] OR "root canal sealer"[Title/Abstract] OR "root canal filling materials"[MeSH Terms] OR "gutta percha"[Title/Abstract] OR "chloroform"[Title/Abstract] OR "chloroform"[Substance Name] OR "chloropercha"[Title/Abstract] OR "endmethasone"[Title/Abstract]) AND ("controlled clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "multicenter study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR allocat*[Title/Abstract] OR random*[Title/Abstract] OR systematic[*sb*] OR control*[Title] OR "follow up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms])) AND (hasabstract[*text*]) AND (necrotic) AND (adult"[MeSH Terms])

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23 hits.

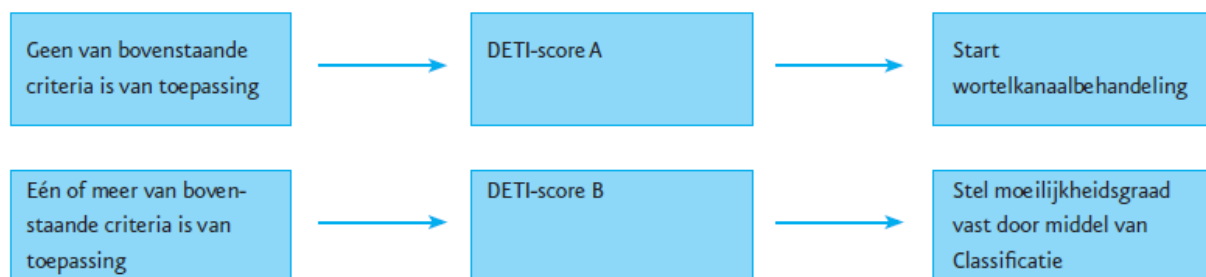
Total: 228 hits after deduplication and publication from 2010.
Published September 17, 2015.

Appendix 7.2 Dutch Endodontic Treatment Index and Classification of Endodontic Treatment.

The Dutch Endodontic Treatment Index (DETI) score.

YES

- Physical limitations/cooperation patient moderate to poor
- Diagnosis difficult to make
- Premolar > 2 root canals
- Molar > 3 root canals/third molar
- Root canal splitting in middle/apical third part
- Moderate to strong rotation and/or inclination of teeth (> 10°)
- Deviating crown and/or root morphology/length of root ≥ 30 mm
- Pre-treatment needed with rubber dam insulation
- Crown, superstructure and/or root post present
- Moderate to strong root canal curvatures (> 10°)
- Obstructions, resorptions, calcifications, perforations and/or open apices
- Dentition previously treated endodontically
- Endo-paro problems
- Trauma in anamnesis



The Classification of Endodontic Treatment.

criteria	1 punt per item gemiddeld risico	2 punten per item bovengemiddeld risico	5 punten per item groot risico
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A. Patiëntgebonden factoren

1. Mondopening en fysieke beperkingen	<input type="checkbox"/> Normale mondopening (≥ 35 mm)	<input type="checkbox"/> Beperkte mondopening ($> 25-35$ mm) <input type="checkbox"/> Moeilijkheden om film vast te houden	<input type="checkbox"/> Zeer beperkte mondopening (≤ 25 mm) <input type="checkbox"/> Beperking om achterover in de stoel te kunnen liggen
2. Röntgenologische problemen	<input type="checkbox"/> Normale condities	<input type="checkbox"/> Sterke braakreflex <input type="checkbox"/> Smal of vlak palatum/ ondiepe mondbodem	<input type="checkbox"/> Moeilijk om een goed beeld te krijgen door gesuperponeerde anatomische structuren
3. Diagnose	<input type="checkbox"/> Duidelijke symptomen en klinische bevindingen: diagnose levert geen problemen op	<input type="checkbox"/> Differentiële diagnose van toepassing bij duidelijke symptomen en klinische bevindingen	<input type="checkbox"/> Complexe symptomen en tegenstrijdige of onduidelijke klinische bevindingen: diagnose is moeilijk te stellen

B. Gebitselementgebonden factoren

4. Positie in tandboog	<input type="checkbox"/> Front en premolaren	<input type="checkbox"/> 1ste of >de molaar	<input type="checkbox"/> 3de molaar
5. Inclinatie en rotatie element	<input type="checkbox"/> Geen/geringe inclinatie ($\leq 10^\circ$) <input type="checkbox"/> Geen/geringe rotatie ($\leq 10^\circ$)	<input type="checkbox"/> Matige inclinatie ($10-30^\circ$) <input type="checkbox"/> Matige rotatie ($10-30^\circ$)	<input type="checkbox"/> Extreme inclinatie ($\geq 30^\circ$) <input type="checkbox"/> Extreme rotatie ($\geq 30^\circ$)
6. Morfologische afwijkingen kroon, isolatie element	<input type="checkbox"/> Normale, oorspronkelijke kroonmorfologie <input type="checkbox"/> Geen voorbehandeling vereist voor isolatie	<input type="checkbox"/> Taurodontie/ microdontie <input type="checkbox"/> Eenvoudige voorbehandeling vereist voor isolatie	<input type="checkbox"/> Dubbeltand/dens in dente* <input type="checkbox"/> Uitgebreide voorbehandeling vereist voor isolatie
7. Toegankelijkheid wortelkanaalstelsel	<input type="checkbox"/> Normale toegankelijkheid	<input type="checkbox"/> Discrepantie lengtes wortel en kroon <input type="checkbox"/> Amalgaambouw zonder wortelstift in pulpakamer	<input type="checkbox"/> Gegoten, porseleinen of goudporseleinen restauratie <input type="checkbox"/> Compositie topbouw in pulpakamer <input type="checkbox"/> Wortelstift/ gegoten stiftopbouw*
8. Wortel- en kanaalmorfologie	<input type="checkbox"/> I-vormige kanaalconfiguratie <input type="checkbox"/> Geen of geringe kanaalkromming ($< 10^\circ$) <input type="checkbox"/> Frontelement of premolaar met 1 kanaal	<input type="checkbox"/> J-vormige kanaalkromming <input type="checkbox"/> Matige kanaalkromming ($10-30^\circ$) <input type="checkbox"/> Frontelement of premolaar met 2 kanalen <input type="checkbox"/> Molaar met ≤ 3 kanalen <input type="checkbox"/> Kanaalbehandeling reeds gestart, maar niet voltooid, door vorige behandelaar	<input type="checkbox"/> C- of S-vormige kanaalkromming <input type="checkbox"/> C-vormig kanaalsysteem <input type="checkbox"/> Extreme kanaalkromming ($\geq 30^\circ$) <input type="checkbox"/> Premolaar met 3 kanalen <input type="checkbox"/> Molaar met > 3 kanalen <input type="checkbox"/> Kanaalsplitsing in middelste of apicaal derde deel <input type="checkbox"/> Zeer lange wortel (≥ 30 mm)
9. Morfologie apex	<input type="checkbox"/> Gesloten (=volgroeide) apex		<input type="checkbox"/> Open apex (onvolgroeide apex/apexresectie zonder retrograde afsluiting)
10. Kanaalcalcificaties	<input type="checkbox"/> Goed zichtbare kanalen	<input type="checkbox"/> Pulpakamer/kanalen zichtbaar maar aanzienlijk vernauwd <input type="checkbox"/> Pulpastenen	<input type="checkbox"/> Bijna geheel of gedeeltelijk onzichtbaar kanaalverloop <input type="checkbox"/> Kanalen niet zichtbaar*
11. Resorpties		<input type="checkbox"/> Interne resorptie zonder perforatie <input type="checkbox"/> Apicale resorptie	<input type="checkbox"/> Interne resorptie met perforatie* <input type="checkbox"/> Externe resorptie met* of zonder perforatie
12. Iatrogene incidenten		<input type="checkbox"/> Perforaties boven botniveau	<input type="checkbox"/> Afgebroken instrument* <input type="checkbox"/> Ledging* <input type="checkbox"/> Apicale transportaties* <input type="checkbox"/> Perforaties onder botniveau*

C. Additionele factoren

13. Revisie van eerder voltooide kanaalbehandeling			<input type="checkbox"/> Revisie van eerder voltooide kanaalbehandeling <input type="checkbox"/> Zilverstiftsectie*
14. Trauma in anamnese	<input type="checkbox"/> Ongecompliceerde kroonfractuur <input type="checkbox"/> Wortelfractuur in apicaal derde deel <input type="checkbox"/> Contusie	<input type="checkbox"/> Gecomplieerde kroon (-wortel) fractuur van element met volgroeide apex <input type="checkbox"/> Wortelfractuur in middelste derde deel <input type="checkbox"/> Subluxatie/fractuur processus alveolaris	<input type="checkbox"/> Gecomplieerde kroon (-wortel) fractuur van element met onvolgroeide apex <input type="checkbox"/> Wortelfractuur in cervicaal derde deel <input type="checkbox"/> Andere luxaties/avulsies
15. Endo-paraloesie			<input type="checkbox"/> Mobiliteit/pocket/fenestratie/dehiscentie <input type="checkbox"/> Furcatieproblematiek <input type="checkbox"/> Wortelresectie/hemisectie uitgevoerd of noodzakelijk
Subtotaal	<input type="checkbox"/> x 1 =	<input type="checkbox"/> x 2 =	<input type="checkbox"/> x 5 =
*Deze criteria vallen automatisch in Klasse III		Totaal: →	<input type="checkbox"/> 14-18 punten <input type="checkbox"/> 19-24 punten <input type="checkbox"/> > 24 punten
			Klasse I Klasse II Klasse III

Classificatie van een endodontische behandeling aan de hand van moeilijkheidsgraad en risico-inventarisatie

- A. Er worden 3 categorieën onderscheiden die van invloed kunnen zijn op de behandeling: patiëntgebonden factoren, gebitselementgebonden factoren en additionele factoren.
- B. Voor elke categorie worden er criteria gedefinieerd die in 3 risiconiveaus worden onderverdeeld: gemiddeld, bovengemiddeld en groot risico.
- C. Aan elk risiconiveau wordt een bepaalde score toegekend:
- | | | |
|-----|-----------------|-------------------|
| I | gemiddeld: | 1 punt per item |
| II | bovengemiddeld: | 2 punten per item |
| III | groot: | 5 punten per item |
- D. De totale som van alle punten geeft aan in welke klasse de casus valt. Als één van de **vet en cursief gedrukte criteria met een sterretje*** van toepassing is, hoeft er niet verder gescoord te worden, maar valt de casus automatisch in klasse III.
- I. Klasse I: gemiddeld risico (14-18 punten)
De preoperatieve status is ongecompliceerd tot weinig gecompliceerd. Voor een ervaren practicus is het mogelijk een voorspelbaar behandelresultaat te verkrijgen.
 - II. Klasse II: bovengemiddeld risico (19-24 punten)
De preoperatieve status is gecompliceerd. Voor een ervaren practicus kan het verkrijgen van een voorspelbaar behandelresultaat moeilijk zijn.
 - III. Klasse III: groot risico (> 24 punten)
De preoperatieve status is extreem gecompliceerd. Het verkrijgen van een voorspelbaar behandelresultaat stelt zelfs aan een zeer ervaren en kundig practicus zeer hoge eisen. Deze behandeling vereist grote specifieke deskundigheid (uitgebreide nascholing) alsmede het gebruik van specifieke apparatuur en instrumentarium.

8. Orthograde re-treatment

Introduction⁴³

Background

The goal of endodontic treatment, namely that the element is asymptomatic and free of infection and there is no evidence of apical periodontitis, is not always achieved. Pain, swelling and fistula associated with the element previously treated endodontically are all indications of a persistent or newly developed infection of the root canal or of a non-endodontic problem such as a cleft tooth. A frequent problem is that of a clinically asymptomatic previously endodontically treated element with radiographic signs of periapical bone loss or persistence of previous bone loss. Such a situation may deteriorate into an acute complaint of pain and swelling. Dental elements with an initial diagnosis of periapical bone loss require time to heal; follow-up studies have shown that the time required for this to occur can vary from several months to several years. The diagnosis of apical periodontitis associated with a root-filled tooth is fairly certain when there are clinical signs and indications of periapical bone loss. This is also true when an X-ray shows an increase in the area of bone loss or the development of a new lesion. However, if the only evidence consists of persistence of previously observed bone loss, then the diagnosis is less certain, but more likely the more time that has passed since the primary root filling.

Treatment options

Apart from extraction, there are several options: first, orthograde or retrograde re-treatment and second, "intentional replantation. Orthograde retreatment (revision of the root filling) involves the practitioner re-accessing the root canals with the aim of treating the infection mechanically and chemically. The infected area is often difficult to access for technical reasons. In addition, the microorganisms are usually more resistant than during the primary root canal infection.

Retrograde re-treatment (apical surgery) involves access to the root canal system through a surgical procedure. Several millimeters of the root tip are removed. This is usually followed by some form of root tip preparation and disinfection of the exposed root canal. The cavity that has been prepared is then closed with what is known as a retrograde root filling. The complexity of this varies according to the accessibility of the root, the skill of the practitioner and the availability of special equipment.

This systematic review discusses *orthograde re-treatment*. The outcome measures are similar to those of primary endodontic treatment. If the treated element is asymptomatic after a certain recovery period and there is no clinical or radiographic evidence of apical periodontitis, the treatment outcome is successful. Evidence was also sought for methods by which postoperative complications due to re-treatment can be successfully prevented or treated.

Exit questions:

1. How does the number of treatment sessions, instrumentation, disinfection protocol or root filling material affect the outcome of *orthograde* re-treatment?
2. Are there effective methods for preventing or treating postoperative complications after re-treatment?

Search and selection

A search was conducted November 15, 2016 in PubMed (Appendix 8.1). This found 897 potentially relevant studies. Of these, 5 were found to meet the inclusion criteria. The Swedish HTA report included 2 studies on bone loss as a potential prognostic factor for the outcome of orthograde re-treatment. The Swedish HTA report included neither studies comparing different instrumentation techniques, disinfection protocols or filling materials nor studies on avoiding or treating postoperative complications.

The summary of the literature discusses only the studies on *orthograde re-treatment*.

⁴³ This introduction is based in part on *Methods of Diagnosis and Treatment in Endodontics. A systematic review (2012)* and supplemented where necessary.

Selection Criteria

Type of patients	- patients with permanent teeth whose roots are filled and with symptoms or radiographic signs of apical periodontitis (i.e. persistent bone loss or enlargement of the area of bone loss)
Type of Intervention	- orthograde re-treatment of an element whose roots have been filled
Check	- orthograde re-treatment of an element whose roots have been filled - orthograde re-treatment: <ul style="list-style-type: none"> o treatment in one or more sessions o treatment with various disinfectants o treatment with different instrumentation techniques o treatment using different filling materials
Type of outcome measures	- apical periodontitis - postoperative complications (based on both clinical and radiographic evaluation) - minimum 12-month follow-up - in case of postoperative complications, evaluation should have taken place around the time of completion of treatment - cost
Type of setting	- general practitioners - dental endodontists
Inclusion and exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - human in vivo studies - For persistent bone loss, a follow-up duration of at least 12 months - in randomized or controlled trials at least 15 elements per group - in cohort studies at least 30 elements - Dutch or English-language studies published as of 2010. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - non-comparative observational studies - in vitro, ex vivo (human) studies

Summary of literature

How does the number of treatment sessions, instrumentation, disinfection protocol or root filling material affect the outcome of orthograde re-treatment?

No studies were found, insofar as they met the inclusion criteria, that examined the effect of the number of treatment sessions, instrumentation, disinfection protocol or root filling material in a comparative observational or experimental study. All included studies aimed to detect prognostic factors for treatment outcome.

The authors of the Swedish HTA study found inconsistent evidence on the prognostic role of bone loss for the outcome of orthograde re-treatment. Caliskan et al. (2005) found no difference in outcomes between bone loss less than or greater than 5 mm in diameter. However, Sundquist et al. (1998) found that elements with less bone loss (mean 3.7 mm) had a more favorable prognosis than elements with mean 5.6 mm bone loss.

In a recent study (Neskovic et al., 2016), orthograde re-treatment proved successful (PAI score 1 or 2) in 93 of 100 patients in the absence of periapical radiolucency, and in 68 of 100 patients if there were signs of periapical radiolucency prior to re-treatment.

Over time, several cohort studies (Farzaneh 2004; De Chevigny et al., 2008; Ng et al., 2011¹, 2011²) with multivariate analysis of potential prognostic factors have been published that can provide a better picture of the prognostic significance of bone loss, and perhaps reveal more prognostic factors. Study characteristics are briefly summarized in Table 8-1.

4 studies evaluated potential prognostic factors for lack of success regarding apical status (Farzaneh 2004; De Chevigny et al., 2008; Ng et al., 2011¹). Table 8-1 summarizes the prognostic factors that were significant and the strength of their effect.

Factors that (greatly) reduce the risk of "failure" of orthograde re-treatment are:

- *adequate* preoperative quality of root filling;
- Satisfactory restoration of the crown;
- No extrusion of the root filling;
- good accessibility to the canal and
- additional use of EDTA as an irrigation solution.

Table 8-1 Study characteristics

Study	Aim	Setting	Inclusion (IC) and exclusion criteria (EC).	Number of teeth undergone 2 nd RCTx	Study duration
Ng 2011 ¹	To investigate the probability of and factors influencing <i>periapical status</i> of teeth following primary (1RCTx) or secondary (2RCTx) root canal treatment	Unit of Endodontology, UCL Eastman Dental Institute, University College London, London; Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK	IC: patients undergoing 1 st RCTx or 2 nd RCTx, patients were over 15 years of age when treatment commenced and had either 1 st RCTx or 2 nd RCTx completed and had at least a semi-permanent restoration placed EC: Teeth were excluded from this study if they had pre-operative periodontal disease or prior surgical endodontic treatment, or if the apex/apices under investigation was/are not discernible on any of the periapical radiographs. The teeth were excluded from the analysis of 'periapical status following treatment' if: (i) they were not followed-up for at least 2 years, (ii) they were extracted for reasons not related to endodontic problems, (iii) information on the periapical status at the time of the extraction was not available and (iv) a completed pre- and intraoperative data collection form was not available for each tooth	1.113	October 1997 - June 2005
Ng 2011 ²	To investigate the probability of and factors influencing <i>tooth survival</i> following primary (1 st RCTx) or secondary (2 nd RCTx) root canal treatment	Dental Institute, University College London, London; Department of Medical Statistics, London School	Ditto	858	idem

Study	Aim	Setting	Inclusion (IC) and exclusion criteria (EC).	Number of teeth undergone 2 nd RCT _x	Study duration
The Chevigny 2008	Thus, the purpose of this study was 2-fold: (1) to systematically assess the 4- to 6-year outcome of orthograde retreatment in Phases 3 and 4 of the Toronto Study and (2) to examine outcome predictors for orthograde retreatment in the pooled samples of Phases 1-4	of Hygiene and Tropical Medicine, London, UK Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada,	IC & EC not reported	477	January 1998 - December 2001
Farzaneh 2004	The goal was to assess associations between the outcome and the preoperative, intraoperative, and post-operative factors that can be valuable for projecting the prognosis of treatment and prevention of AP in root-filled teeth	Endodontics, Faculty of Dentistry University of Toronto, Canada	IC & EC not reported	523	September 1993 - December 1997

Factors that (greatly) increase the risk of "failure" of orthograde re-treatment are:

- preoperative presence of a periapical lesion, as well as its extent;
- preoperative presence of a fistula;
- preoperative presence of a perforation;
- channel not adequately cleaned to terminus;
- inadequate intra-operative length of root filling;
- use of 2% chlorhexidine in addition to sodium hypochlorite and
- pain or swelling between appointments.

Table 8-2 Potential prognostic factors for outcomes related to periapical status of orthograde re-treatment

Potential prognostic factor	Farzaneh 2004	Farzaneh 2004	The Chevigny 2008	Ng 2011
	Elements without breakage	Elements without fracture and without preoperative perforation	Elements without breakage	Primary root canal treatment and re-treatment combined; no significant difference between the two.
	Outcome: presence of periodontitis apicalis, signs or symptoms	Outcome: presence of periodontitis apicalis, signs or symptoms	Outcome: periapical index ≥ 3 , or presence of symptoms or clinical signs other than tenderness in percussion	Outcome: no success (success defined as absence of pain, clinical evidence of inflammation or swelling and conventional radiographic criteria of complete healing/presence of normal space with the periodontal ligament or incomplete healing if the size of the lesion was reduced without return to normal space with the periodontal ligament) all still divide at 1 so 1/0.51 et cetera
Radiolucency (0 = absent; 1 = present) / periapical lesion (0 = absent; 1 = present)	-	-	OR = 3.33↑↑↑↑ (1,19-9,36)	OR = 1.96↑↑ (1,25-3,13)
Extent of periapical lesion	-	-	-	OR = 1.16↑ (1,10-1,23)
Preoperative quality of root filling (0 = inadequate, 1 = adequate)	OR = 6.61 ↑↑↑↑ (1.42-30.73)	OR = 7.29 ↑↑↑↑ (1.27-41.80)	OR = 4.18 ↑↑↑↑ (1,72-10,12)	-
Quality of restoration				
- no extrusion root filling (0 = absent, 1 = present)				OR = 0.13 ↓↓↓↓ (0,04-0,44)
- Satisfactory crown restoration (0 = absent, 1 = present)				OR = 0.09 ↓↓↓↓ (0,03 - 0,27)
Preoperative fistula (0 = absent, 1 = present)	-	-	-	OR = 1.89 ↑↑↑ (1,30 - 2,78)
Preoperative perforation (0 = absent, 1 = present)	OR = 26.52 ↑↑↑↑ (5.23-134.42)	-	OR = 4.01 ↑↑↑↑ (1,28-12,62)	OR = 2.17 ↑↑↑ (0,98 - 4,76) (p=0,06)
Cleaning channel as close to terminus as possible (0 = adequate, 1 = inadequate)	-	-	-	OR = 1.15 ↑ (1,03 - 1,27)
Channel accessibility (1=yes, 0=no)	-	-	-	OR = 0.45↓↓ (0,28 - 0,72)
Intra-operative length of root filling (0 = adequate, 1 = inadequate)	-	OR = 6.76 ↑↑↑↑ (1,19-38,59)	-	OR = 2.63 (1,85 - 3,70)
Additional use of chlorhexidine as an irrigation solution (in addition to NaOCl) (1=yes, 2=no)	-	-	-	OR = 2.13↑↑ (1,20 - 3,85)
Additional use of EDTA as	-	-	-	OR = 0.44↓↓

Potential prognostic factor	Farzaneh 2004	Farzaneh 2004	The Chevigny 2008	Ng 2011
	Elements without breakage	Elements without fracture and without preoperative perforation	Elements without breakage	Primary root canal treatment and re-treatment combined; no significant difference between the two.
	Outcome: presence of periodontitis apicalis, signs or symptoms	Outcome: presence of periodontitis apicalis, signs or symptoms	Outcome: periapical index ≥ 3 , or presence of symptoms or clinical signs other than tenderness in percussion	Outcome: no success (success defined as absence of pain, clinical evidence of inflammation or swelling and conventional radiographic criteria of complete healing/presence of normal space with the periodontal ligament or incomplete healing if the size of the lesion was reduced without return to normal space with the periodontal ligament) all still divide at 1 so 1/0.51 et cetera (0,26 - 0,73)
an irrigation fluid (1=yes, 2=no)				
Restoration at follow-up (0 = permanent, 1 = temporary)	OR = 14.00 $\uparrow\uparrow\uparrow$ (2.09-93.99)	OR = 20.49 $\uparrow\uparrow\uparrow$ (2,52-166,74)	-	-
Pain or swelling between appointments (1=yes, 2=no)				OR = 1.89 $\uparrow\uparrow$ (1,27 - 2,78)

odds ratios (OR) <1.50 (or >0.67): weak association (\uparrow, \downarrow), $1.50 \leq OR \leq 2.99$ (or $0.33 < OR < 0.67$): moderate association ($\uparrow\uparrow, \downarrow\downarrow$) and $OR \geq 3.0$ (or ≤ 0.33): strong association ($\uparrow\uparrow\uparrow, \downarrow\downarrow\downarrow$) (Reference: Davis et al., 2013). \downarrow =decrease in risk; \uparrow =increase in risk

Ng et al. (2011²) evaluated potential prognostic factors for periapical status in addition to potential prognostic factors for element survival after orthograde re-treatment (Table 8-3). 95 out of 100 elements were still present after 4 years.

Factors that (greatly) reduce the risk of losing an element after orthograde re-treatment are:

- accessibility to channel terminus (insofar as loss is within 22 months of treatment);
- postoperative cast restoration and
- Dentition with two proximal contacts.

Factors that (greatly) increase the risk of losing an element after orthograde re-treatment are:

- diabetes mellitus and systemic therapy with corticosteroids;
- pocket depth ≥ 5 mm;
- preoperative pain;
- preoperative sinus, and pre- or peroperative perforation;
- extrusion of gutta-percha root filling (to the extent that loss of element occurs within 22 months);
- molded stem assembly;
- postoperative temporary restoration and
- 'most-distally' located dentition.

Table 8-3 Potential prognostic factors for loss of dentition undergoing orthograde re-treatment

Potential prognostic factor	Ng 2011
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	Primary root canal treatment and re-treatment combined; no significant difference between the two. Outcome: loss of element within 48 months
Diabetes mellitus (1=yes, 0=no)	HR = 3.21-3.46 (1.27-8.36) ↑↑↑
Systemic therapy with corticosteroids (1=yes, 0=no)	HR = 2.96-3.40 (1.09-9.30) ↑↑↑
Pocket depth ≥5mm (1=yes, 0=no)	HR = 2.04-2.35 (0.86-5.45) (p<0.10) ↑↑
Preoperative pain	
- within 22 months	HR = 3.10-3.12 (1.53-6.29) ↑↑↑
- after 22 months	HR = 2.39-2.46 (1.19-4.94) ↑↑
Preoperative sinus (1=yes, 0=no)	HR = 2.22 (1.29-3.81) ↑↑
Pre- or intra-operative perforation	HR = 3.68-3.77 (1.62-8.60) ↑↑↑
Accessibility to channel terminus within 22 months of loss element (1=yes, 0=no)	HR = 0.29-0.31 (0.13-0.70) ↓↓↓
Extrusion of gutta-percha root filling after 22 months of loss element (1=yes, 0=no)	HR = 2.84 - 2.98 (1.39-6.09) ↑↑
Cast pin assembly (1=yes, 0=no)	HR = 2.58-2.60 (1.13-5.87) ↑↑
Postoperative temporary restoration (1=yes, 0=no)	HR = 7.53-8.26 (3.31-19.03) ↑↑↑
Postoperative cast restoration (1=yes, 0=no)	HR = 0.38-0.43 (0.22-0.72) ↓↓
Dentition with 2 proximal contacts (1=yes, 0=no)	HR = 0.47 (0.29-0.76) ↓↓
Dentition 'most-distally' located (1=yes, 0=no)	HR = 1.93 (1.13-3.31) ↑↑
hazard ratios (HR) <1.50 (or >0.67): weak association (↑,↓), 1.50≤HR≤2.99 (or 0.33<HR<0.67: moderate association (↑↑,↓↓) and HR ≥3.0 (or ≤0.33): strong association (↑↑↑,↓↓↓) (Reference: Davis et al., 2013). ↓=decrease in risk; ↑=increase in risk	

Quality of evidence prognostic factors for periapical healing and survival

The quality of evidence is low (Appendix 8.2). The main reason is due to the fact that all studies are so-called phase 1 prognostic studies. This type of studies look for *potential* prognostic factors. In phase 2, a potential prognostic factor is rigorously evaluated based on a hypothesis (Huguet et al., 2013). An additional reason is that all studies had high potential for bias, due in part to the large dropout rate and ambiguities in patient selection (Appendix 8.3).

Conclusion

Low	<i>Potential prognostic factors for periapical healing and survival of dentition</i>
GRADE	More than 10 potential prognostic factors were identified for both outcome measures (Table 8-2 and Table 8-3) were found, most of which have a moderate to strong effect on the probability of periapical healing or dental survival. Farzaneh 2004; De Chevigny et al., 2008; Ng et al., 2011 ¹ , 2011 ²

Are there effective methods for preventing or treating postoperative complications after re-treatment?

No studies were found that met the inclusion criteria.
See recommendations in the acute complaints section.

Considerations

Values and preferences

Virtually all patients will want to make a well-informed choice (orthograde re-treatment or other options), and therefore will want to be informed about important risk factors for inadequate healing or tooth loss when orthograde re-treatment is used.

Recommendations

Inform the patient in whom orthograde re-treatment is being considered, preferably also in writing, of the magnitude of the risk of inadequate healing of periodontitis apicalis.

Rational

The guideline working group attaches great importance to a well-informed patient.

Knowledge gaps

Phase 1 and 2 prognostic studies are needed to determine the extent to which one or more of the following factors significantly affect the success rate of orthograde re-treatment:

- extent of the periapical lesion;
- expertise of the practitioner (endodontist vs. general practitioner);
- systemic diseases;
- presence of broken instruments in the channel or other blockages;
- presence of perforations, and the influence of their locations, size and time;
- Presence of some kind of root marker;
- procedures during root canal re-treatment: removal of the old root canal filling, type of mechanical preparation, irrigation and filling, and
- type of element (single-channel elements versus multi-channel elements).

Literature

de Chevigny C, Dao TT, Basrani BR, Marquis V, Farzaneh M, Abitbol S, Friedman S. Treatment outcome in endodontics: the Toronto study--phases 3 and 4: orthograde retreatment. *J Endod.* 2008 Feb;34(2):131-7.

Farzaneh M, Abitbol S, Friedman S. Treatment outcome in endodontics: the Toronto study. Phases I and II: Orthograde retreatment. *J Endod.* 2004 Sep;30(9):627-33.

Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Systematic Reviews.* 2013;2:71. doi:10.1186/2046-4053-2-71.

Nesković J, Zivković S, Medojević M, Maksimović M. Outcome of orthograde endodontic retreatment--A two-year follow-up. *Srp Arh Celok Lek.* 2016 Mar-Apr;144(3-4):174-80.

Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of non-surgical root canal treatment: part 2: tooth survival. *Int Endod J.* 2011 Jul;44(7):610-25.

Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of nonsurgical root canal treatment: part 1: periapical health. *Int Endod J.* 2011 Jul;44(7):583-609.

Appendix 8.1 Search strategy

Sensitive search filter:

"controlled clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "multicenter study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR allocat*[Title/Abstract] OR random*[Title/Abstract] OR systematic[sb] OR "comparative study"[Publication Type] Filters: Publication date from 2010/01/01

AND

("surgical retreatment"[Title/Abstract] OR "recurrence"[MeSH Terms] OR "treatment outcome"[MeSH Terms] OR "disease progression"[MeSH Terms] OR "time factors"[MeSH Terms] OR "time course"[Title/Abstract] OR "success rate"[Title/Abstract] OR "failure"[Title/Abstract] OR "outcome"[Title] OR "adverse effects"[MeSH Sub-heading] OR "discomfort"[Title] OR adverse effect*[Title] OR adverse event*[Title] OR adverse outcome*[Title] OR "retreatment"[MeSH Terms] OR "reoperation"[MeSH Terms]) Filters: Publication date from 2010/01/01

AND

("root canal therapy"[MeSH Terms] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR "pulpectomy"[MeSH Terms] OR "pulpectomy"[Title/Abstract] OR "root canal obturation"[MeSH Terms] OR "root canal obturation"[Title/Abstract] OR "Dental pulp diseases/surgery"[MeSH] OR "apical surgery"[Title/Abstract] OR "apical microsurgery"[Title/Abstract]) Filters: Publication date from 2010/01/01

Specific search filter

"root canal therapy"[MeSH Major Topic] AND "retreatment"[MeSH Terms] AND "treatment outcome"[MeSH Terms] Filters: Publication date from 2010/01/01

Appendix 8.2 GRADE assessment

Starting level of quality of evidence: moderate (all studies are phase 1 exploratory studies)

Risk of bias: downgrade by one (all studies are at serious risk; see Appendix 8.3)

Inconsistency: do not downgrade because to the extent that a prognostic factor was examined in multiple studies, there were overlapping confidence intervals

Indirectness: not applicable

Inaccuracy: do not downgrade because all potential prognostic factors were found to be significant.

Quality of evidence: low.

Appendix 8.3 Risk of bias assessment

FARZANEH 2004 (PHASE 1 EXPLORATORY PROGNOSTIC STUDY)

Study participation:

- Percentage of patients meeting study inclusion criteria who were asked to participate: *not reported*.
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on key prognostic factors and outcome measures? *Non-response analysis performed. Result: age - usually important prognostic factor - differs significantly between responders and non-responders.*

->Moderate risk of bias

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *More than 50% dropouts.*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *Not verified.*

->Serious risk of bias

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*
- It clearly describes how the prognostic factors were measured, including the cutoff points. *Most clearly described.*

->Low risk of bias *

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *Sufficiently clearly described.*

->Low risk of bias *

Confounders:

- All significant confounders were defined and reliably and validly measured and included in the analysis. *This appears to be the case.*

->Low risk of bias *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order*
- Sufficient data to determine adequacy of statistical analysis. *Interaction effects were not examined. Borderline statistically significant factors were not reported.*

->Moderate risk of bias

Conclusion: 'Serious risk of bias'

DE CHEVIGNY 2008 (PHASE 1 EXPLORATORY PROGNOSTIC STUDY)

Study participation:

- Percentage of patients meeting study inclusion criteria and asked to participate >50%. *Not reported.*
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on key prognostic factors and outcome measures? *Non-response analysis performed. Results: age - usually important prognostic factor - differed significantly between responders (older!) and non-responders. In addition, significantly more women were among the responders.*

->'Serious risk of bias'

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *More than 50% dropouts*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *Not verified.*

->'Serious risk of bias'

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*
- It clearly describes how the prognostic factors were measured, including the cutoff points *Most clearly described.*

->Low risk of bias *

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *Sufficiently clear.*

->Low risk of bias *

Confounders:

- All significant confounders were defined and reliably and validly measured and included in the analysis. *This appears to be the case.*

->Low risk of bias *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order.*

Sufficient data to determine adequacy of statistical analysis. *Interaction effects were not examined. Borderline statistically significant factors were not reported.*

->Moderate risk of bias

Conclusion: 'Serious risk of bias'

Ng 2011¹ (PHASE 1 EXPLORATORY PROGNOSTIC STUDY)

Study participation:

- Percentage of patients meeting study inclusion criteria and asked to participate >50%. *Not reported.*
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on key prognostic factors and outcome measures? *Non-response analysis performed. Results: number of patients in the study with a periapical lesion was significantly more than in the non-responders.*

->Moderate risk of bias

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *Percent dropout rate just over 20%.*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *Not reported.*

->'Moderate risk of bias'

Measurement of prognostic factor:

- At most one-third of a scale was imputed → no risk of bias. *No imputation took place.*
- It is clearly described how the prognostic factors were measured, including the cut-off points → no risk of bias. *In order.*

->'Low risk of bias' *

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *In order.*

->'Low risk of bias' *

Confounders:

- All significant confounders were defined AND reliably AND validly measured AND included in the analysis → no risk of bias.

->'Low risk of bias' *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order.*
- Sufficient data to determine adequacy of statistical analysis. *In order (interaction effects also measured)*

->'Low risk of bias' *

Conclusion: 'Serious risk of bias'

NG 2011² (PHASE 1 EXPLORATORY PROGNOSTIC STUDY)

Study participation:

- Percentage of patients meeting study inclusion criteria and asked to participate >50%. *Not reported.*
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on key prognostic factors and outcome measures? *Not performed.*

->'Serious risk of bias'

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *Just over 20%*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *Not reported*

->'Moderate risk of bias'

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*
- It clearly describes how the prognostic factors were measured, including the cutoff points. *In order.*

->'Low risk of bias' *

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *In order.*

->'Low risk of bias' *

Confounders:

- All major confounders were defined and reliably and validly measured and included in the analysis. *In order.*

->'Low risk of bias' *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order.*
- Sufficient data to determine adequacy of statistical analysis. *Also measured interaction effects.*

->'Low risk of bias' *

Conclusion: 'Serious risk of bias'

9. Acute complaints and pain management

Introduction⁴⁴

Pain and swelling associated with infection of the pulp and periapical tissues are common complaints of patients who make an emergency dental visit. The goal of emergency treatment is to relieve pain and discomfort. The measures that can be taken depend on the nature and severity of the complaint. In some cases, treatment may be limited to the prescription of pain-relieving medication, possibly in combination with surgical drainage.

If the tooth in question is severely damaged by caries or extensive trauma and found to be irreparable, the best treatment may be extraction of the tooth.

If the goal is to preserve the element then it is often necessary to open the root canal. In such cases, in addition to relieving pain and discomfort, it is important that the emergency treatment does not compromise the prognosis of follow-up treatment of the element.

The principles of endodontic treatment in such situations are the same as those for asymptomatic conditions, namely shaping and disinfection of the root canal system of the tooth. In cases of emergency consultation, time is often the limiting factor for what can be accomplished. Therefore, the following focuses on treatment options that can quickly and effectively relieve or remedy acute dental pain caused by pulpitis or apical periodontitis.

Specific questions are:

1. Is removal of the contents of the pulpal chamber in symptomatic pulpitis or symptomatic apical periodontitis as effective in terms of symptom relief as total removal of the contents of the root canal system?
2. Is there difference in effect on pain between oral antibiotics and placebo or pain medication in patients with irreversible pulpitis?
3. Is there a difference in effect on pain, flare-up and swelling between systemic antibiotics and placebo, combined or not with surgical intervention, combined or not with pain medication, in patients with symptomatic apical periodontitis or acute apical abscess?
4. [update 2022/3] Is there a difference in effect on pain, flare-up and swelling between inclusion of an intravenous drug and not inclusion of intravenous drug?
5. [update 2022/3] Is there a difference in effect on postoperative pain between refrigerated and nonrefrigerated irrigants in patients with irreversible pulpitis or pulpal necrosis?
6. [update 2022/3] What is the *relative* efficacy and safety of oral analgesics given postoperatively (i.e., after nonsurgical endodontic treatment) to patients with irreversible pulpitis or pulpal necrosis?
7. [update 2022/3] What is the *relative* efficacy and safety of oral premedication on postoperative pain in patients with irreversible pulpitis?
8. [update 2022/3] What is the *relative* effectiveness of local anesthetics for molars and premolars in the mandible, in terms of success of *inferior alveolar nerve* blockade, in patients with irreversible pulpitis? How safe are these local anesthetics?

Search and selection

The systematic review *Methods of Diagnosis and Treatment in Endodontics* (2012) was used as a starting point for an update. The search strategy contained therein was used for this update.

The search strategy was conducted in October 2015 through a search in PubMed (Appendix 9.1). A total of 44 articles were found, of which 2 were eligible for inclusion. These included 1 systematic review (Cope et al., 2014) of 2 randomized controlled trials. Four studies (Moskow et al., 1984; Nagle et al., 2000; Henry et al., 2001; Ehrmann et al., 2003) were included in *Methods of Diagnosis and Treat-*

⁴⁴ This introduction is based in part on *Methods of Diagnosis and Treatment in Endodontics. A systematic review (2012)* and supplemented where necessary.

ment in *Endodontics* (2012), of which 1 (Henry et al., 2001) was included in Cope et al. (2014). Thus, a total of five studies.

[update 2022/3] Regarding the baseline questions on *oral and systemic antibiotics*, two Cochrane Reviews (Agnihotry et al., 2019; Cope et al., 2018) were found. However, these did not include more recent studies. Regarding the question on the effect of *cooling irrigants* on postoperative pain, one systematic review of good quality was included (Almohaimede & Al-Madi, 2021). With respect to the baseline question on inclusion of *intracanal medication*, one systematic review of very good quality was included (Ahmad et al., 2022). Regarding the primary question on the *relative efficacy and safety of oral analgesics given postoperatively*, one systematic review and network meta-analysis of very good methodological quality was found (Zanjir et al., 2020). Regarding the starting question on the *relative effectiveness and safety of oral premedication*, one systematic review and network meta-analysis of very good methodological quality was found (Nagendrababu et al., 2019a). Regarding starting question on the *relative effectiveness of local anesthetics* for molars and premolars in the mandible, one systematic review and network meta-analysis of very good methodological quality was found (Nagendrababu et al., 2019b).

Selection Criteria

Type of patients	- patients with permanent teeth with symptomatic pulpitis or symptomatic apical periodontitis
Type of Intervention	- removal of the contents of the pulp chamber - incision, apical trepanation, analgesics and antibiotics, alone or in combination with complete instrumentation of the root canal system, cooling of irrigants
Check	- complete instrumentation of the root canal or - placebo
Type of outcome measures	- relief of symptoms after treatment - evaluation after completion of treatment step or completion of treatment - results in relation to preoperative diagnosis - cost
Type of setting	- general practitioners - dental endodontists
Inclusion and exclusion criteria	Inclusion criteria: - human in vivo studies - it is indicated whether teeth have been previously treated endodontically and separate presentation of these outcomes - pain and discomfort can be attributed to a specific tooth - comparative observational studies - (quasi-) randomized) or controlled experimental studies - systematic reviews (with or without meta-analyses) Exclusion criteria: - non-comparative observational studies - in vitro, ex vivo (human) studies

Summary of literature

Is removal of the contents of the pulpal chamber in symptomatic pulpitis or symptomatic apical periodontitis as effective in terms of symptom relief as total removal of the contents of the root canal system?

Neither in *Methods of Diagnosis and Treatment in Endodontics* (2012) nor the literature search found studies that met the inclusion criteria comparing mentioned interventions. The reader is therefore referred to the "syllabus on endodontic emergency treatment in practice (2011).

Is there difference in effect on pain between oral antibiotics and placebo or pain medication in patients with irreversible pulpitis?

Agnihotry et al. (2019) found one study (Nagle et al., 2000) comparing penicillin with placebo. Nagle et al. (2000) examined the effect of penicillin in 40 adult patients with untreated irreversible pulpitis in a randomized controlled trial. Mean age was 30-34 years. The sex ratio (v%) was 58%, but there were four times as many women as men in the placebo group, and twice as many men as women in the experimental group. The teeth (first and second molar and first and second premolar) were from both the lower and upper jaws. Patients received 28 capsules of penicillin (500 mg each, to be taken every 6 hours) for 7 days. No endodontic treatment was performed. All patients also received ibuprofen and paracetamol with codeine (30 mg). For 7 days, patients noted pain, pain on percussion, and number and type of medications used. A 4-point pain scale was used for this purpose. Outcome measures were: sum of differences in pain intensity (SPID), sum of differences in percussion pain (SPPID), and amount of pain medication.⁴⁵

Sum of differences in pain intensity

In both the experimental and control groups, the median was 6.0.

Sum of differences in pain in percussion (SPPID).

The median values were 3.5 and 2.0 in the penicillin and placebo groups, respectively. This difference in favor of the penicillin group was not statistically significant.

Amount of ibuprofen used

The difference in number of tablets used was another -0.5 in favor of the penicillin group. This difference was not statistically significant.

Amount of paracetamol with codeine used

The difference in number of tablets used here was -2.45 in favor of the placebo group. This difference was not statistically significant.

Quality of evidence pain and pain intensity

The quality of evidence is low because of the very small study size (imprecision of outcomes), on the basis of which it was downgraded by two levels for imprecision. No downgrading was done for risk of bias, indirect evidence, inconsistency and publication bias.

Conclusion

Low GRADE	<p><i>Sum of differences in pain intensity and in pain in percussion</i></p> <p>Penicillin appears to reduce pain intensity no more than placebo in patients with pain associated with untreated irreversible pulpitis in whom the symptomatic tooth has not previously received endodontic treatment.</p> <p>Agnihotry et al., 2019 (Nagle et al., 2000)</p>
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⁴⁵ Calculating the sum of differences in pain intensity (SPID) is a strategy to combine relief and duration of pain into a single score. The sum is calculated by multiplying the time-weighted difference in pain intensity (difference between current pain and pain at onset) by the time interval between pain measurements. Higher scores indicate less pain.

Low GRADE	<p><i>Amount of ibuprofen used; paracetamol with codeine</i></p> <p>Penicillin does not appear to result in less use of analgesics than placebo by patients with pain associated with untreated irreversible pulpitis in whom the symptomatic tooth has not previously received endodontic treatment.</p> <p>Agnihotry et al., 2019 (Nagle et al., 2000)</p>
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Is there a difference in effect on pain, flare-up and swelling between systemic antibiotics and placebo, combined or not with surgical intervention, combined or not with pain medication, in patients with symptomatic apical periodontitis or acute apical abscess ?

Cope et al. (2018) included 2 trials with a total of 62 study participants (Henry et al., 2001; Fouad et al., 1996). Surgical intervention was performed in both trials. No trials were found in which *no surgical* intervention was performed.

The mean age of the patients was 36-37 years. One trial had more male patients (Fouad et al.) and the other trial (Henry et al.) had approximately equal numbers of male and female patients. Which teeth were involved was not reported by Cope et al. (2014). Participants had a symptomatic necrotic dentition and spontaneous pain (Henry et al.), or an acute apical abscess with necrosis of the pulp, pain and/or swelling (Fouad et al.).

Major exclusion criteria in the study by Fouad et al. (1996) were: body temperature above 37.8 °C, malaise, diseases or conditions compromising the immune system, renal failure; pregnant women and women using oral contraception, use of antibiotics in the previous 14 days. Main exclusion criteria in the study by Henry et al. (2001) were previous endodontic treatment, use of antibiotics in the previous 30 days, (probable) presence of a fistula.

Although penicillin VK was given in both trials, the dosage differed. Fouad et al. gave 1 gram immediately after treatment followed by a dose of 500 mg every 6 hours for 7 days. Henry et al. gave 500 mg every 6 hours for 7 days. There were also differences in terms of pain medication.

Fouad et al. gave all participants ibuprofen (600 mg) immediately before treatment. After treatment, participants were required to take ibuprofen 4x in 24 hours, and then as needed. Henry et al. advised participants to take 400 mg of ibuprofen as needed, every 4-6 hours. Participants also received a bottle of tablets of paracetamol with codeine (30 mg). They were instructed to use these - 1-2 tablets every 4 hours - when 2 ibuprofen tablets provided insufficient analgesia.

Treatment further consisted of total or partial pulpectomy (Fouad et al.) or total pulpectomy (Henry et al.).

The primary outcome measure was participant-reported pain (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain) and swelling. Swelling was measured slightly differently in both studies. Side effects were reported in one study. Quality of life was not reported in any of the studies.

Pain measured on a 4-point scale after 24 hours

The difference in pain after 24 hours between the two groups was -0.03 (95% BI: -0.53 - 0.47), which can be called a negligible difference.

Pain measured on a 4-point scale after 48 hours

The difference in pain after 48 hours between the two groups was 0.32 (95% BI: -0.22 - 0.86), which may indicate difference in favor of placebo.

Pain measured on a 4-point scale after 72 hours

The difference in pain after 72 hours between the two groups was 0.08 (95% BI: -0.38 - 0.55), which can be called a negligible difference.

Swelling after 24 hours

The difference in swelling after 24 hours between the two groups was 0.27 (95% BI: -0.23 - 0.78), which can be called a negligible difference. 0.27 standard deviations can be characterized as a weak effect in favor of placebo.

Swelling after 48 hours

The difference in swelling after 48 hours between the two groups was 0.04 (95% BI: -0.47 - 0.55), which can be called a negligible difference.

Swelling after 72 hours

The difference in swelling after 72 hours between the two groups was 0.02 (95% BI: -0.49 - 0.52), which can be called a negligible difference.

Side effects

One participant in the placebo group reported diarrhea. One participant in the experimental group reported fatigue and decreased energy levels after the procedure.

Quality of evidence pain intensity and swelling after 24, 48 and 72 hours

The quality of evidence is very low. It was downgraded by one level for risk of bias (high study dropout rate), by one level for indirect evidence (pain medication differs between study groups), and by one level for imprecision (small study size). There was no downgrading for inconsistency and publication bias. See also evidence profile 4 in appendix.

Conclusions

Very low GRADE	<p><i>Pain intensity after 24, 48 and 72 hours</i></p> <p>In case of (partial) pulpectomy, penicillin may not reduce the pain intensity compared to placebo in adult patients with symptomatic apical periodontitis and acute apical abscess and in whom the complaint-causing tooth has not previously received endodontic treatment, but the evidence is very uncertain.</p> <p>Cope et al., 2018 (Fouad et al., 1996; Henry et al., 2001)</p>
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Very low GRADE	<p><i>Swelling after 24, 48 and 72 hours</i></p> <p>In case of (partial) pulpectomy, penicillin may not reduce swelling compared to placebo in adult patients with symptomatic apical periodontitis and acute apical abscess in whom (partial) pulpectomy is performed and in whom the symptomatic tooth has not previously received endodontic treatment, but the evidence is very uncertain.</p> <p>Cope et al., 2018 (Fouad et al., 1996; Henry et al., 2001)</p>
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[Update 2022/3] Is there a difference in effect on pain, flare-up and swelling between inclusion of an intravenous drug and not inclusion of intravenous drug?

Ahmad et al. (2022) conducted a review asking: does calcium hydroxide as an intracanal medication reduce postoperative or "interappointment" pain compared with no dressing or other intracanal medication in patients with primary root canal treatment due to dentition with pulpal necrosis and periodontitis apicalis? They included eighteen randomized studies with a total of 1192 patients. These

studies were conducted in Pakistan (n=6), Egypt (n=5), India (n=2), Australia (n=1), Nigeria (n=1), Brazil (n=1), Iran (n=1) and Turkey (n=1).

In eight studies, the dentition had a single radix and in five studies multiple radices. Three studies had a combination of both. Two studies did not report on number of radices.

Various forms of calcium hydroxide were used: in the form of powder mixed with a saline solution, in the form of a paste, as ApexCal (calcium hydroxide plus polyethylene glycol), as Calcipulpe (Septodont; calcium hydroxide plus polyethylene glycol) and as Metapex (Meta Biomed; calcium hydroxide plus iodoform).

What was calcium hydroxide compared to? These are: no drug, chlorhexidine, antibiotic plus steroid, combination of antibiotics (TAP).

Six studies measured pain intensity using a 0-100 VAS scale. Five studies using a 0-10 VAS scale. Six studies used a numeric scale (0-10 NRS) and one study used the Heft-Parker scale (0-170 mm). Because of the different pain scales, all outcomes were reduced to a standardized mean difference (SMD), or units standard deviation.⁴⁶

Effectiveness of pain reduction

The results of the various comparisons between calcium hydroxide and other interventions are shown in Table 9-1. Apart from the pain intensity after 6 hours, the use of *calcium hydroxide* always gives a *lower* pain intensity than the *non-inclusion of a medication*. Compared with *calcium hydroxide*, the combination of a steroid and antibiotics or a combination of antibiotics or chlorhexidine results in *less pain* than *calcium hydroxide* after 6 to 48 or 72 hours. Where Table 9-1 does not answer is the question to what extent the difference in analgesic effect of calcium hydroxide and that of other medications is trivial or at least a small but significant difference. The same question applies to a difference in analgesic effect between other medications (other than calcium hydroxide) among themselves. The first question can be answered as follows. An SMD of between 0.2 and 0.5 is considered a small but significant effect. Of the eleven comparisons (between three other agents at different times), the effect is greater than 0.2 in ten comparisons. In other words, there seems to be a small but significant difference in effect between other medication and calcium hydroxide, in favor of other medication.

Through a largely indirect comparison of the effects of different drugs, the second question of which drugs have a small but significant difference in effect on pain can be answered (Table 9-2).

From the data in Table 9-1 and Table 9-2 the following can be deduced that:

- the antibiotic combination seems somewhat more effective than calcium hydroxide
- the antibiotic combination appears to be less effective than chlorhexidine
- chlorhexidine - except after 6 hours - seems no less effective than steroid + antibiotic which seems to give the most pain reduction.

Table 9-1 Pain intensity postoperatively or 'interappointment': calcium hydroxide vs. no or other intracanal drugs (EC)

Pairwise comparison of analgesics	Difference (SMD) in pain intensity after 6 hours	Significance of difference in pain intensity
calcium hydroxide vs. no medication	0,36 (-0,54; 1,26)	Less pain in EG
calcium hydroxide vs. steroid + antibiotic	2,87 (-0,27; 6,00)	Less pain in EG
calcium hydroxide vs. antibiotic combination	0,19 (-0,30; 0,67)	Less pain in EG
calcium hydroxide vs. chlorhexidine	0,63 (-0,34; 1,61)	Less pain in EG
	Difference (SMD) in pain intensity after 24 hours	Significance of difference in pain intensity
calcium hydroxide vs. no medication	-0,71(-0,03; -1,38)	More pain in EG
calcium hydroxide vs. steroid + antibiotic	0,86 (-0,29; 2,01)	Less pain in EG
calcium hydroxide vs. antibiotic combination	0,28 (-0,05; 0,60)	Less pain in EG
calcium hydroxide vs. chlorhexidine	0,78 (-2,17; 3,73)	Less pain in EG

⁴⁶ 0.2, 0.5 and 0.8 standard deviation is generally understood as a small, moderate and large effect, respectively.

	Difference (SMD) in pain intensity after 48 hours	Significance of difference in pain intensity
calcium hydroxide vs. no medication	-1,82 (-0,31; -3,33)	More pain in EG
calcium hydroxide vs. steroid + antibiotic	0,77 (-0,09; 1,62)	Less pain in EG
calcium hydroxide vs. antibiotic combination	0,35 (0,03; 0,67)	Less pain in EG
calcium hydroxide vs. chlorhexidine	0,63 (-1,26; 2,52)	Less pain in EG

	Difference (SMD) in pain intensity after 72 hours	Significance of difference in pain intensity
calcium hydroxide vs. no medication	-0,24 (0,05; -0,53)	More pain in EG
calcium hydroxide vs. steroid + antibiotic	0,73 (0,53; 0,94)	Less pain in EG
calcium hydroxide vs. antibiotic combination	0,30 (-0,07; 0,67)	Less pain in EG

Table 9-2. Pain intensity postoperatively or 'interappointment': intracanal drugs other than calcium hydroxide compared among themselves

Pairwise comparison of analgesics	Difference (SMD) in pain intensity after 6 hours‡	Significance of difference in pain intensity*
antibiotic combination vs. steroid + antibiotic	2,87 - 0,19 = 2.68 (95% BI: -0.45; 5.81)	steroid + antibiotic much more effective than antibiotic
chlorhexidine vs. steroid + antibiotic	2,87 - 0,63 = 2.24 (95% BI: 1.26; 3.22)	steroid + antibiotic much more effective than chlorhexidine
chlorhexidine vs. antibiotic combination	0,19 - 0,63 = -0.44 (95% BI: -1.43; 0.55)	chlorhexidine slightly more effective than antibiotic combination

	Difference (SMD) in pain intensity after 24 hours‡	Significance of difference in pain intensity*
antibiotic combination vs. steroid + antibiotic	0,86 - 0,28 = 0.58 (95% BI: -0.62; 1.78)	steroid + antibiotic more effective than antibiotic
chlorhexidine vs. steroid + antibiotic	0,86 - 0,78 = 0.08 (95% BI: -3.09; 3.25)	steroid + antibiotic trivial difference from chlorhexidine
chlorhexidine vs. antibiotic combination	0,28 - 0,78 = -0.50 (95% BI: -3.47; 2.47)	chlorhexidine more effective than antibiotic combination

	Difference (SMD) in pain intensity after 48 hours‡	Significance of difference in pain intensity*
antibiotic combination vs. steroid + antibiotic	0,77 - 0,35 = 0.42 (95% BI: -0.49; 1.33)	steroid + antibiotic slightly more effective than antibiotic
chlorhexidine vs. steroid + antibiotic	0,77 - 0,63 = 0.14 (95% BI: -1.93; 2.21)	steroid + antibiotic trivial difference from chlorhexidine
chlorhexidine vs. antibiotic combination	0,35 - 0,63 = -0.28 (95% BI: -2.20; 1.64)	chlorhexidine slightly more effective than antibiotic combination

*difference (SMD) of 0.2-0.5: small but significant; 0.5-0.8: moderate difference; from 0.8: large difference in effectiveness.

‡: calculation by the working group.

Swelling and flare-up

Flare-up was defined in two studies as pain and/or swelling that required an unscheduled appointment and corresponded to an increase of 20 or more points on a 0-100 VAS scale. In the group in which no intravenous drug was included, 11.1% had flare-up, compared with 3.1% in the calcium hydroxide group, 24 hours postoperatively. One study reported 11.4% flare-up in the chlorhexidine plus calcium hydroxide group versus 5.7% in the calcium hydroxide group, while one study reported no difference between chlorhexidine plus calcium hydroxide group and calcium hydroxide. Seven studies did not report differences in the degree of flare-up between control and experimental groups.

Quality of evidence pain intensity after 24, 48, 72 and 6-72 hours and swelling and flare-up

Pain intensity after 24, 48 and 72 hours for the comparison calcium hydroxide versus no drug included: the quality of evidence is very low. Downgrading by one level for risk of bias due to ambiguities about blinding of allocation to study groups and blinding of outcome assessors, and by two levels for very severe imprecision: the confidence interval (-0.03; -1.38) and (-0.31; -3.33) and (0.05; -0.53) crossed SMD -0.2, -0.5 and -0.8 and SMD -0.5 and -0.8 and SMD -0.2 and -0.5, respectively. When two values are crossed, downscaling by two levels is warranted.

Pain intensity for all intrathecal drug comparisons: the quality of evidence is very low. It was downgraded by one level because of risk of bias and by two levels for very indirect evidence and very severe imprecision. For swelling and flare-up, the quality of evidence is indeterminate: most studies did not report or incompletely reported on these outcome measures.

Conclusion

Very low GRADE	<p><i>Pain intensity after 24 and 48 hours</i></p> <p><i>Compared with non-inclusive intracanal medication, calcium hydroxide as an intracanal medication appears to (significantly) reduce pain intensity in patients with symptomatic apical periodontitis in whom the symptomatic tooth has not previously received endodontic treatment, but the evidence is highly uncertain.</i></p> <p>Ahmad et al., 2022</p>
Very low GRADE	<p><i>Pain intensity after 72 hours</i></p> <p><i>Compared with non-inclusive intracanal medication, calcium hydroxide as an intracanal medication appears to somewhat reduce pain intensity in patients with symptomatic apical periodontitis in whom the symptomatic dentition has not previously received endodontic treatment, but the evidence is highly uncertain.</i></p> <p>Ahmad et al., 2022</p>
Very Low GRADE	<p><i>Pain intensity after 6- 72 hours</i></p> <p><i>Combination antibiotics as an intravenous drug seems somewhat more effective than calcium hydroxide as an intravenous drug, but the evidence is very uncertain.</i></p> <p><i>Combination antibiotics as intra-channel medications seem to be less effective than chlorhexidine, but the evidence is very uncertain.</i></p> <p><i>Chlorhexidine - except after 6 hours - seems no less effective than steroid + antibiotic, but the evidence is very uncertain.</i></p> <p>Ahmad et al., 2022</p>

<p>-----</p> <p>GRADE</p>	<p><i>Swelling and flare-up</i></p> <p>Studies did not report on swelling and flare-up to a sufficient extent to make a somewhat numerically based statement on this.</p> <p>Ahmad et al., 2022</p>
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[update 2022/3] Is there a difference in effect on postoperative pain between refrigerated (1.5° to 4° Celsius) and non-refrigerated (room temperature) of irrigants in patients with irreversible pulpitis or pulpal necrosis?

Cryotherapy or cooling was introduced into endodontic treatment as a method of intra-canal irrigation to reduce postoperative endodontic pain. The mechanism of action in reducing pain involves reducing tissue temperature as well as blood flow and metabolic activity.

Almohaimede & Al-Madi (2021) included sixteen randomized studies. Where these studies were conducted, the reviewers did not mention. Seven studies reported percentage pain reduction and were not suitable for meta-analysis. Nine studies with a total of 878 patients remained for meta-analysis. In the sixteen studies, the number of patients ranged from 30 to 240 and the age ranged from 18 to 70 years. Eleven studies included patients with irreversible pulpitis, three studies included patients with necrotic pulp, and 12 studies included pulpal and periradicular pathology or normal periradicular tissues.

Pain intensity was measured by 0-10 VAS scale in most studies, 0-100 VAS scale in three studies. All outcomes on pain intensity were reduced to an outcome on a 0-10 VAS scale. Pain was measured after 6, 24, 48 and 72 hours.

Preoperative pain was verified in thirteen studies: in two studies patients had no pain; in two studies mild pain; in two studies moderate pain and severe pain in six studies.

The temperature of the final irrigant ranged from 1.5 to 4° C. The volume ranged from 5 ml [three studies], 10 ml [three studies] to 20 ml [eight studies] for 1 minute [three studies], 2 minutes [one study] to 5 minutes [ten studies].

In nine studies, root canal treatment was completed in one session, in six studies in two sessions (one study did not report on this).

Table 9-3. Pain intensity: difference between refrigerated and non-refrigerated irrigants

Outcome measure	Difference (MD) in pain intensity (VAS scale 0-10)† :
	Chilled versus non-chilled irrigants
Pain intensity after 6 hours:	-1.11 (95% BI: -1.72; -0.50)
Pain intensity after 24 hours:	-1.08 (95% BI: -1.79; -0.38)
Pain intensity after 48 hours:	-0.38 (95% BI: -0.73; -0.02)
Pain intensity after 72 hours:	-0.69 (95% BI: -1.34; -0.05)

†MD = mean difference.

On a 0-100 VAS scale, a difference of at least 10 is interpreted as an effect that patients perceive as a relevant reduction in pain. On a 0-10 VAS scale, this corresponds to a difference of at least 1. Table 9-3 shows that only the first 24 hours a relevant difference in pain intensity is observable. After that, the difference is trivial, i.e., less than 1 on a 0-10 VAS scale.

For information: Whether pain intensity after cooling reduces more or less according to diagnosis (irreversible pulpitis or pulpa necrosis, whether or not combined with pulpal and periradicular pathology) was not analyzed by the reviewers. However, there are only three studies with patients diagnosed with pulpa necrosis, which would severely limit the value of such an analysis. What can be mentioned about it is the following. For pain intensity after 6, 24, 48 and 72 hours, the three studies with diagnosis of pulpa necrosis provide six outcomes combined. Three of these give greater pain reduction and

three of these give lesser pain reduction than the mean pain reduction of all the studies. In short, there is no evidence of a difference in pain reduction according to the diagnosis of irreversible pulpitis or pulpal necrosis.

Quality of evidence pain intensity after 6, 24, 48 and 72 hours

One level was downgraded for severe risk of bias for all outcome measures. According to the reviewers, four studies presented serious risk of bias because of deviations from the intended intervention; two studies because of many dropouts, and five studies because of unblinded measurement of outcomes. In addition, we downgraded for severe imprecision for pain intensity after 6, 24 and 72 hours: the confidence interval did not exclude a trivial or a relevant beneficial effect. For pain intensity after 48 hours, *there was no* downscaling for severe imprecision: the confidence interval is entirely within -1 and +1. In other words, there is no doubt that the effect here is trivial.

Conclusions

Low GRADE	<p><i>Pain intensity after 6 and 24 hours</i></p> <p>Irrigant cooling in patients with irreversible pulpitis or pulpal necrosis, whether or not combined with pulpal or periradicular pathology, appears to <i>slightly</i> reduce pain compared with no cooling.</p> <p>Almohaimede & Al-Madi, 2021</p>
Low to fair GRADE	<p><i>Pain intensity after 48 and 72 hours</i></p> <p>Refrigeration of irrigants in patients with irreversible pulpitis or pulpal necrosis, whether or not combined with pulpal or periradicular pathology, is unlikely to reduce pain <i>significantly, if at all</i>, compared with no refrigeration.</p> <p>Almohaimede & Al-Madi, 2021</p>

[update 2022/3] What is the relative efficacy and safety of oral analgesics given postoperatively (i.e. after nonsurgical endodontic treatment) to patients with irreversible pulpitis or pulpal necrosis?

Zanjir et al. (2020) included 11 randomized studies evaluating eight interventions in their systematic review and network meta-analysis⁴⁷ :

- NSAIDs,
- NSAIDs + paracetamol,
- NSAIDs + benzodiazepines,
- NSAIDs + opioids,
- corticosteroids,
- opioids,
- paracetamol, and
- placebo.

Outcome measures were postoperative pain at 6-8, 12, 24 and 48 hours, measured by a 0-100 VAS scale, 10-point VAS scale or 0-11 NRS scale, and adverse events. Most studies were conducted in the United States (n=6) and Iran (n=3). A total of 706 adults (18-68 years) were included. Pulpal diagnoses were: irreversible pulpitis (symptomatic: n=8 or asymptomatic: n=1) and pulpal necrosis (n=4). Peri-

⁴⁷ Network meta-analysis is a technique for simultaneously comparing three or more interventions in a single analysis by combining both direct and indirect evidence in a network of studies.

Network meta-analysis results in estimates of the relative effects among a few interventions in the network and usually provides more precise estimates than a single direct or indirect estimate. It also allows estimation of the ranking and hierarchy of interventions: what are the more effective, what are the less effective interventions.

apical diagnoses were: normal apical tissue (n=5), periodontitis apicalis (symptomatic: n=4 or asymptomatic: n=1), and acute apical abscess (n=3).⁴⁸ All but one study recruited patients with *moderate (4-6 on 10-point VAS scale) to severe (7-9 on 10-point VAS scale) preoperative pain.*

A network meta-analysis examined the effectiveness of the analgesics relative to each other, all compared with placebo. A network meta-analysis also compares agents that have not been *directly* compared in one or more studies. An example is the comparison NSAIDs + benzodiazepines versus NSAIDs + opioids.⁴⁹ For pain after 6-8 hours, the difference between the two agents is ca.1 on a scale of 0-100 (Table 9-4). Because both agents were compared with placebo, the agents can be compared to each other and a difference calculated in the degree of reduction of postoperative pain.

The results of the network meta-analysis are presented in Table 9-4.⁵⁰ NSAIDs, whether or not combined with another analgesic, seemingly emerge as the most effective and paracetamol and opioids as the least effective.

Table 9-4. Relative effect on postoperative pain of all postoperatively given analgesics compared to placebo

	Painkillers	Mean difference [MD] (95% BI) [‡]	Mean difference [MD] (95% BI) [‡]
		after 6-8 hours	after 24 hours
1	NSAIDs	-20,69 (-28,03; -13,35)	-16,77 (-24,49; -9,04)
2	NSAIDs + paracetamol	-19,78 (-27,10; -12,46)	-14,68 (-24,89; -4,46)
3	NSAIDs + benzodiazepines	-21,22 (-38,31; -4,12)	-8,23 (-24,38; 7,92)
4	NSAIDs + opioids	-20,28 (-32,69; -7,88)	-17,26 (-30,01; -4,50)
5	Corticosteroids	-14,56 (-30,88; 1,76)	-14,90 (-31,85; 2,06)
6	Opioids	-7,15 (-18,12; 3,83)	0,39 (-10,68; 11,47)
7	Paracetamol	-2,76 (-15,29; 9,77)	-
8	Placebo	-	-

[‡] MD: mean difference

Regarding medication safety, Zanjir et al. (2020) mentioned the following: only six of 16 studies presented data on safety and reported that the interventions were safe with no major side effects; 17.6% of patients taking NSAIDs (flurbiprofen or ibuprofen) reported headache or drowsiness in three studies, and 9.9% experienced gastrointestinal symptoms such as vomiting or nausea.

In assessing effectiveness, it is important to determine whether it is low, moderate or high, and how certain a low, moderate or high effect is.

⁴⁸ Diagnoses were confirmed using thermal testing and/or electrical pulp testing and/or radiographs, and/or patient-reported symptoms or clinical and radiographic examination. Three studies reported no information on confirmation of diagnosis.

⁴⁹ Other agents that have not been directly compared are the following. Pain after 6-8 hours: paracetamol - NSAIDs; paracetamol - opioids; corticosteroids - NSAIDs + benzodiazepines; corticosteroids - opioids. Pain after 12 hours: opioids - NSAIDs + benzodiazepines; corticosteroids - opioids. Pain after 24 hours: tramadol - opioids; NSAIDs + benzodiazepines - NSAIDs + opioids; NSAIDs + benzodiazepines - corticosteroids; corticosteroids - opioids.

⁵⁰ The working group re-ran the network meta-analysis and did so as a frequentist network meta-analysis. This was done with netmeta and meta packages of R version 4.0.2 (RStudio, Boston, MA). The reasons for redoing the network meta-analysis were: 1) GRADE for network meta-analysis requires both direct and indirect effect estimation. The review by Zanjir et al. (2020) does not provide it; 2) the table of pain intensities for the different analgesics at different time points (table 2) contains obvious errors, in both Ryan 2008 and Salarpoor 2013. The study group consulted the original studies and used the correct data.

The study group uses the following criteria for classification by degree of effectiveness (measured on a 0-100 VAS scale) with respect to reduction of postoperative pain:

- an average difference >-10 is a trivial effect;
- an average difference >-20 and ≤-10 is a small but significant difference;
- an average difference >-30 and ≤-20 is a fairly large difference;
- an average difference ≤-30 is a large difference.⁵¹

This classification plays an important role in assessing the quality of evidence and drawing conclusions.

For information, three of the included studies included patients with pulpitis in addition to patients diagnosed with pulpal necrosis, approximately 37%. None of these studies reported outcomes related to pain intensity by diagnosis type. This was apparently done on the assumption that there is no evidence to expect a difference in this regard.

Quality of evidence

To assess the GRADE criterion of imprecision, the following applies. When the confidence interval crosses one threshold, it is downgraded by one level, when crossing two thresholds by two levels, and when crossing three thresholds by three levels. An example. NSAIDs compared with placebo reduce pain (after 6-8 hours) by 20.69 on 0-100 VAS scale. The confidence interval is -28.03; -13.35. The confidence interval crosses the value 20: thus, downgrading by one level. NSAIDs reduce pain (after 24 hours) compared with placebo by 16.77 on 0-100 VAS scale. The confidence interval is -24.49; -9.04. The confidence interval crosses the value 20 and 10: thus, downgrading by two levels.

Table 9-5 shows, for the NMA effect estimate and for both direct and indirect effect, the quality of evidence for postoperative pain at 6-8 and at 24 hours, with the reasons for discounting.⁵²

Table 9-5. Direct and indirect and network effect estimates (NMA effect) for postoperative pain and quality of evidence after postoperative medication

Analgesic vs. placebo	Direct effect [95% CI]	CoE‡,‡‡ ‡	Indirect Effect [95% CI]	CoE‡,‡‡ ‡	NMA Effect [95% CI]	CoE‡,‡‡‡
<i>Difference [MD] in pain intensity (0-100 VAS scale)§ after 6-8 hours</i>						
Paracetamol	3,00 [-19,52; 25,52]	High	-5,34 [-20,41; 9,73]	Fair (s-incon.)	-2,76 [-15,29; 9,77]	Fair (s-impr.)
Corticosteroids	-14,56 [-30,88; 1,76]	Low (s-RoB; s-incon.)	-	-	-14,56 [-30,88; 1,76]	Very low (vs. impr.)
NSAIDs	-26,01 [-35,38; -16,64]	Low (s-RoB; s-incon.)	-12,23 [-24,04; -0,42]	Fair (s-incon.)	-20,69 [-28,03; -13,35]	Low (s-impr.)*
NSAIDs + paracetamol	-16,19 [-24,98; -7,41]	Reasonable (s-incon.)	-27,91 [-41,15; -14,68]	High	-19,78 [-27,10; -12,46]	Fair (s-impr.)
NSAIDs + benzodiazepines	-14,70 [-38,61; 9,21]	Fair (s-RoB)	-28,04 [-52,49; -3,58]	Reasonable (s-RoB)	-21,22 [-38,31; -4,12]	Very low (vs. impr.)
NSAIDs + opioids	-18,69 [-37,70; 0,32]	Fair (s-RoB)	-21,47 [-37,83; -5,10]	Reasonable	-20,28 [-32,69; -7,88]	Very low (vs. impr.)

⁵¹ There are many studies showing that a difference of 10 on a 0-100 VAS scale is perceived by patients as a relevant reduction in pain. This is a small but significant effect. The remaining values 10-20, 20-30, 30+ were determined by the study group itself.

⁵² Outcomes are not shown for 12 and 48 hours postoperatively because insufficient data were available for several agents.

				(s-RoB)		impr.)
Opioids	-11,45 [-29,65; 6,75]	Fair (s-RoB)	-4,69 [-18,44; 9,07]	Low (s-RoB; s-incon.)	-7,15 [-18,12; 3,83]	Very low (s-impr.).
<i>Difference [MD] in pain intensity (0-100 VAS scale) § after 24 hours</i>						
Paracetamol	-	-	-	-	-	-
Corticosteroids	-14,90 [-31.85; 2.06].	Fair (s-incon.)	-		-14,90 [-31.85; 2.06].	Very low (vs. impr.)
NSAIDs	-21,13 [-30.89; -11.37].	Fair (s-incon.)	-9,44 [-22.08; 3.19].	Low (vs. Incon.)	16,77 [-24.49; -9.04].	Very low (vs. impr.)
NSAIDs + paracetamol	-9,60 [-23.18; 3.98].	Fair (s-incon.)	-21,30 [-36.81; -5.79].	Fair (s-incon.)	-14,68 [-24,89; -4,46]	Very low (vs. impr.)
NSAIDs + benzodiazepines	-2,50 [-24.51; 19.51].	Reasonable (s-RoB)	-14,92 [-38.69; 8.86].	Reasonable (s-incon.)	-8,23 [-24.38; 7.92].	Very low (vs. impr.)
NSAIDs + opioids	-12,05 [-31.41; 7.32].	Reasonable (s-RoB)	-21,25 [-38.21; -4.29].	Fair (s-incon.)	-17,26 [-30.01; -4.50].	Very low (vs. impr.)
Opioids	-1,90 [-19.51; 15.71].	Low (s-RoB; s-incon.)	1,89 [-12.35; 16.13]	Fair (s-incon.)	0,39 [-10.68; 11.47]	Theylook low (vs. impr.)

‡‡Cursive effect estimate contributes most to NMA effect and determines initial quality of evidence of NMA effect; ‡‡CoE: quality of evidence; S-RoB: serious risk of bias; s-incon.: serious inconsistency; vs-incon.: very serious inconsistency; s-impr.: serious imprecision; vs-impr.: very serious imprecision; incoh.: incoherence. §MD: mean difference.

Conclusions

	<i>(Endodontic) pain measured by 0-100 VAS scale, 6-8 hours after postoperative medication*</i>
	Considering all interventions, <u>NSAIDs + paracetamol</u> probably have a <i>small but significant beneficial</i> effect on postoperative pain and <u>paracetamol</u> probably has a <i>trivial</i> effect on postoperative pain (Table 9-6).
See last column of Table 9-6	All interventions considered, <u>NSAIDs, whether or not in combination with benzodiazepines or opioids</u> , appear to have a <i>moderately beneficial</i> effect on postoperative pain, but the evidence is highly uncertain (Table 9-6).
GRADE	All interventions considered, <u>corticosteroids</u> seem to have a <i>small but significant beneficial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-6).
	All interventions considered, <u>opioids</u> seem to have a <i>trivial</i> effect on postoperative pain, but the evidence is highly uncertain (Table 9-6).
	Zanjir et al, 2020

*patients had moderate to severe preoperative pain.

See last column of Table 9-7 GRADE	<i>(Endodontic) pain measured by 0-100 VAS scale, 24 hours after postoperative medication*</i>
	All interventions considered, <u>NSAIDs</u> , <u>whether or not in combination with paracetamol or opioids</u> , and <u>corticosteroids</u> seem to have a <i>small but significant beneficial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-7).
	All interventions considered, <u>NSAIDs + benzodiazepines</u> and <u>opioids</u> seem to have a <i>trivial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-7).
	Zanjir et al, 2020

*patients had moderate to severe *preoperative* pain.

Table 9-6. Classification of interventions based on network meta-analysis for postoperative endodontic pain after 6-8 hours after postoperative medication

Classification of intervention	Intervention	Mean difference [MD]§ (95% BI) after 6-8 hours	P-value*	Quality of evidence
Moderately large effect (≤ -20)	NSAIDs	-20,69 (-28,03; -13,35)	0,76	Low
	NSAIDs + benzodiazepines	-21,22 (-38,31; -4,12)	0,74	Very low
	NSAIDs + opioids	20,28 (-32,69; -7,88)	0,73	Very low
Small effect (> -20 & < -10)	NSAIDs + paracetamol	-19,78 (-27,10; -12,46)	0,72	Fair
	Corticosteroids	-14,56 (-30,88; 1,76)	0,53	Very low
Trivial effect (≥ -10)	Opioids	-7,15 (-18,12; 3,83)	0,28	Very low
	Paracetamol	-2,76 (-15,29; 9,77)	0,17	Fair
	Placebo	-		

* The higher the P value, and closer to 1, the more likely a therapy is at the top of the rank order of effectiveness; the closer 0 the more likely a therapy is at the bottom of the rank order of effectiveness. However, these P values do not take into account the clinical relevance of differences in reducing pain intensity nor the quality of evidence of effect size. §MD: mean difference.

Table 9-7. Classification of interventions based on network meta-analysis for postoperative endodontic pain after 24 hours following postoperative medication

Classification of intervention	Intervention	Mean difference [MD]§ (95% BI) after 24 hours	P-value*	Quality of evidence
Small effect (> -20 & < -10)	NSAIDs + opioids	-17,26 (-30,01; -4,50)	0,76	Very low
	NSAIDs	-16,77 (-24,49; -9,04)	0,76	Very low
	Corticosteroids	-14,90 (-31,85; 2,06)	0,66	Very low
	NSAIDs + paracetamol	-14,68 (-24,89; -4,46)	0,66	Very low

Classification of intervention	Intervention	Mean difference [MD]§ (95% BI) after 24 hours	P-value*	Quality of evidence
Trivial effect (≥-10)	NSAIDs + benzodiazepines	-8,23 (-24,38; 7,92)	0,42	Very low
	Opioids	0,39 (-10,68; 11,47)	0,12	Very low
	Paracetamol	-	-	-
	Placebo	-	-	-

* The higher the P value, and closer to 1, the more likely a therapy is at the top of the rank order of effectiveness; the closer 0 the more likely a therapy is at the bottom of the rank order of effectiveness. However, these P values do not take into account the clinical relevance of differences in reducing pain intensity nor the quality of evidence of effect size. §MD: mean difference.

[update 2022/3] What is the relative efficacy and safety of oral premedication on postoperative pain in patients with irreversible pulpitis?

Nagendrababu et al. (2019a) included 16 randomized studies evaluating six interventions in their systematic review and network meta-analysis:

- NSAIDs,
- corticosteroids,
- opioids,
- Cox-2 inhibitors
- Gabapentin, and
- Placebo.

Outcome measures were postoperative pain at 6, 12, and 24 hours, measured by a 0-100 VAS scale, 10-point VAS scale, or 0-170 VAS scale and adverse events.

Most studies were conducted in Iran (n=7) and India (n=4). A total of 1005 adults (17-65 years) were included. Nagendrababu et al. (2019a) did not mention a specific diagnosis, only that the patients required root canal treatment. Preoperative pain scores ranged from 20 to 88 on a 0-100 VAS scale, with the median value: 60.⁵³

The results of the network meta-analysis are presented in Table 9-8. NSAIDs seemingly emerge as least effective and corticosteroids as most effective.

Regarding the safety of analgesics, Nagendrababu et al. (2019a) mentioned the following: side effects reported for tapentadol [an opioid] and etodolac [an NSAID] were nausea, vomiting, headache, dizziness, and heartburn, while studies of ketorolac [an NSAID] reported headache and dizziness. One study of lornoxicam [an NSAID] reported gastrointestinal pain, while with respect to zintoma (a powder of ginger root), indomethacin [an NSAID], prednisolone [a corticosteroid], and ibuprofen [an NSAID], no side effects were reported.

Table 9-8. Relative effect on postoperative pain of premedication compared with placebo

Painkillers	Mean difference [MD]§ (95% BI) after 6 hours	Mean difference [MD]§ (95% BI) after 12 hours	Mean difference [MD]§ (95% BI) after 24 hours
1 NSAIDs	-8,39 (-21,17,4,39)	-7,70 (-17,46,2,07)	-4,56 (-16,31,7,20)
2 Corticosteroids	-18,14 (-32,90,-3,37)	-22,17 (-36,03,-8,32)	-21,50 (-37,95,-5,06)
3 Opioids	-11,99	-10,99	-11,15

⁵³ Nagendrababu et al. (2019a) did not mention the preoperative VAS score. Searching the original publications yielded ten preoperative scores. Three articles were in Iranian which made it impossible to look up the preoperative VAS score. Three other articles did not provide preoperative scores.

4	Cox-2 inhibitors	(-41,03,17,05)	(-37,57,15,58)	(-43,00,20,69)
		-	-18,06	-10,06
5	Gabapentin	(-53,05,16,94)	(-36,60,5,89)	(-44,76,24,64)
		-	-15,35	-12,33
6	Placebo	(-36,60,5,89)	(-38,16,13,49)	
		-	-	

§MD: mean difference.

In assessing effectiveness, it is important to determine whether it is minor, reasonable or major and how certain a minor, reasonable or major effect is.

The study group uses the following criteria for classification by degree of effectiveness (measured on a 0-100 VAS scale) with respect to reduction of postoperative pain:

- a mean difference >-10 is a trivial effect;
- an average difference >-20 and ≤-10 is a small but significant difference;
- an average difference >-30 and ≤-20 is a fairly large difference;
- an average difference ≤-30 is a large difference.⁵⁴

This classification plays an important role in assessing the quality of evidence and drawing conclusions.

Quality of evidence

For an explanation of the assessment of imprecision see page 181. *Table 9-9* shows for the NMA effect estimate and direct and indirect effect the quality of evidence for postoperative pain after 6-8 and after 24 hours with the reasons for discounting.

⁵⁴ There are many studies showing that a difference of 10 on a 0-100 VAS scale is perceived by patients as a relevant reduction in pain. This is a small but significant effect. The remaining values 10-20, 20-30, 30+ were determined by the study group itself.

Table 9-9. Direct and indirect and network effect estimates (NMA effect) for postoperative pain and quality of evidence after premedication

Medication vs. placebo	Direct effect [95% CI]	CoE‡,‡‡‡	Indirect effect [95% CI]	CoE‡,‡‡‡	NMA effect [95% CI]	CoE‡,‡‡‡
<i>Difference in pain intensity [MD]§ (0-100 VAS scale) after 6 hours</i>						
Corticosteroids	20,15 (4,67,35,63)	Low (vs. In-con.)	-6,86 (-61,66,47,94)	Very low (intran.; s-incon.)	18,14 (3,37,32,90)	Very low (vs. impr.)
NSAIDs	5,48 (-4,00,14,95)	Fair (s-incon.)	59,52 (16,72,102,31)	Very low (intran.; s-incon.)	8,39 (-4,39,21,17)	Very low (vs. impr.)
Opioids	-	-	11,99 (-17,05,41,03)	Very low (intran.; s-incon.)	11,99 (-17,05,41,03)	Very low (vs. impr.)
<i>Difference in pain intensity [MD]§ (0-100 VAS scale) after 12 hours</i>						
Corticosteroids	21,73 (6,19,37,27)	Fair (s-incon.)	27,73 (-23,31,78,77)	Very low (intran.; s-incon.)	22,17 (8,32,36,03)	Very low (vs. impr.)
NSAIDs	7,20 (-3,29,17,68)	Low (vs. In-con.)	23,43 (-34,86,81,71)	Very low (intran.; s-incon.)	7,70 (-2,07,17,46)	Very low (vs. impr.)
Opioids	-	-	10,99 (-15,58,37,57)	Very low (intran.; s-incon.)	10,99 (-15,58,37,57)	Very low (vs. impr.)
COX-2	-	-	18,06 (-16,94,53,05)	Very low (intran.; s-incon.)	18,06 (-16,94,53,05)	Very low (vs. impr.)
Gabapentin	16,70 (-9,04,42,44)	High	10,27 (-39,95,60,49)	Very low (intran.; s-incon.)	15,35 (-5,89,36,60)	Very low (vs. impr.)
<i>Difference in pain intensity [MD]§ (0-100 VAS scale) after 24 hours</i>						
Corticosteroids	21,56 (2,96,40,16)	Fair (s-incon.)	22,21 (-39,59,84,01)	Very low (intran.; s-incon.)	21,50 (5,06,37,95)	Very low (vs. impr.)
NSAIDs	3,79 (-8,72,16,30)	Low (vs. In-con.)	28,27 (-40,60,97,15)	Very low (intran.; s-incon.)	4,56 (-7,20,16,31)	Very low (vs. impr.)
Opioids	-	-	11,15 (-20,69,43,00)	Very low (intran.; s-incon.)	11,15 (-20,69,43,00)	Very low (vs. impr.)
COX-2	-	-	10,06 (-24,64,44,76)	Very low (intran.; s-incon.)	10,06 (-24,64,44,76)	Very low (vs. impr.)
Gabapentin	10,00 (-21,49,41,49)	High	20,96 (-39,84,81,75)	Very low (intran.; s-incon.)	12,33 (-13,49,38,16)	Very low (vs. impr.)

‡‡Cursive effect estimate contributes most to NMA effect and determines initial quality of evidence of NMA effect; ‡‡CoE: quality of evidence; s-incon.: serious inconsistency ; vs-incon.: very serious inconsistency; intran.: intransitivity; vs-impr.: very serious imprecision; §MD: mean difference.

Conclusions

See last column of Table 9-10 GRADE	<p><i>(Endodontic) pain measured by 0-100 VAS scale, 6 hours after preoperative medication*</i></p> <p>All interventions considered, <u>corticosteroids</u>, and <u>opioids</u> seem to have a <i>small but significant beneficial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-10).</p> <p>All interventions considered, <u>NSAIDs</u> seem to have a <i>trivial</i> effect on postoperative</p>
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	ve pain, but the evidence is very uncertain (Table 9-10). Nagendrababu et al., 2019a
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See last column of Table 9-11 GRADE	<p><i>(Endodontic) pain measured by 0-100 VAS scale, 12 hours after preoperative medication*</i></p> <p>All interventions considered, <u>corticosteroids</u> seem to have a <i>moderate, beneficial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-11).</p> <p>All interventions considered, <u>opioids, cox-2 inhibitors and gabapentin</u> seem to have a <i>small but significant beneficial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-11).</p> <p>All interventions considered, <u>NSAIDs</u> seem to have a <i>trivial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-11).</p> <p>Nagendrababu et al., 2019a</p>
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See last column of Table 9-12 GRADE	<p><i>(Endodontic) pain measured by 0-100 VAS scale, 24 hours after preoperative medication*</i></p> <p>All interventions considered, <u>corticosteroids</u> appear to have a <i>moderately large, beneficial</i> effect on postoperative pain, but the evidence is highly uncertain (Table 9-12).</p> <p>All interventions considered, <u>opioids, cox-2 inhibitors and gabapentin</u> seem to have a <i>small but significant beneficial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-12).</p> <p>All interventions considered, <u>NSAIDs</u> seem to have a <i>trivial</i> effect on postoperative pain, but the evidence is very uncertain (Table 9-12).</p> <p>Nagendrababu et al., 2019a</p>
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*patients had moderate to severe *preoperative* pain

Table 9-10. Classification of interventions based on network meta-analysis for postoperative endodontic pain at 6 hours after premedication

Classification of intervention	Intervention	Mean difference [MD] § in pain intensity (95% BI) after 6 hours	SUCRA*	Quality of evidence
Small effect (>-20 & <-10)	Corticosteroids	-18,14 (-32,90, -3,37)	83,5%	Very low
	Opioids	-11,99 (-41,03,17,05)	58,4%	Very low
Trivial effect (>-10)	NSAIDs	-8,39 (-21,17,4,39)	47,5%	Very low
	Placebo	-	10,6%	-

*SUCRA values range from 0 to 100%. The higher the SUCRA value and the closer to 100%, the more likely an intervention is to be in one of the top positions; the closer to 0 the SUCRA value, the more likely an intervention is to be in the bottom regions. §MD: mean difference.

Table 9-11. Classification of interventions based on network meta-analysis for postoperative endodontic pain at 12 hours after premedication

Classification of intervention	Intervention	Mean difference [MD] § in pain intensity (95% BI) after 12 hours	SUCRA*	Quality of evidence
Moderate effect (<-20)	Corticosteroids	-22,17 (-36,03, -8,32)	80,3%	Very low
Small effect (>-20 & <-10)	Cox-2	-18,06 (-53,05; 16,94)	62,4%	Very low
	Gabapentin	-15,35 (-36,60,5,89)	61,2%	Very low
	Opioids	-10,99 (-37,57, 15,58)	47,9%	Very low
Trivial effect (>-10)	NSAIDs	-7,70 (-17,46,2,07)	38,1%	Very low
	Placebo	-	10,1%	-

§MD: mean difference.

Table 9-12. Classification of interventions based on network meta-analysis for postoperative endodontic pain at 24 hours after premedication

Classification of intervention	Intervention	Mean difference [MD]§ in pain intensity (95% BI) after 24 hours	SUCRA*	Quality of evidence
Moderate effect (<-20)	Corticosteroids	-21,50 (-37,95,-5,06)	82,6%	Very low
Small effect (>-20 & <-10)	Gabapentin	-12,33 (-38,16,13,49)	57,5%	Very low
	Opioids	-11,15 (-43,00,20,69)	54,0%	Very low
	Cox-2	-10,06 (-44,76,24,64)	50,8%	Very low
Trivial effect (>-10)	NSAIDs	-4,56 (-16,31,7,20)	36,0%	Very low
	Placebo		18,9%	-

§MD: mean difference.

[update 2022/3] What is the relative effectiveness of local anesthetics for molars and premolars in the mandible, in terms of success of inferior alveolar nerve blockade, in patients with irreversible pulpitis? How safe are these local anesthetics?

Nagendrababu et al. (2019b) included 11 randomized studies with a total of 750 patients, both men and women, in their systematic review and network meta-analysis related to the above question. These studies were conducted in several countries (Brazil [n=5], Canada [n=1], India [n=3], Iran [n=1] and the United States [n=1]). Studies that investigated the anesthetic effect of inferior alveolar nerve blockade supplemented with infiltration anesthesia as well as studies that used premedication to increase the likelihood of success of inferior alveolar nerve blockade were excluded by Nagendrababu et al. (2019b).

The age of the patients ranged from 18 to 57 years. The following five anesthetics were compared: mepivacaine, lidocaine, articaine, bupivacaine and prilocaine. The four anesthetics lidocaine, articaine, bupivacaine and mepivacaine contained adrenaline as a vasoconstrictor while prilocaine was combined with felypressine as a vasoconstrictor. Not all studies used the same amounts of an anesthetic and vasoconstrictor. For example, some studies gave 3.6 ml of 2% lidocaine with 1 : 100 000 adrenaline, others 1.8 ml of 2% lidocaine with 1 : 200 000 adrenaline.

Outcome measure was success of an inferior alveolar nerve blockade evaluated during access to the root canal and pulpectomy of teeth in the mandible (molars and premolars) with irreversible pulpitis. A network meta-analysis examined, among other things, the success rate of the listed anesthetics for inferior alveolar nerve blockade, all compared with lidocaine. Because these agents were compared with lidocaine, the agents can be compared among themselves.

The results of the network meta-analysis are presented in Table 9-13. Mepivacaine and prilocaine seemingly emerge as the most effective and articaine and bupivacaine as the least effective, both for molars and molars + premolars.⁵⁵

⁵⁵ Nagendrababu et al. (2019b) mentioned that "separate analysis for pre-molars could not be performed due to the limited number of studies."

Table 9-13. Relative effect of local anesthetics on success of nervus alveolaris inferior blockade, compared to LIDOCAINE⁵⁶

Anesthetic	% success (95% BI) (molars + premolars)	% success (95% BI) (molar)
1 mepivacaine	18,5% (1,8%; 41,8%)	17,2% (1,3-38,3%)
2 articaine	7,0% (0,9%; 14,1%)*	7,0% (-2,6; 19,4%)
3 bupivacaine	5,3% (-8,8%; 24,6)	6,6% (-5,7; 22,4%)
4 prilocaine	14,1% (-15,0%; 71,7%)	12,8% (-15,0; 66%)

*This is the direct effect estimate and not the network effect estimate. See quality of evidence for an explanation.

Regarding medication safety, Nagendrababu et al. (2019) mentioned the following:

- prilocaine is associated with a significant increase in paresthesia and greater risk of methemoglobinemia,
- bupivacaine has some risk of cardiac and CNS toxicity.

The Pharmacotherapeutic Compass and Lareb report that during pregnancy the listed anesthetics are probably safe.

In assessing effectiveness, it is important to determine whether it is low, moderate or high, and how certain a low, moderate or high effect is.

The working group uses the following criteria for classification by degree of effectiveness/success:

- a percentage <10 is a trivial effect;
- a percentage ≥10 and <20 is a small but significant success;
- a percentage ≥20 and <30 is a reasonable success;
- a percentage ≥30 is a great success.⁵⁷

This classification plays an important role in assessing the quality of evidence and drawing conclusions.

Quality of evidence

To assess the GRADE criterion of imprecision, the following applies. When the confidence interval crosses one threshold (e.g., a success rate of 10) is downgraded by one level, when crossing two thresholds (e.g., success rates of 10 and 20) by two levels, and when crossing three thresholds by three levels.

For the assessment of the GRADE indirectness criterion, the following applies. The fact that the same amounts of an anesthetic and vasoconstrictor were not used in all studies means that much of the evidence is indirect evidence. Therefore, we downgraded by one level for serious indirectness.

Note regarding articaine estimates: the confidence interval of the network estimate is wider than that of the direct estimate. Usually, on the contrary, the confidence interval of the network estimate is narrower. After all, this is one of the purposes of a network meta-analysis: a more precise estimate of the effect. A wider confidence interval sometimes occurs and is a consequence of little data for some comparisons (Brignardello-Petersen et al., 2019). Therefore, the direct effect estimate rather than the network effect estimate is used for articaine.

Table 9-14 shows for the NMA effect estimate and for both direct and indirect effect, the quality of evidence for success of *inferior alveolar nerve* blockade (with reasons for depreciation).

⁵⁶ All effects were converted by the working group from the risk ratios reported by Nagendrababu et al. (2019b) to absolute differences based on the median success rate that can be calculated from the success rates reported for lidocaine in Table 1 of Nagendrababu et al. (2019).

⁵⁷ This classification was made by the working group and based on the fact that the studies in which lidocaine was evaluated showed a median success rate of 44%.

Table 9-14. Direct and indirect and network effect estimate (NMA effect) for success of inferior alveolar nerve blockade (for molars + premolars) and quality of evidence of local anesthetics⁵⁸

Local anesthetic vs. lidocaine	Direct e [95% CI]	CoE‡,‡‡ ‡	Indirect Effect [95% CI]	CoE‡,‡‡‡	NMA Effect [95% CI]	CoE‡‡
mepivacaine	20,2% (1,8; 47,1%)	Low (s-RoB; s-indir.)	11,9% (-20,2; 86,2%)	Low (s-RoB; s-indir.)	18,5% (1,8%; 41,8%)	Very low (vs. impr.)
articaine	7,0% (0,9; 14,1%)	Very low (s-RoB; s-indir.; s-impr.)	40,9% (-16,7; 100,0%)	Low (s-RoB; s-indir.)	9,2% (-0,4; 20,7%)	Very low (vs. impr.)
bupivacaine	7,9% (-4,8; 24,6%)	Low (s-RoB; s-indir.)	-20,7% (-39,2; 59,4%)	Low (s-RoB; s-indir.)	5,3% (-8,8; 24,6%)	Very laag (vs-impr.)
prilocaine	58,5% (-11,4; 100%)	Fair (s-RoB)	27,7% (-26,8;100,0%)	Low (s-RoB; s-indir.)	14,1% (-15,0; 71,7%)	Very low (vs. impr.)

‡Cursive effect estimate contributes most to NMA effect and determines initial quality of evidence of NMA effect, imprecision not assessed; ‡‡CoE: quality of evidence; S-RoB: serious risk of bias; s-impr.: serious imprecision; vs-impr.: very serious imprecision; s-indir.: serious indirectness.

Conclusions

See last column of Table 9-15	<i>Success of local anesthetics for inferior alveolar nerve blockade for molars + premolars (reference: lidocaine)*</i>
	All interventions considered, <u>mepivacaine</u> and <u>prilocaine</u> seem to have a <i>small but significant success</i> , but the evidence is very uncertain (Table 9-15).
GRADE	All interventions considered, <u>articaine</u> and <u>bupivacaine</u> seem to have a <i>trivial</i> effect, but the evidence is very uncertain (Table 9-15).
	Nagendrababu et al., 2019b

*Supposed median success rate of 44 for inferior alveolar nerve blockade was derived from the studies in which lidocaine was examined.

⁵⁸ All effects were converted by the study group from the risk ratios reported by Nagendrababu et al. (2019) to absolute differences based on the median success rate that can be calculated from the success rates reported for lidocaine in Table 1 of Nagendrababu et al. (2019).

Table 9-15. Classification of interventions based on network meta-analysis for success rate of inferior alveolar nerve blockade (for molars + premolars) of local anesthetics compared to lidocaine

Classification of intervention	Intervention	Success rate of al-veolar nerve inferior blockade	P-value*	Quality of evidence
Moderately large effect ($\geq 20\%$ and $< 30\%$)				
Small effect ($\geq 10\%$ and $< 20\%$)	mepivacaine	18,5% (1,8%; 41,8%)	0,81	Very low
	prilocaine	14,1% (-15,0; 71,7%)	0,62	Very low
Trivial effect ($< 10\%$)	articaine	7,0% (0,9; 14,1%)	0,54	Very low
	bupivacaine	5,3% (-8,8; 24,6%)	0,41	Very low
	lidocaine	-	0,13	

* The higher the P value, and closer to 1, the more likely a therapy is at the top of the rank order of effectiveness; the closer 0 the more likely a therapy is at the bottom of the rank order of effectiveness. However, these P values do not take into account the clinical relevance of differences in degree of success nor the quality of evidence of effect size.

Considerations

Regarding *antibiotics in the context of pain management*:

- The *quality of evidence* is low that penicillin does not reduce pain more than placebo.
- The *quality of evidence* is low that penicillin does not reduce the use of analgesics such as ibuprofen or paracetamol.
- The quality of evidence is very low that penicillin reduces swelling no more than placebo.
- A major undesirable effect of an antibiotic such as penicillin is increase in resistance.
- Because penicillin is unlikely to be effective as an analgesic and may lead to resistance, there is no reason to use an antibiotic as an analgesic.

[Update 2022/3] Relating to inclusion of an intracanal medication and not inclusion of intracanal medication in the context of pain management:

- The *quality of evidence* is very low for (strong) reduction of postoperative pain by the inclusion of an antibiotic combination, calcium hydroxide and chlorhexidine as an intra-canal medication as well as for differences between intra-canal medications regarding reduction of postoperative pain.
- There are also many disadvantages to the use of an intravenous drug according to the working group (see rationale) so that the benefits of reduced postoperative pain do not outweigh these disadvantages

[Update 2022/3] Relating to refrigerated and non-refrigerated irrigants in patients with irreversible pulpitis or pulpal necrosis in the context of pain management:

- The *quality of evidence* ranges from low to fair that cooling provides a small (6-24 hours post-operatively) and no (48-72 hours postoperatively) reduction in postoperative pain, respectively.
- Additional measures (e.g., refrigerator for separate storage of syringe cooled irrigants) are needed for irrigant cooling. According to the study group, this does not outweigh the small ef-

fect of cooling on postoperative pain.

[Update 2022/3] Relating to postoperatively given oral analgesics in patients with irreversible pulpitis or pulpal necrosis in the context of pain management:

- The *quality of evidence* is reasonable that paracetamol (6-8 hours postoperatively) provides little or no reduction in postoperative pain.
- The *quality of evidence* is low to fair that NSAID + paracetamol (6-8 hours postoperatively) and NSAID provides a relevant reduction in postoperative pain.
- The quality of evidence is very low that NSAID + paracetamol and NSAIDs (24 hours postoperatively) provide a relevant reduction in postoperative pain. For paracetamol, the quality of evidence is lacking regarding pain intensity 24 hours postoperatively.
- It is the practical experience of the study group members that analgesia with paracetamol is often sufficient. The fact that the network meta-analysis shows that paracetamol probably has no effect may be explained by the fact that the pain intensity of the patients in the studies is significantly higher than in practice. If there is evidence of significant afterpain in patients, the combination of NSAID and paracetamol should be preferred.

[Update 2022/3] Relating to oral premedication in patients with irreversible pulpitis or pulpal necrosis in the context of pain management:

- The quality of evidence is very low that NSAIDs (6, 12 and 24 hours postoperatively) do not reduce pain intensity much, if at all.
- The quality of evidence is very low that corticosteroids (6, 12 and 24 hours postoperatively) reduce pain intensity to a mild to reasonable degree.
- The quality of evidence is very low that opioids, cox-2 inhibitors and gabapentin slightly reduce pain intensity.
- The study group believes that both because of the very low strength of evidence and because of the fact that only "heavy" premedication, such as corticosteroids, seems to have a significant effect on postoperative pain, while "lighter" postoperative analgesics, such as the combination of paracetamol and NSAIDs have at least as great an effect, premedication has no place in pain management.

[Update 2022/3] Regarding success of inferior alveolar nerve blockade of local anesthetics:

- Quality of evidence is very low (i.e., relatively high uncertainty about degree of success) for all anesthetics discussed
- Mepivacaine and prilocaine both may have a small but significant beneficial effect on postoperative pain.

One study gave 1.8 or 3.6 ml of 2% mepivacaine with 1 : 100 000 adrenaline, two studies gave 3.6 ml of 2% mepivacaine with 1 : 100 000 adrenaline.

Applicability: mepivacaine (in combination with adrenaline) is not available in the Netherlands,

Regarding *incision related to swelling*:

- No studies were found that met the inclusion criteria.
- Expert opinion as contained in the syllabus "the endodontic emergency treatment in practice" (2011) was used. The proposed incision will quickly reduce pain and swelling and may allow further endodontic treatment to take place at a later stage.

Recommendations

The recommendations below apply to patients in whom the symptomatic tooth has not previously been treated endodontically by the general practitioner or dental endodontist.

Use of antibiotics in acute complaints related to irreversible pulpitis or symptomatic apical periodontitis and acute apical abscess is not recommended in the context of pain management.

[unchanged after update 2022/3]

Rationale

The guideline working group gave considerable weight to the finding that an antibiotic is unlikely to be effective as an analgesic and may lead to resistance and hypersensitivity.

*As part of pain management, consider **not** using an intracanal medication.*

[update 2022/3: new recommendation]

Rational

Although the use of chlorhexidine and calcium hydroxide as intracanal medicament has a beneficial effect on postoperative pain, the study group does not recommend it because of its various disadvantages. For example, calcium hydroxide is difficult to remove, dentin weakens with prolonged presence of an intracanal medication, adhesion of the filling material is impaired and an unfavorable shift in biofilm may occur.

The working group does not recommend cooling irrigants.

[update 2022/3: new recommendation]

Rational

The study group believes that additional measures to provide cooling irrigants are disproportionate to the small effect they might be expected to have on postoperative pain.

Use of premedication is not recommended.

[update 2022/3: new recommendation]

Rationale

Premedication seems to be effective only when using relatively 'heavy' analgesics, such as corticosteroids. 'Lighter' agents such as paracetamol and NSAIDs have at least the same effect when given *post-operatively*.

The study group does not provide a recommendation regarding mepivacaine.

[update 2022/3: new recommendation]

Rationale The study group has noted the promising results of mepivacaine (i.c.w. adrenaline) but notes that this drug is not available in the Netherlands. The use of articaine and bupivacaine can be continued.

In cases of fluctuating swelling, an abscess incision is indicated.

Patients with severe swelling who also have fever and/or swallowing symptoms should be referred to an MKA surgeon immediately for treatment.

[unchanged after update 2022/3]

Rational

The proposed incision will quickly reduce pain and swelling and may allow further endodontic treatment to take place at a later stage.

As analgesia, in acute complaints associated with irreversible pulpitis or symptomatic apical periodontitis, paracetamol (whether or not in combination with an NSAID) can be given. If this medication does not provide adequate analgesia, the WHO pain ladder can be consulted (see Appendix 2 in Chapter 9 of this guideline).

Use of the combination paracetamol and codeine is not recommended.

[unchanged after update 2022/3]

Rational

Paracetamol can be used safely. [update 2022/3] *In severe postoperative pain, there is a reasonable degree of certainty that paracetamol is ineffective and the combination of paracetamol and NSAIDs or NSAIDs alone provide adequate analgesia.* Use of NSAIDs may be contraindicated in patients. The efficacy of the paracetamol-codeine combination has not been demonstrated in clinical studies. The advice regarding paracetamol/NSAIDs and the WHO pain ladder is taken from the NHG standard "Pain.

If there is a previously endodontically treated element

All of the above recommendations and treatment strategies also apply to these. However, the treatment of these elements is more challenging because the old canal treatment will have to be removed first. In such cases, it is worth considering referring the patient to a dental endodontist. If the treatment is not going to be performed immediately, pain relief can also be prescribed in this case.

[unchanged after update 2022/3]

Rational

The guideline working group sees no reasons (pathophysiological or practical) why the recommendations formulated in connection with acute complaints in an element not previously endodontically treated should not be applicable for an element that has been previously endodontically treated.

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Appendix 9.1 Search strategy

Source: PubMed

("emergency"[title] OR "emergencies"[title] OR "acute"[title] OR "exacerbation"[title] OR "symptomatic"[title] OR "acute disease"[MeSH Terms] OR "emergencies"[MeSH Terms]) AND ("Pulpitis"[MeSH Terms] OR "Pulpectomy"[MeSH Terms] OR "Pulpotomy"[MeSH Terms] OR "Periapical Periodontitis"[MeSH Terms] OR "pulpitis"[title] OR "pulpotomy"[title] OR "pulpectomy"[title] OR "apical periodontitis"[title] OR "endodontic"[title] OR (("dental"[title] OR "pulpal"[title] OR "tooth"[title]) AND ("pain"[title] OR "painful"[title])))

AND

((("evaluation"[title] OR "observational"[Title] OR "Clinical report"[Title] OR "Follow-Up Studies"[Mesh Terms] OR "comparative study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "review"[Publication Type] OR "retrospective"[Title] OR "retrospective studies"[MeSH Terms] OR random*[Title/Abstract] OR allocat*[Title/Abstract] OR systematic[sb] OR "time factors"[MeSH Terms]))

Publication date: ≥2010; Humans; English

Appendix 9.2 WHO pain ladder

WHO pain ladder as adopted from the NHG standard Pain.

- Step 1: paracetamol;
- Step 2: NSAID;
- Step 3: add tramadol (weak-acting opiate) to paracetamol or NSAID if they have insufficient effect;
- Step 4: strong-acting opiates (oral or patch) and

Step 5: subcutaneous or intravenous administration of strong-acting opiates.

10. Permanent and temporary restoration of elements

Introduction⁵⁹

The goal of root canal treatment is not only an infection-free, healthy but also a functional tooth. In other words, some form of restoration is needed after completion of the root filling to protect this element from fracture and leakage to prevent reinfection. The complexity of the restoration is generally determined by the degree of tissue loss. Coronal tissue may be lost due to caries, fracture or previously fabricated restoration.

If the crown is lost for the most part, it is not unusual to place a root post for additional retention and resistance of the coronal restoration.

When selecting the type of restoration, the practitioner must consider a number of factors. Tissue loss has weakened a tooth, and there is a risk that mechanical forces from chewing or from clamping the teeth together will lead to crown and crown root fractures. However, little is known about the causes of this type of complication. An indirectly fabricated crown that encompasses the dentition and covers the nodes is thought to provide more protection than intra-coronary restorations that merely replace the missing tooth tissue. Nevertheless, in cases of limited structural loss of an element, a full crown may be an unnecessarily expensive treatment option, which incidentally also requires removal of healthy tooth tissue. It is therefore important for the practitioner to know which type of coronal restoration leads to better preservation of elements that have undergone root canal treatment, not least because of cost considerations.

When most or all of the coronary structure is lost, an artificial crown must be made for replacement. This can be done on site - directly in the mouth - or in a laboratory by a dental technician. A prefabricated or cast root post with build-up may improve the crown's resistance but may lead to weakening of the root or complications. A root post can also increase the risk of root fracture.

An endocrown is another indirectly fabricated one-piece restoration that performs the function of buildup and crown. The endocrown is anchored in the pulp chamber and also adhesively attached to the outline, providing both macro- and micro-mechanical retention.

Sometimes an element where root canal treatment is performed is provided with a temporary coronal restoration, that is, a restoration applied between treatment sessions in which the root canal is sealed to protect against bacterial penetration, and to protect the remaining structure of the element from fracture. Temporary restorations are also applied to control the outcome of endodontic treatment before proceeding to a permanent root filling and restoration. Many different temporary materials are used. However, there is still little information available to answer the question of which materials most effectively prevent bacterial invasion and fracture during root canal treatment. There is also the question of how to adequately close an element with a temporary restoration and keep the pulp chamber and canals accessible for continued canal treatment in a subsequent treatment session.

⁵⁹ This introduction is based in part on *Methods of Diagnosis and Treatment in Endodontics. A systematic review (2012)* and supplemented where necessary.

Specific questions are:

1. What factors influence the survival of a tooth that has undergone root canal treatment?
2. What factors are associated with change in periapical status, insofar as the initial PAI score is ≥ 2 ?
3. What is the relative effect of root canal filling and coronal restoration on the outcome peri-odontitis apicalis?
4. What are causes of failure of restorations with different types of fiber-reinforced posts combined with a synthetic resin cement or "passive" posts with a traditional cement (zinc phosphate or glass ionomer cement)?
5. What is the effect of the amount of remaining coronal dentin and placement of prefabricated or an individual fiber-reinforced post on the survival of endodontically treated teeth?
6. Is there a difference in effect between restorations with a cast post structure, or with prefabricated posts or a composite restoration without a post?
7. Is there a difference in effect between indirect restoration (metal-ceramic crown) with post compared to adhesive composite?
8. Is there a difference in effect between restorations with metal pins compared to restorations with fiber-reinforced pins?
9. Is there any difference in effect between restoration with post and crown compared to restoration with crown only?
10. Is there a difference in effect between direct posterior composite and indirect posterior composite restorations for excessive tissue loss of a molar?
11. *[update 2022/3]* Is there a difference in effect between an endocrown and a conventional crown in the case of damaged endodontically treated teeth?
12. *[update 2022/3]* Is there any difference in effect between a cotton ball or Teflon as 'endodontic space maintainer' ?

Search and selection

A literature search was conducted in PubMed/Medline on September 10, 2016. See Appendix 10.1. 266 studies were found, of which 12 met the inclusion criteria (Ng et al., 2010; Rasimick et al., 2009; Gillen et al., 2011; Ferrari et al., 2012; Ploumaki et al., 2013; Koyuturk et al., 2013; Tsesis et al., 2013; Sarkis-Onofre et al., 2014; Yang et al., 2015; Sequeira-Byron et al., 2015; Figueiredo et al., 2015; Sorrentino et al., 2016). In addition, 4 studies from the eponymous chapter in the Swedish MTA report were included (Valderhaug et al., 1997; Ferrari et al., 2007; Salvi et al., 2007; Cagidiaco et al., 2008). *[Update 2022/3]* Added 1) editorials or commentaries related to key studies and 2) (articles from) systematic reviews of sufficient methodological quality (AlSaleh et al., 2021; De Kuijper et al., 2021; Martins et al., 2021; Mathew et al., 2021; Batista et al., 2020; Govare & Contrepolis, 2020; Khatab & Abdelhafez, 2020; Ferrari et al., 2019; Prabhakar et al., 2018; Brignardello-Petersen, 2018, 2017; Olsson et al., 2017; Sarkis-Onofre et al., 2017; Yee et al., 2017; Skupien et al., 2016).⁶⁰

Selection Criteria

Type of patients	- permanent teeth with (partially) filled root canals that require restoration or construction
Type of Intervention	- restoration or reconstruction of lost tooth substance, with or without post retention
Check	- temporary or permanent restorations, with or without marker retention - Control group and/or comparison for relevant factors in the cohort
Type of outcome measures	- long-term survival of restoration and element - follow-up duration of at least one year for permanent restorations - patient satisfaction - quality of life - caries - periodontal status

⁶⁰ For methodological assessment of the systematic reviews, see pp. **Fout! Bladwijzer niet gedefinieerd.**

	- cost
Type of setting	- general practitioners - dental endodontists
Inclusion and exclusion criteria	Inclusion criteria: - (quasi-) randomized trials - comparative (including various prognostic factors) observational studies - human in vivo studies - individual element is basis for evaluation Exclusion criteria: - non-comparative observational studies - in vitro, ex vivo (human) studies

Summary of literature

What factors influence the survival of a tooth that has undergone root canal treatment?

The review by Ng et al. (2010) included 14 studies that examined what factors influenced the survival of a tooth that had undergone root canal treatment.

Of these 14 studies, only 3 studies (Caplan et al., 2002, 2005; Aquilino & Caplan, 2002) applied multivariate analysis and explicitly tested a hypothesis. The main purpose of applying multivariate analysis is to avoid "sham relationships".

The hypotheses in the 3 studies mentioned were:

1. Aquilino & Caplan (2002) tested the hypothesis of whether placement of a crown ("crown covering") is associated with better survival of an element that has undergone root canal treatment.
2. Caplan et al. (2002) tested the hypothesis that two proximal contacts at access is associated with better survival.
3. Caplan et al. (2005) tested that elements that had undergone root canal treatment were more likely to be removed than elements that had not undergone root canal treatment.

Aquilino & Caplan (2002) found that endodontically treated elements on which a crown was *not placed* after closure were six times more likely to be extracted within a 5- to 10-year period.

Caplan et al. (2002) found that elements with ≤ 1 proximal contact were three times more likely to be extracted within a 5- to 10-year period.

Caplan et al. (2005) found that elements that had undergone root canal treatment were more likely to be extracted within a 5- to 10-year period. A clear difference was observed between non-molars and molars to the detriment of molars: molars that had undergone root canal treatment were more than seven times more likely to be extracted than molars without root canal treatment, while non-molars were almost twice as likely. A retrospective study not included in this review (Skupien et al., 2013) also found that anterior element restorations and premolars had a lower risk of restoration failure (HR: 0.45 and 0.59 with 95% BI: 0.25 - 0.82 and 0.38 - 0.92, respectively).

The remaining 11 studies limited themselves to univariate analyses with the aim of detecting one or more factors that have a significant on survival (see Table 10-1).

Main findings from studies with *univariate* analysis:

- None of the studies found an effect of *gender or age* on element survival.
- The effect of *practitioner qualification* on element survival is inconsistent.
- *Preoperative pain, a non-vital pulp, periodontitis apicalis, a preoperative pocket or a periapical lesion* seem to reduce the probability of element survival.
- *A root canal filling more than 2 mm ending before the root tip* seems to reduce the probability of element survival.

- Elements that acted as an "abutment" for a fixed or removable prosthesis appear to have a lower probability of survival.

Combining all studies, Ng et al. (2010) found the following rates for 2-3, 4-5 and 8-10 year survival of endodontically treated elements: 86% (95% BI: 75-98%), 93% (95% BI: 92-94%) and 87% (95% BI: 82-92%). Thus, almost 90% of elements that have undergone root canal treatment have a minimum lifespan of approximately 10 years.

[Update 2022/3] To what extent does later placement of a (post) superstructure and crown after non-surgical endodontic treatment affect the survival of treated teeth is a question that Yee et al. (2017) investigated in a large database (n=160040 patients) based observational study. The average age of the patients was 45 years (SD: 13 years). 55.4% involved a treated molar, 31.4% a premolar, and 13.2% an anterior element. 29% of endodontic treatments were performed by an endodontist. 38% received a post build-up, 62% build-up without a post, and 80% a metal crown. Overall element survival after crown placement was 99.1% after 1 year, 96.0% after 3 years, 92.3% after 5 years and 83.8% after 10 years.⁶¹

No significant differences were seen in the survival of an element between patients who received a (post) buildup 15-59 days after endodontic treatment and those who received it after 0-14 days, or between patients who received a crown 15-59 days after placement of a (post) buildup and those who received it after 0-14 days (Hazard ratios: 0.96 ; 95% BI: 0.91-1.01 and 0.98; 95% BI: 0.92-1.04, respectively). Placement of a (post) build-up more than 60 days after endodontic treatment showed a 1.08-fold higher risk of element non-survival versus a (post) build-up placed 0-14 days after endodontic treatment (Hazard ratio: 1.08; 95% BI: 1.02-1.15). Crowns placed 60 or more days after placement of a (post) buildup had a 1.14 times higher risk of element non-survival versus a crown placed 0-14 days later (Hazard ratio: 1.14; 95% BI: 1.08-1.21). However, in absolute terms, the differences are small and may not be significant for a patient: 1% to 2% and 1% to 2.5% less survival of an element after 5-10 years when placement of a (post-) buildup occurred more than 60 days after endodontic treatment and placement of a crown more than 60 days after placement of a (post-) buildup, respectively. (Brignardello-Petersen, 2018).

[Update 2022/3] To what extent, when applying a partial crown of lithium disilicate, whether or not to use a post has an effect on the survival of an element (molar or premolar) is a question Ferrari et al. (2019) investigated.⁶² Ferrari et al. (2019) randomized 120 consecutive patients (56 elements in the maxilla and 64 in the mandibula with at least 50% of the coronal structure intact) to two groups of 60 patients. One group received a marker, the other group did not. Both groups were undivided into subgroups: molars (n=30) and premolars (n=30). The study population consisted of 55 men and 45 women, ranging in age from 18 to 69 years. Overall three-year survival was 100% in the case of molars, both in those in whom a post was placed during endodontic treatment and in those in whom no post was placed, and in the case of premolars when a post was placed. When no marker was placed in the case of premolars, survival after three years was 93.3%.⁶³

Comparing no marker versus marker gives a Hazard Ratio of 0.388; 95% BI: 0.1-1.5): no marker seems to give slightly shorter survival (molars and premolars taken together). Comparing premolar versus molar gives a Hazard Ratio of 0.123; 95% BI: 0.015-0.997).

Quality of evidence prognostic factor placement of crown on endodontically treated element, number of proximal contacts, yes/no root canal treatment, molar/no molar, survival 3-5 years

⁶¹ Elements were classified as surviving if no endodontic re-treatment, apical resection or extraction occurred during the follow-up period.

⁶² This randomized study was the only study found by Ferrari et al. (2022) in their systematic review titled "Survival Rates of Endodontically Treated Posterior Teeth Restored with All-Ceramic Partial-Coverage Crowns: When Systematic Review Fails."

⁶³ Survival was defined as the absence of absolute failure: root fracture leading to extraction of the element, crown fracture and periapical lesion requiring re-treatment.

Regarding Ng et al. (2010): The quality of evidence was assessed only from the studies that applied multivariate analysis (Aquilino & Caplan, 2002; Caplan, 2002; 2005). The quality of evidence was moderate for the prognostic factors examined in Aquilino & Caplan (2002), Caplan (2002) and Caplan (2005; yes/no root canal treatment). The quality of evidence was downgraded by one because of selection bias and limitations in statistical analysis (insufficiently controlled for confounders). For the prognostic factor molar versus nonmolar examined in Caplan (2005), it was also downgraded for imprecision because no confidence interval was reported. See Appendix 10.2.

[Update 2022/3] Regarding Yee et al. (2017) and Brignardello-Petersen (2018): the quality of evidence from observational studies starts as low. No reason was found to downgrade for other GRADE factors. Regarding Ferrari et al. (2019): due to ambiguity regarding the randomization procedure and lack of information on allocation blinding, the quality of evidence was downgraded by one level for risk of bias. There was downgraded by one level for indirect evidence due to limited follow-up duration (three years). Furthermore, one level was downgraded for imprecision as evidenced by the very wide confidence intervals. Thus, the quality of evidence is very low.

Conclusions

Fair	<i>Prognostic factor placement of crown on endodontically treated element</i>
GRADE	Placement of a crown on an endodontically treated element probably results in better element survival. Aquilino & Caplan, 2002
Fair	<i>Prognostic factor number of proximal contacts</i>
GRADE	Elements with >1 proximal contact are likely to have a better chance of element survival. Caplan et al., 2002
Fair	<i>Prognostic factor receiving versus not receiving root canal treatment</i>
GRADE	Elements that have undergone root canal treatment probably have a lower chance of survival than elements that have not undergone root canal treatment. Caplan et al., 2005
Low	<i>Prognostic factor molar versus non-molar</i>
GRADE	Non-molars may have a better chance of survival than molars. Caplan et al., 2005

Low GRADE	<p><i>Effect on long-term survival (5-10 years)</i></p> <p>60 days or later versus within 2 weeks after endodontic treatment placement of a (post) buildup and 60 days or later versus within 2 weeks after placement of a (post) buildup placement of a crown may have little effect on denture survival.</p> <p>Yee et al., 2017; Brignardello-Petersen, 2018</p>
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Very low GRADE	<p><i>Effect on long-term survival (3 years)</i></p> <p>When applying a partial crown of lithium disilicate, whether or not to use a post seems to have little or no effect on molar or premolar survival, but the evidence is very uncertain.</p> <p>Ferrari et al., 2019</p>
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Table 10-1 Potential prognostic factors for (worse) element survival

	Lazarski et al. (2001)	Aquilino & Caplan (2002)	Caplan et al. (2002)	Dammaschke et al. (2003)[temporary cement].	Alley et al. (2004)	Lynch et al. (2004)
Qualification practitioner	generalist vs. endontologist: NS				generalist RR: 5.42* vs. endodontist	
Gender	NS		NS	NS		
Age	NS	NS	NS	NS		
Ethnicity						
Medical condition			NS (medication for hypertension/heart)			
Element, type and location	Premolars: RR=1.10* Molars: RR=.14* both vs.front elements	Second molars: HR: 3.9 (2.0-7.9) relative to other elements†	Second molars: HR: 4.3 (1.8-10.2) vs. 1 ^e molar†	NS		
Preoperative pain						
Pulpa status						
Periapical status		NS			36% loss of elements in periapical lesion vs. 16% in absence of lesion (S)	
1st vs. 2nd root canal treatment			NS			
Preoperative pocket						
Preoperative cracks						
Degree and quality of filling root			NS	root canal filling ending > 2mm from root tip greater risk of element loss (S)	root canal filling ending > 2mm from root tip greater risk of element loss RR:1.75*	
Length of time between		NS				

	Lazarski et al. (2001)	Aquilino & Caplan (2002)	Caplan et al. (2002)	Dammaschke et al. (2003)[temporary cement].	Alley et al. (2004)	Lynch et al. (2004)
root filling and restoration						
Proximal contacts		NS	0 or 1 proximal contact: HR: 3.1 (1.9-5.1) relative to 2 proximal contacts.			
Type of restoration		No crown: HR: 6.0 (3.2-11.3) relative to crown	Crowned at entrance: HR: 6.1 (2.6-14.3) Never crowned: HR: 13.6 (7.1-26.1) Both vs. initial crowned after closure	retention post + crown less loss of element (S)		Temporary restoration (no crown): RR: 7.89* RR: 3.85* vs. cast or composite restoration
Type of core			NS	NS		
Presence and type of pin	cast pin assembly vs. prefabricated pin assembly RR:1.33*	NS				
Superstructure ("abutment").	multi-unit restorations vs. single-unit restorations RR: 1.54*				NS	

Continued Table 10-1

	Salehrabi & Rotstein (2004)	Tilashalski et al. (2004)	Caplan et al. (2005)	Stoll et al. (2005)	Tan et al. (2006)	Chen et al. (2007)	Salvi et al. (2007)
Qualification practitioner		generalist vs. end-ontologist: NS		student vs. dentist: NS			
Gender					NS		
Age							
Ethnicity					NS		
Medical condition							
Element, type and location			Molars worse survival than non-molars*†		Most posterior elements: RR: 4.9 (1.2-20)	Molar: RR: 1.25* Premolar: RR: 1.11* relative to front elements	NS
Preoperative pain				Painful: RR: 1.57* versus pain-free			
Pulpa status				Non-vital: RR: 1.68* vs. vital			
Periapical status				chronic apical periodontitis: RR: 3.00 vs. no chronic apical periodontitis			
1st vs. 2nd root canal treatment				NS			
Preoperative pocket					Present pocket: RR: 4.9 (1.2-20)*		
Preoperative cracks							
Degree and quality of filling root				root canal filling ending > 2mm from root tip greater			

	Salehrabi & Rotstein (2004)	Tilashalski et al. (2004)	Caplan et al. (2005)	Stoll et al. (2005)	Tan et al. (2006)	Chen et al. (2007)	Salvi et al. (2007)
				risk of element loss RR: 3.93*			
Length of time between root filling and restoration							
Proximal contacts							
Type of restoration	No crown: RR:5.69*						Single-unit metal-ceramic crown vs. Direct composite crown (NS)
	vs. crown with or without pin						
Type of core							
Presence and type of pin							NS (teeth Restored with the use of intra-radicular retention (prefabricated titanium stem or cast stem assembly vs. no stem)
Superstructure ("abutment").							

* p<0.05; †: multivariate analysis

What factors are associated with change in periapical status, insofar as the initial PAI score is ≥ 2 ?

Tsesis et al. (2013) examined through a cohort study what effect a number of factors may have on change in periapical status, insofar as the initial PAI score was ≥ 2 . These factors are: age, sex, follow-up duration, presence of a marker, quality of root canal filling and quality of coronal restoration.

The quality of root canal filling was evaluated radiographically, and described as "adequate" when all canals were closed, there were no voids, and the canal filling ended 0-2 mm before the radiographic apex. If the filling of the canal did not meet these criteria, its quality was described as 'inadequate'.

The quality of the coronal restoration was evaluated radiographically and was described as 'adequate' if a permanent restoration appeared radiographically intact. The coronal restoration was described as 'inadequate' when the permanent restoration showed detectable protrusions ('overhangs'), or with open edges and with recurrent caries.

74 patients with a total of 200 endodontically treated elements with a periapical lesion met the inclusion criteria (including presence of two consecutive complete evaluations of periapical status at least 4 years apart). 28.5% of lesions remained unchanged, 51.5% showed an increase in PAI score (ie, worsening), and 20% showed a decrease in PAI score (ie, improvement). In a multivariate analysis that presumably did not adjust for all confounders of interest (e.g., oral hygiene, crown/no crown) and did not provide information on the magnitude of effects, inadequate quality of root canal filling and restoration were found to have a negative effect on periapical lesion. Age, sex, and the presence of a marker had no significant effect.

Quality of evidence periapical status

Initial quality of evidence is reasonable because no hypothesis is tested. For risk of bias, it was downgraded by one level because it involved a select group of patients and the statistical analysis did not clarify the relative weight of the prognostic factors in terms of odds ratio or regression coefficient. Also, it was downgraded by one level because of imprecision: no confidence intervals were reported for the prognostic factors. Therefore, the quality of evidence is very low.

Conclusion

Very low	<i>Deterioration of periapical status</i>
GRADE	Insufficient quality of root canal filling and restoration seem to have a negative effect on the periapical lesion. Tsisis et al., 2013

What is the relative effect of root canal filling and coronal restoration on the outcome periodontitis apicalis?

The question of the review by Gillen et al. (2011) concerns which of the two, root canal filling or coronal restoration, has the greatest effect on the clinical outcome periodontitis apicalis. The reviewers defined three comparisons:

- *Adequate* coronal restoration and *adequate* root canal filling (AR/AE) versus *adequate* coronal restoration and *inadequate* root canal filling (AR/IE).
- *Adequate* coronal restoration and *adequate* root canal filling (AR/AE) versus *inadequate* coronal restoration and *adequate* root canal filling (IR/AE).
- *Inadequate* coronal restoration and *adequate* root canal filling (IR/AE) versus *adequate* coronal restoration and *inadequate* root canal filling (AR/IE).

An odds ratio was calculated for each of these comparisons, adjusting for significant confounders. These confounders were:

- type of evaluation (radiological evaluation versus radiological AND clinical evaluation);
- calibration assessors (calibration or no calibration);
- Use of 5-point scale for radiographic assessment of periapical status;
- yes versus no, and
- closure and length (both quality of lateral closure and length of root filling were evaluated versus evaluation of length only).

Gillen et al. (2011) were able to include 9 studies that met the inclusion criteria, including a follow-up duration of at least one year. The methodological quality of these studies was not assessed by the reviewers. Nor were the characteristics of the studies described.

Combining the data for each of the aforementioned comparisons indicates inconsistent results in all cases given the non-overlap of various confidence intervals and the spread in effect estimates. By combining the aforementioned confounders into four sets based on "data dredging," the reviewers reduced the inconsistency.

This yields the following results:

- AR/AE versus AR/IE: OR = 2.73; 95% CI, 2.40-3.11), i.e., adequate filling of the root canal gives a *lower* probability of periodontitis apicalis.
- AR/AE versus IR/AE (OR = 2.81; 95% CI, 2.40-3.29), i.e., adequate coronal restoration gives a *lower* probability of periodontitis apicalis.
- IR/AE versus AR/IE (OR = 1.04; 95% CI, 0.90- 1.20), or inadequate coronal restoration and adequate root canal filling gives the same risk of periodontitis apicalis as adequate coronal restoration and inadequate root canal filling.

Quality of evidence periodontitis apicalis

Apart from the lack of assessment of the methodological quality of the included studies, an important limitation is that the subgroup analysis is based on 'data dredging' (post hoc analysis) and not on pre-specified hypotheses. 'Data dredging' increases the likelihood of 'false' explanations and ditto outcomes (Cochrane Handbook, 9.6.6 'Interpretation of subgroup analyses and meta-regressions').

Conclusions

See quality of evidence GRADE	<i>Chance of periodontitis apicalis</i>
	Adequate coronal restoration and adequate filling of the root canal seem to be of equal importance in curing periodontitis apicalis.
	Gillen et al., 2011

What are causes of failure of restorations with different types of fiber-reinforced posts combined with a synthetic resin cement or "passive" posts with a traditional cement (zinc phosphate or glass ionomer cement)?

In a systematic review, Rasimick et al. (2009) investigated which causes underlie the failure of a restoration if root posts as mentioned above were involved, the follow-up duration was at least two years, and one of the study groups had at least 50 elements. They distinguished the following causes: root post loosening, apical lesion, crown loosening, post fracture, and root fracture. Of the 15 studies on fiber-reinforced posts that were included, not all reported on apical lesions.

Table 10-2 and Table 10-3 summarize the causes and their prevalence. The most common causes of restoration failure are loosening of the post and presence of an apical lesion. Rasimick et al. (2009) also collected a number of studies in which a "passive" post with traditional cement (zinc phosphate or glass ionomer) was used. Loosening of the marker is again the most common cause, and even seems to be somewhat more common than in the case of fiber-reinforced markers. Moreover, Rasimick et al. (2009) caution against directly comparing failure rates between fiber-reinforced and "passive" pins: studies with "passive" pins had longer follow-up durations, and unlike the studies on fiber-reinforced pins, studies on "passive" pins mostly involved bridge restorations.

A review by Sorrentino et al. (2016) based in part on the same literature confirmed that loosening of the marker is the most frequent cause of restoration failure.

Table 10-2 Failure of restorations when using different pins in combination with a synthetic resin cement

Pin type	Percent failure rate	Percent failure due to			
		Releasing marker	Apical lesion	Root fracture	Other causes
Glass fiber	7,1% (81/1145)	49% (40/81)	27% (22/81)	2% (2/81)	21% (17/81)
Carbon fiber	5,3% (59/1122)	29% (17/59)	41% (24/59)	3% (2/59)	27% (16/59)
Quartz fiber	6,7 % (42/625)	26% (11/42)	(55%) (23/42)	2% (1/42)	17% (7/42)

Zirconium	(0.0)				
	(0/87)				
Polyethylene	(7.5)	1/5			4/5
	(5/67)				
<i>Total</i>	6.1%	37%	37%	2%	24%
	(187/3046)	(69/187)	(69/187)	4/187	(45/187)

Table 10-3 Failure of restorations when using different pins in combination with a traditional cement (zinc phosphate or glass ionomer)

	Percent failure rate	Percent failure due to			
		Release marker	Apical lesion	root	Other causes
<i>Total</i>	10.3%	42%	16%	23%	17%
	(245/2381)	(104/245)	40/245)	(57/245)	(42/245)

Quality of evidence failure

Quality of Evidence was not graded because this was not a prognostic, diagnostic or interventional study.

Conclusion

<p>-----</p> <p>GRADE</p>	<p><i>Failure of restoration</i></p> <p>Loosening of fiber-reinforced posts and presence of apical lesions are the most common causes of failure of restorations with glass fiber, carbon fiber, quartz fiber, zirconium and polyethylene root posts.</p> <p>Loosening of "passive" pins is the most common cause of restoration failure.</p> <p>Rasimick et al., 2009; Sorrentino et al., 2016</p>
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What is the effect of the amount of residual coronal dentin and placement of prefabricated or an individual fiber post on the survival of endodontically treated teeth?

Cagidiaco et al. (2008) examined whether the amount of remaining coronal dentin and placement of prefabricated (DT Light Post) or an individual fiber-reinforced post (Ever Stick Post) had a significant effect on the 3-year survival of endodontically treated *premolars*. The control group included teeth for which there was no post construction. All teeth were restored with metal-ceramic crowns. The mean 3-year survival was 76.7%. The prognosis was better for elements with post buildup than for elements without post buildup.

Ferrari et al. (2007) examined the importance of marker retention and the amount of remaining tooth substance on element and restoration survival at a follow-up duration of 2 years.

Only premolars were included. 240 elements were divided into 6 treatment groups, stratified according to the amount of remaining tooth substance. In each group, half of the elements were restored with pins and half with a crown. Treatment was successful in 81% of cases, with failure defined as loss of restoration as well as root fracture occurring primarily in those elements where there was extensive loss of tooth substance. Two elements developed apical periodontitis after detachment of the crown with post. The outcome for elements fitted with crown with post was significantly better than for elements without post retention.

Combining the data from both studies on the effect of the presence or absence of marker retention and the amount of remaining tooth substance on restoration failure, the results are as follows:

- The probability of restoration failure in the presence of one or more coronal walls or of a ferrule is about one-third of the probability of failure in the absence of a ferrule (RR: 0.37; 95% BI: 0.28 - 0, 50). In absolute terms, 282 fewer elements whose restoration fails per 1,000 restored elements (95% BI: 182 to 384 fewer per 1,000).
- The probability of restoration failure in the presence of a pin structure is 60% lower than the probability of failure in the absence of a pin structure (RR: 0.40; 95% BI: 0.29 - 0, 54). In absolute terms: 204 fewer elements whose restoration fails per 1,000 restored elements (95% BI: 135 to 274 fewer per 1,000).

Yang et al. (2015) conducted a meta-analysis of randomized and non-randomized studies specifically on the effect of residual coronal dentin/ferrule presence or absence on the failure of restorations with fiber-reinforced composite post build-ups. They found 5 studies that met the inclusion criteria (cohort studies or controlled trials in which coronal dentin/ferrule presence or absence was an indicator variable). The main characteristics of these studies are shown in Table 10-4.

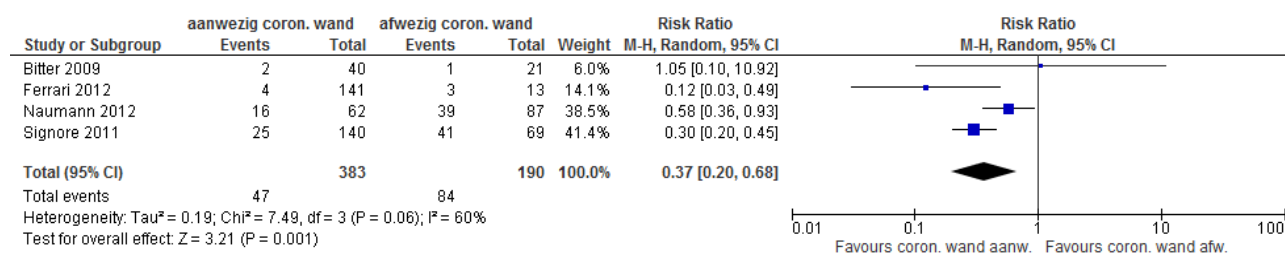
Table 10-4 Study characteristics

Study	Setting	Study design	Study scope (number of patients/ Number of elements)	Gender (M/F)	Average age (range)	Type of element	Restoration type	Average or median follow-up duration
Ferrari 2012	Italy	RCT	345/360	-	58 (18-76)	Premolar	Metal porcelain crown	72 months
Signore 2011	Italy	Cohort study	144/164	63/81	56 (18-72)	Premolar	ceramic crown	42 months
Naumann 2012	Germany	cohort study	119/149	52/67	53 (15-98)	63 anterior elements, 86 posterior elements	Single crown, fixed partial dentures, combined fixed and removable partial dentures	105 months
Bitter 2009	Germany	RCT	90/120	41/49	50 (20-80)	25 anterior elements, 95 posterior elements	Direct composite restorations, partial crowns, full crowns	32 months
Mancebo 2010	Spain	Cohort study	87/87	32/55	53 (23-78)	46 anterior elements, 41 posterior elements	Metal-ceramic or all-ceramic crowns	36 months

Note: RCT = randomized study. Source: Yang et al., 2015

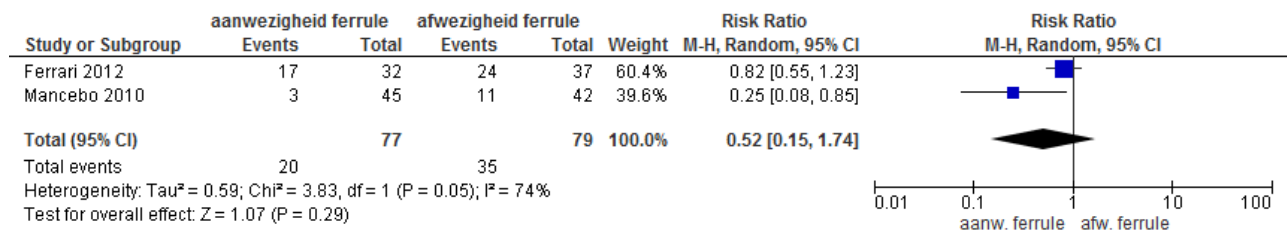
Combining the data from both studies on the effect of the presence or absence of a coronal wall or the presence or absence of a ferrule shows that the presence of a wall or ferrule significantly reduces the risk of restoration failure (Figure 10-1), although in the case of a ferrule the effect is not statistically significant (Figure 10-2).

Figure 10-1 Effect of presence or absence of coronal wall on failure of restoration



Note: random effect meta-analysis

Figure 10-2 Effect of presence or absence of ferrule on failure of restoration



Note: random effect meta-analysis

[Update 2022/3] Several systematic reviews published after 2016 of sufficient methodological quality (AlSaleh et al., 2021; Batista et al., 2020; Sarkis-Onofre et al., 2017) examined the above baseline question. Their results are consistent with the conclusions expressed below.

Quality of evidence failure

The quality of evidence is low because none of the studies adjusted for confounding variables and there was also inconsistency (size of risks varies widely without explanation).

[Update 2022/3] Randomized studies start as high quality of evidence. Non-randomized studies as low quality of evidence. Several systematic reviews of sufficient methodological quality published after 2016 examined the above starting question. However, this does not mean that the quality of evidence has changed. Sarkis-Onofre et al. (2017) reported that most of the nine randomized studies were not "low risk of bias. In addition, there was severe heterogeneity (wide dispersion of outcomes of individual studies), making the quality of evidence low.⁶⁴ Alsaleh et al. (2021) included mostly non-randomized studies (three out of a total of five studies) with logically significant risk of bias. Again, there was severe heterogeneity, making the quality of evidence very low. However, it was upgraded for a dose-response effect: the more walls (0,1,2,3 and 4), the lower the risk of failure. This puts the quality of evidence at low.⁶⁵ In the review by Batista et al. (2020), most of the four studies, three of which were randomized studies, had severe risk of bias. Again, there was severe heterogeneity, making the quality of evidence low.⁶⁶

Conclusions

Low	<i>Failure of restoration</i>
	Placement of a post (construction) may reduce the risk of restoration failure.
GRADE	Ferrari et al., 2007; Cagidiaco et al., 2008

Low	<i>Failure of restoration</i>
	Presence of one or more coronal walls or a ferrule potentially reduces the risk of restoration failure.
GRADE	Ferrari et al., 2007; Cagidiaco et al., 2008; Bitter et al., 2009; Mancebo et al., 2010; Signore et al., 2011; Naumann et al., 2012; Ferrari et al., 2012

⁶⁴ The authors also classified the quality of evidence in GRADE itself as "low.

⁶⁵ Regarding dispersion of outcomes from individual studies, see Figure 3 of Alsaleh et al., 2021. Regarding the dose-response relationship, 0, 1, 2, 3 and 4 raised walls are associated with an incidence of failure of 23, 15, 2, 1 and 0%, respectively (see Figure 3).

⁶⁶ I² - a measure of statistical heterogeneity - although low at 18%, given the small number of studies and small size of the studies, the power of the test is low. The distribution of individual outcomes is more informative. Risk ratios: 1.05, 0.25, 0.73, 0.83. See Figure 2 of Batista et al. (2020).

Is there a difference in effect between restorations with a cast post structure, or with prefabricated posts or a composite restoration without a post?

The review by Ploumaki et al. (2013) includes two prospective studies (Ellner et al., 2003; Fokkinga et al., 2007) that allow evaluation of the success of different types of posts.⁶⁷ Success was defined in these studies as follows: restorations that had undergone no intervention of any kind during the follow-up period of at least 6 years. Extraction of the element was considered restoration failure. In addition, interventions directed at pins, such as because a loosened pin was re-cemented, were also considered failures.

Ellner et al. (2003) in a randomized study evaluated four different types of metal posts (prefabricated or cast post construction of precious metal) with a follow-up duration of 6-10 years. The number of roots was 50 and the number of patients was 31, ranging in age from 18-76 years. The percentage of restorations that failed ranged from 3-6%. There was no significant difference between the different types of posts.

Fokkinga et al. (2007) evaluated three different types of restorations in a randomized study: restoration with cast post build-up and crown, prefabricated metal and resin composite posts with crown, and post-free all-composite restoration with crown. This study included 257 patients ranging in age from 17-71 years, over 60% of whom were women, and counted 307 restorations. Restorations occurred for (pre-)molars as well as cuspids and incisors. The follow-up duration was 15-17 years. The type of build-up used for the restoration - with or without a post - had no effect on the survival of the restoration. The failure rate at the tooth level ranged from 8 to 17%. In the case of metal pins, the presence of the amount of remaining dentin was found to be a prognostic factor: a higher probability of failure when a "minimal" amount of dentin remains.

Quality of evidence failure

The quality of evidence is low. First, both studies did not report the method of randomization or how allocation was blinded. Also, outcome assessors were not blinded. Due to the long duration of the study by Fokkinga et al. (2007), there was a loss-to-follow-up of 32% after 17 years, which may have biased the results. Data on differences in dentition and applied restoration between the dropouts and non-dropouts were not presented. Second, the number of "events" (number of failed restorations) was well below the required 250-300 to obtain sufficiently accurate outcomes. It was downgraded by one level because of risk of bias and by one level because of imprecision.

Conclusion

Low	<i>Failure of restoration</i> Between restorations with a cast post structure, or with prefabricated posts or a restoration with composite without a post, there may be no difference in the rate of failure at a follow-up duration of at least 6 years.
GRADE	Ellner et al., 2003; Fokkinga et al., 2007

⁶⁷ The reviewers omitted the following studies by Naumann et al. reviewed in the Swedish report: Naumann M, Blankenstein F, Dietrich T. Survival of glass fiber reinforced composite post restorations after 2 years-an observational clinical study. J Dent 2005;33:305-12. 12. Naumann M, Reich S, Nothdurft FP, Beuer F, chirmmeister JF, Dietrich T. Survival of glass fiber post restorations over 5 years. Am J Dent 2008;21:267-72. Naumann M, Sterzenbach G, Alexandra F, Dietrich T. Randomized controlled clinical pilot trial of titanium vs. glass fiber prefabricated posts: preliminary results after up to 3 years. Int J Prosthodont 2007;20:499-503. The reasons were: insufficient relevant data and too short follow-up duration. Main conclusions from these studies were: 1) the remaining substance of an element is a more important predictor of survival than the type of post, 2) contrary to the findings of Skupien et al. (2013), front elements had worse survival than posterior elements. Ploumaki et al. (2013) did not mention the main characteristics of their studies in their review.

Is there a difference in effect between indirect restoration (metal-ceramic crown) with post compared to adhesive composite?

Sequeira-Byron et al. (2015) found 1 study (Mannocci et al., 2002) that met the inclusion criteria. This study included 117 patients with premolars with a root canal filling that were restored with a carbon fiber post, followed by randomization to the group in which a metal-ceramic crown was applied or to the group in which an adhesive composite was applied.

Catastrophic failure (that is, an unrepairable restoration) did not occur in either group.

Regarding *non-catastrophic failure* ("marginal fit," wear, presence of fractures), there was no significant difference between the two groups (1/54 versus 3/53; RR 0.33; 95% BI: 0.04 - 3.05).

Regarding *marker failure*, there was no difference between the two groups (2/54 versus 1/53; RR 1.96; 95% BI: 0.18 - 21.01) after 3 years.

[Update 2022/3] De Kuijper et al. (2021) focused on randomized studies for the aforementioned question regarding the outcomes 'short-term restorative failure' (FDI score ≥ 4) and 'short-term retention of the element'. Although non-randomized studies were searched for and 20 were found, they found them to be insufficiently useful because of a (very) serious risk of confounding: direct restorations were namely performed when the prognosis of the element was unfavorable or when one 'marginal ridge' remained.

In addition to the study by Mannocci et al. (2002) already included in the guideline, they included Skupien et al. (2016). This study involved 57 elements (14 anterior, 21 premolars and 22 molars) of 47 patients in whom a restoration after endodontic treatment was required in an element with one upright wall. A fiber-reinforced post was used as the post and for the build-up: composite with a metal-ceramic crown.

When the two studies are combined, the following results are found for "short-term restorative failure" and "short-term retention of the element": direct restorations increase the probability of restorative failure and loss of retention after 3 years by (more than) a factor of 2: odds ratio = 2.31 [95% BI: 0.59, 9.08] and 2.06 [0.08, 53.52], respectively. In absolute terms, the difference is 6.5% (95% BI: -2.2% to 29.5%) for restorative failure, to the detriment of adhesive composite.

There was no information on patient satisfaction, quality of life, caries, periodontal status and cost.

Quality of evidence restorative failure

Mannocci et al. (2002) did not apply any blinding and information on the characteristics of dropouts was not reported. In Skupien et al. (2016), randomization and allocation blinding was adequate. However, bias may have biased the results of Skupien et al. (2016) because the treatment groups were not equal in terms of number of elements of the same type, so composite restorations could be less likely to be successful than restorations with a metal-ceramic crown - composite was used more in premolars and molars and less in anterior elements compared to the metal-ceramic crown (Brignardello-Petersen, 2017). For the aforementioned reasons, we downgraded for severe risk of bias by one level. The confidence interval of the combined estimates (odds ratio) is very wide (2.2% less to 29.5% more restorative failure for adhesive composite).

On this basis, two levels were downgraded for very severe imprecision. No downgrading was done for other GRADE factors.⁶⁸ Thus, the quality of evidence is very low.

Conclusion

⁶⁸ In this, the working group deviates from the assessment by De Kuijper et al. (2021) who marked down by one level for imprecision. Clarification: suppose that 0-10% difference would be a small effect, 10-20% a moderate effect and $\geq 25\%$ a large effect, then the confidence interval crosses two thresholds (10% and 20%. On this basis, downscaling by two levels is indicated. See: Schünemann et al. (2022).

Very low GRADE	<p><i>Restorative failure</i></p> <p>Indirect restorations (metal-ceramic crown) seem to reduce failure of restorations at 3 years compared to adhesive composite, but the evidence is very uncertain.</p> <p>De Kuijper et al., 2021 (Skupien et al., 2016; Mannocci et al., 2002)</p>
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Is there a difference in effect between restorations with metal pins compared to restorations with fiber-reinforced pins?

[update 2022/3] The review by Martins et al. (2021) included studies that met the following criteria:

- Randomized and non-randomized studies with a direct comparison between metal markers and fiber reinforced markers, with
- at least 10 patients who received a single crown or partial denture in permanent endodontically treated elements, with
- A follow-up duration of at least one year.

Martins et al. (2021) found six randomized and four non-randomized studies. In total, the studies involved 704 study participants with a mean age of 43 years. Follow-up duration ranged from 12 to 154 months. The number of endodontically treated elements was 844, of which 453 restorations were done with a fiber-reinforced post and 391 were done with a metal post. A total of 400 endodontically treated elements (210 fiber-reinforced and 189 metal posts) in the anterior region and 413 endodontically treated elements (208 fiber-reinforced and 161 metal posts) in the posterior region were evaluated.

Through a meta-analysis, Martins et al. (2021) calculated an 18% lower probability of failure of a fiber-reinforced marker compared to a metal marker (RR: 0.82; 95% BI: .52 - 1.29). There are some things to be said against this calculation. No distinction is made as to the effect on failure:

- between randomized and non-randomized studies. The latter generally tend to overestimate the effect;
- between studies with shorter and longer follow-up durations. Longer follow-up duration is the most relevant term (Figueiredo et al., 2015).

In addition, the researchers did not find the study by Sterzenbach, Franke & Naumann (2012) in their search and therefore did not include it.

A meta-analysis conducted again by the Working Group distinguishing between randomized and non-randomized studies confirms that the non-randomized studies appear to overestimate the effect of fiber-reinforced markers (Figure 10-3). A second meta-analysis that included only studies with a follow-up duration of 60 months or more showed that of the 18% reduction in failure of fiber-reinforced posts calculated by the reviewers, 7% remained (Figure 10-4; RR: 0.93; 95% BI: 0.76 - 1.13). Looking only at the randomized studies, only 4% reduction in risk of failure remains (RR: 0.96; 95% BI: 0.78 - 1.17). In absolute terms, there is a risk difference in failure between fiber-reinforced and metal pins of 1.1 per 100 less (6.3 less to 4.8 more) in favor of fiber-reinforced pins. In the longer term, therefore, there is hardly any difference.

Figure 10-3 Survival of restorations with fiber reinforced or metal posts with follow-up from 12 months

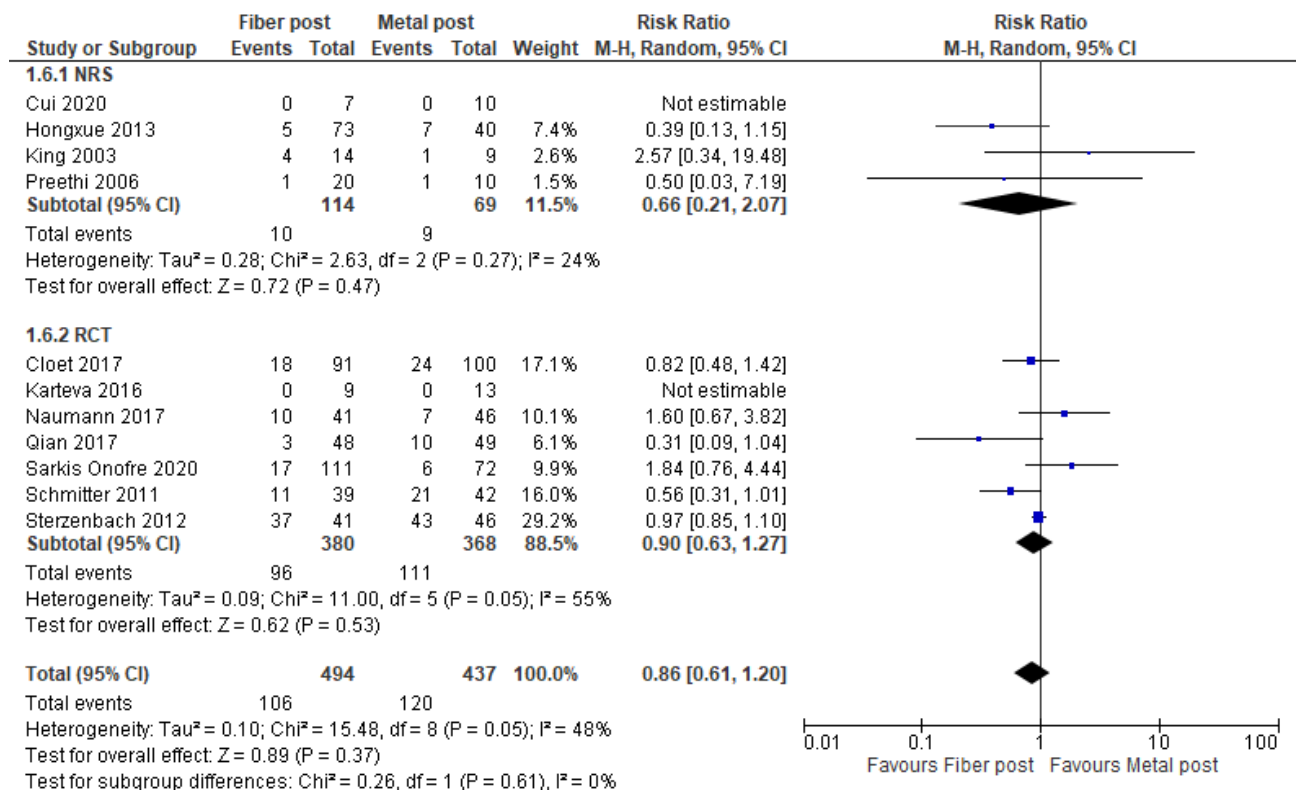
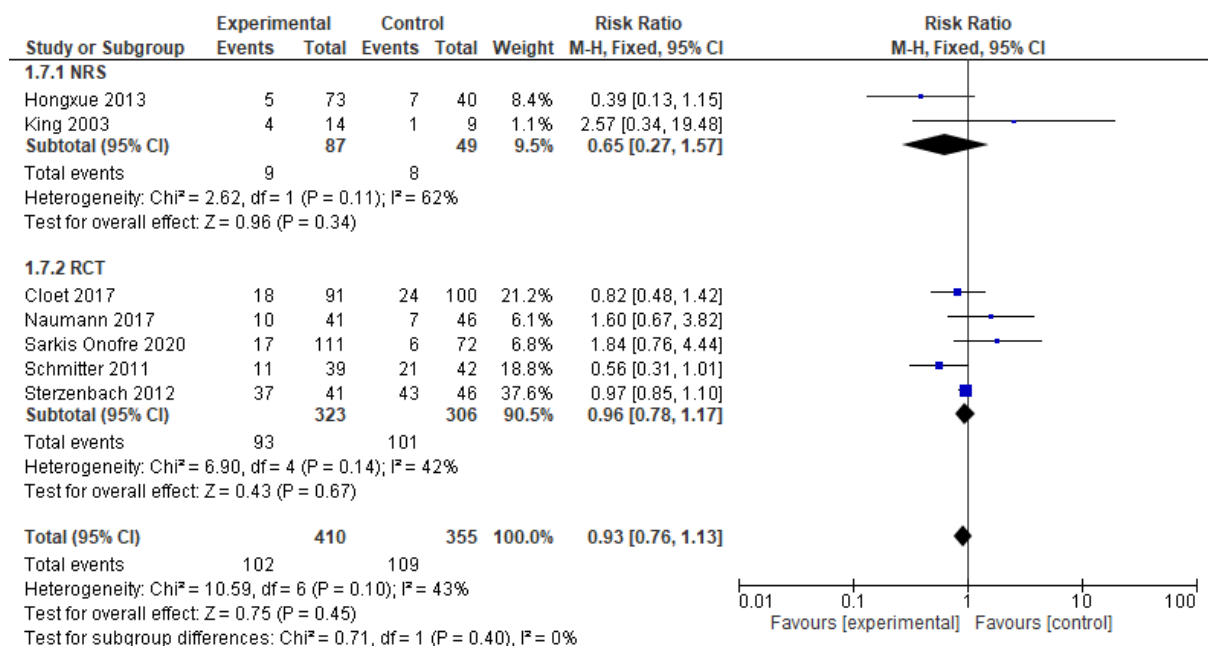


Figure 10-4 Survival of restorations with fiber reinforced or metal posts with follow-up from 60 months



Quality of evidence survival restoration

Only of the randomized studies was the quality of evidence determined. There was no downgrading for risk of bias: the larger studies generally have adequate randomization procedures and blinding of allocation. There is serious imprecision, as the confidence interval crosses RR=1. There is also serious

inconsistency: large dispersion of individual outcomes of studies. There was downgrading by two levels. No downgrading was done for other GRADE factors.

Conclusion

Low GRADE	<p><i>Survival of restoration with fiber reinforced or metal post at follow-up duration from 60 months</i></p> <p>Fiber-reinforced posts do not seem to reduce the failure of a restoration much, if at all, compared to a metal post.</p> <p>Martins et al., 2021 (Sarkis Onofre et al., 2020; Cloet et al., 2017; Naumann et al., 2017; Sterzenbach et al., 2012; Schmitter et al., 2011)</p>
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Is there a difference in effect between restoration with post and crown compared to restoration with a crown only?

Salvi et al. (2007) in a controlled but not randomized study compared the survival of restoration of elements with post (titanium) and crown, with the survival of restoration of elements with crown only. It involved 183 patients with 248 elements in the experimental and 60 elements in the control group. 93.5% of restorations in the experimental group were successful. 95% in the control group were successful after a two-year period.

Quality of evidence survival restoration

The quality of evidence is very low. The study is not randomized and imprecise because of the small number of "events" ("events" is unsuccessful outcome). For this reason, it is downgraded for study limitations by two, and for imprecision by one level.

Conclusion

Very low GRADE	<p><i>Survival of restoration with crown, with or without post</i></p> <p>Presence of a marker over a two-year period appears to have no effect on restoration survival.</p> <p>Salvi et al., 2007</p>
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Is there a difference in effect between direct posterior composite and indirect posterior composite restorations in excessive loss of substance of a molar?

Koyuturk et al. (2013) evaluated in a randomized study in children and adolescents aged 9-15 years whether there was a difference in clinical effectiveness between direct posterior composite (n=13) versus indirect posterior composite restorations (n=16), *when there was excessive loss of substance of a molar*. Almost all of the involved molars were first molars in the mandibula. The follow-up duration was 2 years. Children and adolescents with inadequate oral hygiene, severe periodontal problems and bruxism were not included in this study. How excessive loss of substance was defined, the researchers did not mention. Evaluation of treatment success was done using United States Public Health Service (USPHS) criteria, photographs after staining with alkaline fuchsin and X-ray data. Neither clinical nor radiological data showed a significant difference between indirect and direct composite. After staining with alkaline fuchsin, the edges of the restoration with direct posterior composite appeared discolored after 6 months.

Quality of evidence clinical and radiographic outcomes

One level was downgraded for risk of bias because it was not described how randomization was done, how randomization was blinded, it is unclear whether or not outcome assessors were blinded, and the size of the group to be compared was unequal (16 versus 13; 15/16 and 10/13 elements in the maxilla in both groups) with the possibility of prognostic imbalance. Because of the small number of patients, one level was downgraded for imprecision of outcomes. Therefore, quality of evidence is low.

Conclusion

Low GRADE	<p><i>(USPHS) criteria, photographs after staining with basic fuchsin, and radiographic data after 2 years of evaluation</i></p> <p>The outcomes regarding a difference between indirect posterior and direct posterior composite restorations in children and adolescents with excessive molar substance loss are highly uncertain.</p> <p>Koyuturk et al., 2013</p>
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[update 2022/3] Is there a difference in effect between an endocrown and a conventional crown in the case of endodontically treated elements with severe tissue loss?

Govare & Contrepolis (2020) included two non-randomized studies comparing an endocrown with a conventional crown, with a total of 106 endocrowns and 167 conventional crowns, 186 molars and 87 premolars (Otto & Möhrmann, 2015; Bindle, Richter & Mörmann, 2005). The follow-up period ranged from an average of 55 months to an average of nine years and eight months. The survival rate of conventional crowns on molars ranged from 94.6 to 95.0%, that of premolars from 94.7 to 97.0%. The survival time of endocrowns for molars ranged from 87.1 to 90.5%, that of premolars from 68.8 to 75.0%.

The main causes of endocrown failure were loss of retention, periodontitis and endocrown fracture. For the conventional crown, they were: fracture of the crown, vertical root fracture and irreversible pulpitis.

Govare & Contrepolis (2020) included one non-randomized study comparing an endocrown to a "reduced preparation" crown (Otto, 2004). The mean follow-up duration was only 15 months. The study involved 20 teeth (14 molars and 6 premolars). Survival rate of both endocrown and "reduced preparation" crown was 100%.

Quality of evidence survival endocrown < 4 years follow-up

The quality of evidence for both molars and premolars is very low. Non-randomized studies start as low quality of evidence. The studies did not correct for confounders. In addition, all studies were from the originators of the endocrown and not independent researchers. Thus, we rate down for severe risk of bias. We did not downgrade for other GRADE criteria.

Conclusion

very low GRADE	<p><i>Survival of endocrown after 4-year follow-up compared with conventional crown for damaged endodontically treated molars and premolars</i></p> <p>The survival time of an endocrown for molars appears to be similar to that of a conventional crown, but the evidence is very uncertain. The survival time of an endocrown for premolars appears to be significantly shorter than that of a conventional crown, but the evidence is very uncertain.</p> <p>Govare & Contrepolis, 2020 (Otto & Möhrmann, 2015; Bindle, Richter & Möhrmann, 2005)</p>
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[update 2022/3] Is there a difference in effect between a cotton wool or Teflon as an "endodontic spacer"?

Mathew et al. (2021) investigated whether Teflon (Polytetrafluoroethylene tape) as an "endodontic spacer" reduces microbial contamination compared to a cotton wool when a temporary restoration is performed during root canal treatment. They included three laboratory studies and three clinical studies. In accordance with the inclusion criteria of this guideline, only clinical studies are discussed. Another inclusion criterion of this guideline is that they involve permanent dentition. However, two of the clinical studies involve primary dentition. Therefore, these two primary element-related studies will only be discussed in a "for information" section.

Olsson et al. (2017) investigated in a randomized study in first and second molars (n=48) whether there was a difference in bacterial contamination after a follow-up period of 2-4 weeks between the group in whom cotton wool ("size 2") was used and the group in whom Teflon (2.5 inches in length) was used. Both materials were sterile and the temporary restoration was done with 3-4 mm cavity. The bacterial sample was taken from the pulp chamber before placement of a spacer and after removal of the spacer. The number of colony-forming units (CFU) was chosen as the outcome measure. On this basis, Olsson et al. (2017) calculated that when a cotton wool was used, 15 out of 24 samples were bacterially contaminated and when Teflon was used, 2 out of 24 samples were bacterially contaminated, or - according to a calculation made by the working group - an odds ratio of 0.055 (95%BI: 0.010 - 0.289) and in absolute terms a reduction of 54% (95% BI: 0.28 - 0.72).

For information, for the two randomized studies (Prabhakar et al. , 2018 [n=34]; Khatib & Abdelhafez, 2020 [n=40]) comparing Teflon and a cotton wool as an 'endodontic spacer' in *primary elements* (second molars in the mandibula and bilateral molars, respectively), the study group calculated the number of KVE/ml after 7 days (cotton wool: mean: 1820.59; SD: 982.78 and teflon: mean: 45.29; SD: 128.16 and cotton wool: mean: 30.90; SD: 11.90 and teflon: mean: 9.05; SD: 3.90, respectively) a standardized mean difference (SMD). This SMD is -2.47 (95% BI: -3.39; -1.56) and -2.28 (95% BI: -3.10; -1.46), respectively. The combined SMD calculated using RevMan 5.4 is -2.36 (95% BI: -2.98; -1.75). SMDs of 0.2, 0.5 and 0.8 are generally considered small, moderate and large effect, respectively. Thus, there is a very large effect in these two studies as well as in the study by Olsson et al. (2017). When the combined SMD of -2.28 is converted to an odds ratio and to an absolute reduction, the study group arrives at an odds ratio of 0.014 and an absolute reduction of 59%, almost comparable to the 54% found for the study of permanent dentition.⁶⁹

Quality of evidence endodontic failure

Randomized studies start as high quality evidence. The outcome measure was the number of CFU in the study described. This in itself is not a patient relevant outcome such as element survival or periodontal status. Considering the number of CFU as an indicator of "endodontic failure," this is *very indirect* evidence based on which the quality of evidence is downgraded by two levels.⁷⁰ The study by Olsson et al. (2017) was rated as high risk of bias by Mathew et al. (2021) due to the fact that the researchers knew about the specific intervention: 'cotton wool' or 'Teflon.' However, it is not downgraded for this because it can also be upgraded for very large effect, as was also seen in the studies that invol-

⁶⁹ For conversion from SMD to odds ratio, the following formula was used:
$$\ln OR = \frac{\pi}{\sqrt{3}} SMD$$
. For conversion to absolute reduction, the following formula was used:
$$\text{number fewer per 1000} = 1000 \times \left(ACR - \frac{OR \times ACR}{1 - ACR + OR \times ACR} \right)$$
. See

Cochrane handbook: [https://handbook-5-](https://handbook-5-1.cochrane.org/chapter_12/12_6_3_re-expressing_smds_by_transformation_to_odds_ratio.htm)

1.cochrane.org/chapter_12/12_6_3_re-expressing_smds_by_transformation_to_odds_ratio.htm. ACR is the risk in the control group ("wimp"). For this purpose, 15/25=60% was used.

⁷⁰ There is no consensus on what can be called endodontic failure and success. Failure could be described as recurrence of clinical symptoms along with the presence of periapical radiolucency. See: Tabassum S, Khan FR. Failure of endodontic treatment: The usual suspects. Eur J Dent. 2016 Jan-Mar;10(1):144-147. doi: 10.4103/1305-7456.

ved primary dentition. In other words, the effect is unlikely to be nullified by bias. There is no downgrading for other GRADE factors.

Conclusion

low GRADE	<p><i>Endodontic failure: Teflon versus cotton wool in first and second molars</i></p> <p>In a temporary restoration associated with multiple consecutive appointments, the use of Teflon instead of a cotton ball as an "endodontic spacer" seems to reduce "endodontic failure."</p> <p>Mathew et al, 2021 (Khatab & Abdelhafez, 2020; Prabhakar et al. , 2018; Olsson et al., 2017)</p>
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Considerations

Notes:

Not desirable to formulate a recommendation regarding *later placement of post construction* because immediate placement of a post, which incidentally is common practice, gives better coronal closure and limits the risk of complications. Therefore, there are no arguments to postpone placing post buildup.

Not useful to make a recommendation regarding *whether or not to place marker in partial crown of lithium disilicate*. This is too specific.

Regarding Recommendation 1:

Quality of evidence

The quality of evidence is low.

Patient values and preferences

Most patients want to be informed about the prognosis of an element that has undergone root canal treatment.

Costs and balance of desired and undesired effects are irrelevant to the thrust of the recommendation.

Professional perspective

The presence of coronal walls, ferrule and a non-leaking restoration are important factors affecting prognosis, according to the summarized literature.

Regarding Recommendation 2:

Quality of evidence

The quality of evidence ranges from low to fair.

Patient values and preferences

Most patients will opt for a cheaper solution when no difference in effect (retention of restoration) or unfavorable effect (low biocompatibility) has been demonstrated.

Balance of desired and undesired effects

The fewer remaining coronal walls the less likely the restoration will be preserved. Placement of a post can increase the likelihood of restoration preservation. It does not matter whether direct or indirect post placement is chosen, but the latter option is more expensive.

The biocompatibility of non-metallic markers is better than that of metal markers, according to the guideline working group. [Update 2022/3] With fiberglass posts, the risk of complications is lower. Denture survival is better with a fiberglass post.

However, risk of root fracture with metal pins *does not* seem to be higher than with fiberglass pins. On the other hand, direct marker construction is cheaper.

Cost

Indirect marker construction is more expensive than direct marker construction.

Regarding Recommendation 3:

Quality of evidence

The quality of evidence ranges from low to fair.

Patient values and preferences

Most patients will opt for a cheaper solution when no difference in effect (retention of restoration) or unfavorable effect (low biocompatibility) has been demonstrated.

Balance of desired and undesired effects

Onlay, inlay restorations are not proven to be more effective than a composite overdenture. In case a crown is considered due to limited presence of coronal walls, no difference in effectiveness has been demonstrated between ceramic and metal-ceramic crowns. A better biocompatibility and the aesthetic aspect (color) argue in favor of a ceramic crown, according to the guideline working group.

Cost

The initial cost of indirect restorations (onlay, inlay and crown) is higher than a direct (composite) overdenture restoration. The study group does not comment on cost-effectiveness ("durability").

Regarding draft recommendation 4

Quality of evidence

The quality of evidence is very low for the outcome survival of endocrown.

Patient values and preferences

Most patients will place great value on the survival time of the treated tooth and consider the speed with which treatment takes place of less importance.

Balance of desired and undesired effects

As far as molars are concerned, there seems to be no difference in survival between endocrown and conventional crown with post construction. Nor is there any difference in speed of treatment. Against a three-hour treatment for an endocrown, there are two appointments of about an hour and a half for the conventional crown. Thus, one option has no more desired or undesired effects than the other. In the case of premolars, the apparent better survival of a conventional crown versus an endocrown is the deciding factor.

Cost

These are unlikely to play a significant role.

Regarding draft recommendation 5

Quality of evidence

The quality of evidence is low for the outcome endodontic failure.

Patient values and preferences

Prevention of endodontic failure is a crucial outcome for both practitioner and patient.

Balance of desired and undesired effects

There are no undesirable effects of using Teflon instead of a cotton ball. Therefore, use of Teflon to reduce the risk of endodontic failure compared to use of a cotton ball is the deciding factor.

Cost

These are unlikely to play a significant role.

Recommendations

Inform the patient in whom root canal treatment is being considered that proper coronal closure will affect the outcome of treatment.

[unchanged after update 2022/3]

Rational

The guideline working group places great weight on a well-informed patient.

In a patient in whom root canal treatment is planned and in whom less than two raised walls are present, consider using a fiberglass post.

[unchanged after update 2022/3]

Rational

The working group believes that a fiberglass post can provide additional retention for coronal restoration when insufficient tooth material remains.

In a patient in whom root canal treatment is planned and in whom less than half of the coronal tooth tissue is present, consider fabricating a nodule-covering restoration.

[unchanged after update 2022/3]

Rational

The guideline working group emphasizes the importance of avoiding fracture of an element/node.

For endodontically treated molars with severe tissue loss, consider placing an endocrown or a build-up and conventional crown.

*For endodontically treated premolars with severe tissue loss, consider placing **not an** endocrown but a post buildup with a conventional crown.*

[update 2022/3: new recommendation]

Rational

The survival time of an endocrown for *molars* seems similar to that of a conventional crown, The survival time of an endocrown for *premolars* seems significantly shorter than that of a conventional crown.

For a temporary restoration associated with multiple consecutive appointments, consider using Teflon instead of a cotton ball as an "endodontic spacer," if use of a "spacer" is deemed necessary.

[update 2022/3: new recommendation]

Rational

The working group attaches importance to the prevention of bacterial growth, thereby reducing the risk of endodontic failure.

Knowledge gaps

There needs to be more multicenter randomized research on it comparing interventions that are deemed important. Why is randomized research so necessary? As shown above, there are many (potential) factors that can influence the success of a restoration. Randomized research is the method of choice to distribute known, potential or unknown prognostic factors equally among the study groups. Sub-group analyses can identify which patients benefit more or less from an intervention.

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Appendix 10.1 Search strategy

((("endodontics"[MeSH Terms] OR endodont*[Title/Abstract] OR "root canal therapy"[Title/Abstract] OR "root canal treatment"[Title/Abstract] OR root canal obturation[Title/Abstract] OR root filling*[Title/Abstract]) AND ("dental restoration, permanent"[MeSH Terms] OR "dental restoration"[Title/Abstract] OR coronal restoration[Title/Abstract] OR "apical retrofilling"[Title/Abstract] OR "apical retrograde root fillings"[Title/Abstract] OR "crown"[Title/Abstract] OR "dental post"[Title/Abstract] OR "dental posts"[Title/Abstract] OR "root canal posts"[Title/Abstract] OR "conventional treatment"[Title/Abstract] OR "conventional therapy"[Title/Abstract])) OR (((("Dental Restoration Failure"[Majr]) AND (("Root Canal Therapy"[Mesh] OR "Dental Pulp Diseases/therapy"[Mesh]))) AND (((("cohort studies"[MeSH Terms] OR "randomized controlled trial"[Publication Type] OR "meta analysis"[Publication Type] OR "review"[Publication Type])) OR "comparative study" [Publication Type] OR "clinical trial"[Publication Type]))))Sort by: Relevance Filters:Publication date from 2010/01/01 (266 studies)

Appendix 10.2

AQUILINO & CAPLAN (2002)

Study participation:

- Percentage of patients meeting study inclusion criteria who were asked to participate: *not applicable*.
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on important prognostic factors and outcome measures? *Patient selection: only patients with at least 1 visit to the COD in each 2-year interval from 1985 to 1986 through 1995 to 1996. Reduced rates may have resulted in a population of lower socioeconomic status.*

->Serious risk of bias

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *Not reported*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *Not reported.*

->Serious risk of bias

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*
- There is a clear description of how prognostic factors were measured, including cutoff points. *Whether or not crown placement is prognostic factor.*

->Low risk of bias *

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *Sufficiently clearly described.*

->Low risk of bias (Alley 2004)*

Confounders:

- All significant confounders were defined and reliably and validly measured and included in the analysis. *Not all confounders were measured such as bone loss, socioeconomic status. Restorative procedures were not standardized. Number of carious and filled surfaces could only be derived from pre-treatment radiographs. Oral hygiene care not named.*

->Serious risk of bias *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order*
- Sufficient data to determine whether statistical analysis is adequate. *Adequate (Alley 2004).*

->Serious risk of bias

Conclusion: 'Serious risk of bias'

CAPLAN (2002)

Study participation:

- Percentage of patients meeting study inclusion criteria who were asked to participate: *not applicable*.
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on important prognostic factors and outcome measures? *Patient selection: only patients with at least 1 visit to the COD in each 2-year interval from 1985 to 1986 through 1995 to 1996. Reduced rates may have resulted in a population of lower socioeconomic status.*

->Serious risk of bias

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *Not reported*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *Not reported.*

->Serious risk of bias

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*
- It clearly describes how the prognostic factors were measured, including cutoff points. *Number of proximal contacts is prognostic factor ("Proximal contacts were considered absent if the adjacent Tooth was a root tip, missing or impacted).*

->Low risk of bias *

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *Sufficiently clearly described.*

->Low risk of bias

Confounders:

- All significant confounders were defined and reliably and validly measured and included in the analysis. *Not all confounders were measured, such as bone loss, socioeconomic status, oral hygiene care. Restorative procedures were not standardized. Number of carious and filled surfaces could only be derived from pre-treatment radiographs.*

->Serious risk of bias *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order*
- Sufficient data to determine whether statistical analysis is adequate. *Adequate*

->Serious risk of bias

Conclusion: 'Serious risk of bias'

CAPLAN (2005)

Study participation:

- Percentage of patients meeting study inclusion criteria who were asked to participate: *not applicable*.
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on key prognostic factors and outcome measures?
Only patients who were insured for eight years were included. Insurance status may be associated with differences in occupation, age or education.

->Serious risk of bias

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *Not reported*
- Has it been determined whether patients who did not participate in all measurement measures and patients who completed the entire study differ from each other? If no differences between the two groups on key prognostic factors and outcome measures. *Not reported.*

->Serious risk of bias

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*

It clearly describes how prognostic factors were measured, including cutoff points. *Element that has or has not undergone root canal treatment is prognostic factor.*

> Low risk of bias

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *Sufficiently clearly described.*

->Low risk of bias

Confounders:

- All significant confounders were defined and reliably and validly measured and included in the analysis. *Not all confounders were measured, such as bone loss, socioeconomic status, oral hygiene care. Restorative procedures were not standardized.*

->Serious risk of bias *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order*
- Sufficient data to determine adequacy of statistical analysis. *Age, sex, SES, oral health care not included as confounders in analysis.*

->Serious risk of bias

Conclusion: 'Serious risk of bias'

TSESIS (2013)

Study participation:

- Percentage of patients meeting study inclusion criteria who were asked to participate: *only 74 of 720 periapical status studies could be included, very small sample indeed. Apparently a significant number of cases lacked a second measurement.*
- Has a non-response analysis been done? Does this show that there is no difference between responders versus non-responders on key prognostic factors and outcome measures? *not applicable.*

->Serious risk of bias

Study progression:

- Is dropout rate limited; studies with population up to 200 < 10%, and above n=200 <20%. *No dropouts.*
- Was an assessment made of whether patients who did not participate in all measurement measures and patients who completed the entire study differed? If no differences between the two groups on key prognostic factors and outcome measures. *See study participation.*

->Low risk of bias

Measurement of prognostic factor:

- A maximum of one-third of a scale was imputed. *No imputation took place.*
- It clearly describes how prognostic factors were measured, including cutoff points. *Element that has or has not undergone root canal treatment is prognostic factor.*

->Low risk of bias

Measurement of outcome measure:

- Clear description of outcome measures, including cutoff points. *Sufficiently clearly described. Assessors of outcomes not blinded to prognostic factors and initial periapical status.*

->Moderate risk of bias

Confounders:

- All significant confounders were defined and reliably and validly measured and included in the analysis. *Not all confounders were included in the analysis. For example, oral health, proximal contacts, crown/no crown.*

->Serious risk of bias *

Statistical analysis and reporting:

- No selective reporting of outcome measures. *In order*
- Sufficient data to determine whether statistical analysis is adequate. *Inadequate statistical analysis. No odds ratios or regression coefficients are reported.*

->Serious risk of bias

Conclusion: 'Serious risk of bias'

11. Association between periodontitis apicalis and systemic diseases

Introduction

Over the past decades, studies have appeared finding an association between periodontitis and cardiovascular disease (Koletsi et al., 2021). The pathophysiological mechanism would be that inflammation lead to atherosclerotic changes in the peripheral and coronary circulation (Georgiou et al., 2019).

The possibility that infections emanating from the pulp may have deleterious effects not only on the cardiovascular system but also on other organs has not yet received the same degree of attention.

This chapter presents the scientific evidence on the impact of endodontic inflammatory conditions on heart disease and cardiovascular disease, diabetes mellitus, chronic liver disease, hematologic disease, low bone density, cerebrovascular disease, and upper respiratory disease.

Exit question:

- Can pulpitis or periodontitis apicalis cause systemic disease?

Search and selection

The Swedish report *Methods of Diagnosis and Treatment in Endodontics. A systematic review* (2012) and two systematic reviews whose inclusion criteria met the selection criteria below (Khalighinejad et al., 2016; Berlin-Broner et al., 2016). See Appendix 10.1 for the search strategy in PubMed.

Selection Criteria

Type of patients	- patients with permanent teeth
Type of intervention	- teeth with inflammation and/or infection of the pulp and periapical tissues
Check	- teeth that do not show radiographic or clinical signs suggesting inflammation and/or infection of the pulp or periapical tissues
Type of outcome measures	- heart disease - cardiovascular diseases - diabetes mellitus - chronic liver disease - haematological disorders - low bone density - brain disorders - diseases of the upper respiratory tract
Type of setting	- general practitioners - dental endodontists
Inclusion and exclusion criteria	Inclusion criteria for studies published up to 2010: - primary, directly comparative studies

- systematic reviews (with or without meta-analyses)

Inclusion criteria for update studies:

- English-language systematic reviews (with or without meta-analyses)

Exclusion criteria:

- patient series
- animal research
- non-comparative (observational) studies
- in vitro, ex vivo (human) studies

Endocarditis

The Swedish HTA report included 1 observational study (Lacassin et al., 1995) with high risk of bias that reported the risk of endocarditis in relation to different treatment procedures in the oral cavity, among others. Root canal treatment was associated with a higher risk of endocarditis (OR = 2.5; 95% BI: 1.0-6.5), but in a multivariate model there was no statistically significant outcome (OR = 1.7; 95% BI: 0.5-5.2).

Cardiovascular diseases

The Swedish HTA report included 4 observational studies, including 3 patient-control studies (Jansson et al., 2001; Caplan et al., 2006; Joshipura et al., 2006; ,5) and 1 cross-sectional study (Frisk et al., 2003).

Caplan et al. (2006) reported an association between apical periodontitis and cardiovascular disease in men under 40 years of age and middle-aged men (OR = 1.4). Frisk et al. (2003) found no relationship between apical periodontitis and ischemic heart disease in women after adjusting for a number of prognostic factors.

Jansson et al. (2001) found that poor oral health (operationalized as the sum of scores for number of missing elements, apical lesions, carious lesions and marginal bone loss) combined with plaque was a risk factor for mortality due to cardiovascular disease. For individuals younger than 45 years with more than 10% marginal bone loss, the odds ratio was 2.7 (p=0.04) for mortality from cardiovascular causes compared with the same age group with less than 10% marginal bone loss. They found no significantly increased risk of cardiovascular mortality when only apical periodontitis was involved.

Another patient-control study (Joshipura et al., 2006) with high risk of bias found that individuals receiving medical care in whom 1 or 2 root fillings were present had a higher risk of cardiovascular disease (RR = 1.21, 95% BI: 1.05-1.40).

A systematic review (Khalighinejad et al., 2016) included 5 studies (Segura-Egea et al., 2010; Pasqualini et al., 2012; Costa et al., 2014; An et al., 2016; Gomes et al., 2016) published from 2010. The odds ratios in these studies for cardiovascular mortality varied widely: from 1.77 (barely increased risk) to 5.3 (greatly increased risk). It should be noted that the matching between "cases" and "controls" differed in most studies.

The reviewers therefore conclude that "there may be a relationship between periodontitis apicalis and cardiovascular disease."

Another recent systematic review (Berlin-Broner et al., 2016) reached a similar conclusion: "although most studies - these reviewers included 19 studies (10 patient-control studies, 5 cross-sectional studies and 4 cohort studies - showed a positive association between apical periodontitis and cardiovascular disease, the quality of the existing evidence is moderate to low, and a causal relationship cannot be demonstrated."

Diabetes mellitus

The systematic review by Khalighinejad et al. (2016) included 5 studies (Britto et al., 2003; Segura-Egea et al., 2005; Lopez-Lopez et al., 2011; Marotta et al., 2012; Sanchez-Dominguez et al., 2015). None of these studies had a low risk of bias. 3 studies (Segura-Egea et al., 2005; Lopez-Lopez et al., 2011; Marotta et al., 2011) reported a significant association between periodontitis and prevalence or glycemic control of diabetes mellitus, 2 studies (Britto et al., 2003; Sanchez-Dominguez et al., 2015) found no significant relationship.

Chronic liver disease

In the systematic review by Khalighinejad et al. (2016), 1 patient-control study was included (Castellanos-Cosano et al., 2013a). In this study, apical periodontitis was found to be more prevalent in patients who had undergone liver transplantation than in a control group (OR: 3.7). However, this study did not adjust for differences in prognostic factors between study and control groups.

Hematological disorders

The systematic review by Khalighinejad et al. (2016) included 1 patient-control study (Castellanos-Cosano et al., 2013b). These researchers reported that patients with hemophilia were more likely to have apical periodontitis than the control group (OR=7.4). Again, no adjustment was made for differences in prognostic factors between study and control groups.

Low bone density

The systematic review by Khalighinejad et al. (2016) included 1 patient-control study (Lopez-Lopez et al., 2015). The researchers reported that apical periodontitis was associated with low bone density. However, no adjustment was made for prognostic factors such as age, smoking, alcohol consumption or medical conditions.

Conclusion

None of the studies provided evidence of a causal relationship between systemic disease and pulpitis or periodontitis apicalis.

Considerations

Because of the lack of robust evidence for a cause-and-effect relationship between apical periodontitis and various systemic conditions such as diabetes mellitus et cetera, no recommendations are made.

Knowledge gap

More large, longitudinal studies are needed to quantify the risks to general health when apical periodontitis is left untreated.

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Appendix 11.1

((("oral health"[MeSH Major Topic] OR "dental pulp diseases"[MeSH Terms] OR "periapical diseases"[MeSH Terms] OR "focal infection, dental"[MeSH Terms] OR "dental caries/complications"[MeSH Terms] OR "tooth diseases/complications"[MeSH Major Topic] OR "dental caries/epidemiology"[MeSH Major Topic] OR "dental care/adverse effects"[MeSH Major Topic]) AND ("cerebrovascular disorders"[MeSH Terms] OR "heart diseases"[MeSH Terms] OR "arthritis, rheumatoid"[MeSH Terms] OR "diabetes mellitus"[MeSH Terms] OR "lung diseases, obstructive"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "obstetric labor, premature"[MeSH Terms] OR "infant, low birth weight"[MeSH Terms] OR "sepsis"[MeSH Terms] OR "bacteremia"[MeSH Terms]) AND ("meta analysis"[Publication Type] OR "systematic review"[Filter])) OR (((("root canal*" [Title] OR "rootcanal*" [Title] OR "endodont*" [Title] OR "dental" [Title] OR ("apical" [Title] AND "periodont*" [Title])) AND ("relat*" [Title] OR "conjunction" [Title] OR "risk" [Title] OR "associat*" [Title] OR "correlat*" [Title]) AND ("coronary" [Title] OR "vascular" [Title] OR "bacteremia" [Title] OR "cerebro*" [Title] OR "ischemia" [Title] OR "myocardial" [Title] OR "cardial" [Title] OR "diabet*" [Title] OR "arthritis*" [Title] OR "obstructive" [Title] OR "heart valve" [Title] OR "morbidity" [Title] OR "mortality" [Title] OR "inflam*" [Title] OR "pathol*" [Title] OR "diseas*" [Title] OR "systemic" [Title] OR "athero*" [Title] OR "sepsis" [Title] OR "hematogenous" [Title])) OR ("tooth diseases/mortality" [MeSH Terms] OR ("oldmedline" [Filter] AND "endodontics" [MeSH Major Topic]))) AND ("meta analysis" [Publication Type] OR "systematic review" [Filter])) AND (meta-analysis[Filter] OR systematicreview[Filter])

12. Avoiding and treating complications

Introduction

During root canal treatment, iatrogenic complications, also known as procedural complications, can occur. Some complications have little effect on the treatment outcome, while others significantly worsen the prognosis of the treated tooth. Complications also occur with undesirable side effects of a temporary or permanent nature. Following a survey of general practitioners, it was determined that three major iatrogenic complications can occur, namely

1. Instrument break
2. Perforations
3. Sodium hypochlorites

This chapter describes the scientific rationale for answering the baseline questions for these three complications.

[Update 2022/3] 1a. What are risk factors for instrument breakage?

Instrument-, operator- and patient-related factors can pose a risk for instrument breakage.

Method literature analysis

There is one systematic review (Gomes et al., 2021) of sufficient methodological quality.

Summary of literature

Gomes et al. (2021) examined whether the incidence of fracture of a nickel titanium file differed for reciprocal and continuous rotation. They found 28 studies that reported the incidence. Only one study had a comparative design. Most studies were patient series. From an analysis not adjusted for confounding variables, continuous rotation showed a greater risk of fracture than reciprocal rotation (odds ratio [OR]: 1.4; 95% BI: 0.26-7.48), but the outcome was not statistically significant. This odds ratio means that the incidence of file fracture in case of continuous rotation would increase from about 2.3% to 3.2%, an increase of less than 1%.

Incidentally, an analysis adjusted for confounding variables (country of study, year of publication, type of dentition, type of practitioner, number of times the same file was used) also showed no statistically significant difference. However, it was found that type of practitioner and frequency of file reuse increased the risk of fracture. The general practitioner had a significantly higher risk than the endodontist (OR = 34.9, 95% BI: 2.1-578.8). Repeated use of the file (more than 4 times versus once) gave an odds ratio of OR = 11.3 (95% BI: 3.6-35.3) and 8.1, (95% BI: 1.5-42.9) for a continuous and reciprocating rotary nickel-titanium file, respectively.

Quality of evidence instrument breakage

Most of the studies in the systematic review are non-comparative in design. In addition, the confidence intervals of the odds ratios are very wide, creating uncertainty about the degree of increased risk of fracture. Therefore, the quality of evidence is very low.

Conclusion

Very low GRADE	<i>Instrument break</i> Nature of rotation of a nickel-titanium file - continuous versus reciprocal rotation - appears to have little or no effect on the occurrence of instrument breakage. Repeated use of a nickel titanium file may increase the risk of instrument breakage. Source: Gomes et al. (2021)
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1b. What is the effect of instrument breakage on treatment outcome? How to handle instrument fracture?

Breakage of an endodontic file may occur during root canal preparation. The broken-off fragment can make canal treatment difficult and partially impossible. Remaining of a broken fragment may worsen the prognosis of the treated element. Instrument breakage occurs due to excessive torsional forces and/or metal fatigue during flexion-stretching movements. Manufacturers of endodontic files aim to develop instruments with high cutting capacity and high fracture resistance. With regularity, modifications are made to the alloy of the nickel titanium used and to the design of the instruments. Despite all the developments, a fracture incidence of 1.3 to 10% is reported. Based on the available literature, this guideline describes the effect on treatment outcome of a retained fragment in the root canal and the factors that influence it. A decision tree discusses treatment options and offers a strategy on how to deal with aborted instruments.

Method of literature analysis

No systematic literature search was conducted. Instead, literature available to the working group was used. This is the following recent review study: *Management of Intracanal Separated Instruments*, Madarati et al. (2013).

Summary of literature

Influence of residual aborted fragments on treatment outcome

One of the consequences of instrument rupture is that a fragment of stainless steel or nickel titanium remains in the patient. This fragment can corrode. There is only 1 publication concluding that stainless steel fragments do not cause tissue reaction. No corrosion is observed after two years. No studies have yet been published showing the influence of possible corrosion on treatment outcome.

Another consequence is that canal obstruction occurs when a degraded fragment remains in the canal. At the site and apical to the aborted fragment, the canal is no longer accessible for disinfection. The impact of this consequence has been discussed in several studies. In one of the first publications, Strindberg (1956) reports a success rate that is 19 percentage points lower when a degraded instrument remains in the root canal. The study involved only 15 treatments in which a broken-off fragment remained. Only 4 of these treatments involved preoperative periapical radiolucency. It was hypothesized that the prognosis would be poor when instrument breakage occurred in elements with preoperative periapical radiolucency.

Another study (Grossman, 1969) evaluated 66 treatments with a mean follow-up of 2 years. In elements with a vital pulp or a necrotic pulp without periapical radiolucency, a success rate was found that was no lower than in elements without a degraded fragment, but the success rate decreased from 75-95% to 47% when a degraded fragment remained in an element with a peri-

apical radiolucency. It was concluded that a degraded fragment reduces the treatment outcome only when there is a preoperative periapical radiolucency. The small study group in the above studies does not provide adequate clinical evidence and makes comparison impossible. A study by Fox et al in which 304 treatments were evaluated with a mean follow-up of 7 years provided the same conclusion. 14 of the 19 failed treatments had preoperative periapical radiolucency. With the high success rate of 94%, the authors suggested that an aborted fragment of a NiTi instrument may act as an adequate filler. It is important to note that 67% of the degraded fragments were in already cleaned canals. More recent studies reported no effect of a retained fragment on treatment outcome. Ingle et al. (1994) evaluated 1229 treatments over an average of 2 years. Only 1 treatment out of 104 failures involved an element with a lagging degraded fragment. This study did not include a control group. In a later study by Crump et al. (1970), 178 treatments with a lagging aborted fragment were compared with 136 control elements. Finally, 53 pairs could be compared who met the inclusion criteria. There was no statistically significant difference in success rate between the aborted instruments group and the control group (81% and 74%, respectively). These results suggest a conservative approach to elements in which instrument breakage occurred during root canal treatment. That is, completing the treatment and not proceeding directly to apical surgery or extraction.

Another well-designed study (Spili et al., 2005) investigated the influence of lagging degraded instruments, including NiTi instruments on root canal treatment prognosis. From a collection of 8460 treatments, 146 elements with a residual broken-off fragment were paired as accurately as possible with 146 control elements. The overall healing rate was 92% for the aborted instruments group and 95% for the controls. In the presence of preoperative periapical radiolucency, the healing rate was lower in both groups, 86.7% for the aborted instruments group and 92.9% for the controls. The difference was not statistically significant. It was concluded that only the preoperative presence of a lucency negatively affects this rate.

Of the aforementioned studies, only 2 were included in a meta-analysis (Panitvisai et al., 2010). It was concluded that a lagging degraded fragment does not worsen the prognosis of an element. Murad and Murray (2011) commented on the meta-analysis:

- The limited number of included studies and the insufficient methodological quality of the available studies reduce the power of the meta-analysis.
- The numbers of evaluated elements in both studies are not based on a power calculation.
- The inclusion of Crump and Natkin's study was controversial because it was conducted 40 years ago. At that time, filler materials such as silver markers and phenols were used, which are no longer permissible today. It should also be noted that this study evaluated student treatments. Normally, these are the simpler treatments. However, Spili et al. correctly evaluated treatments by dental endodontists in which NiTi instruments were used.

The meta-analysis indicates that the available evidence is insufficient to support a change in current practice and that more research is needed. Unfortunately, there is no consensus on how to proceed in the event of an aborted instrument. Nevertheless, it is important to know what treatment options are real and what factors influence the decision.

Treatment options

Degraded instruments can be approached surgically or orthograde. Orthograde approach includes the following options:

- Removal of the aborted fragment;
- Passing the aborted fragment or
- Clean and fill to the level of the broken fragment.

The first approach is to remove the aborted fragment, as this allows the intended treatment to continue without complications. However, it is not easy to remove a fragment. It requires experience and training and knowledge of the various techniques and available instruments and tools. Whether a fragment is removable depends on several factors, and removing aborted fragments is not without risk. Therefore, it is important to consider several factors when considering

removal. Many general practitioners prefer referral to a dentist with extensive experience in removing broken instruments.

A. Factors affecting removal of degraded instruments.

Elemental factors

Element-related factors are defined as anatomical factors. These anatomical factors are determined by the type of element, the shape and diameter of the root canal, the position of the aborted fragment in the root canal, the position of the aborted fragment relative to the curvature in the root canal, and the degree of curvature and abruptness of the curve. Removal of the aborted fragment is more predictable in the following situations:

- in maxillary teeth;
- in front elements;
- when the fragment is located in the coronal one-third of the channel;
- when the fragment is in front of the curve and
- when the fragment is in straight or slightly curved channels.

It is stated that a broken fragment is removable when one-third of the fragment can be exposed. Most NiTi instruments will break off apically and beyond the bend, where removal is difficult. The influence of the anatomical factors is mainly related to visibility and accessibility, or the ability to see the fragment and obtain straight, tension-free access to the fragment so that it can be approached with special instruments and tools. For this, the previously mentioned position of the fragment and element type are important, as well as the relationship between the canal wall and the aborted fragment; removal of the fragment is more predictable if there is space between the aborted fragment and the canal wall.

Instrumental factors

Degraded instruments made of NiTi are more difficult to remove than stainless steel instruments. The following explanations are given for this:

- The rotational motion causes them to cut into the canal wall.
- They break faster when attempted removal, especially when using ultrasonic equipment.
- In curved channels, NiTi instruments will stretch and therefore will not be central to the channel, but will always be pressed against the outer wall.
- Of NiTi instruments that break due to torsional forces, a short fragment often remains, quite far to apical in the canal. The longer the broken fragment is, the further to coronal the coronal part of that fragment lies and the easier it is to remove.

The design of the broken instrument is also a determining factor; a K-file is easier to remove than a Hedström file. Compared to K-files, Hedström files have a larger helix angle, deeper windings and a larger rake angle. Because of this design, Hedström files also have a greater cutting capacity and, therefore, would also be able to grip the channel wall better.

Operator-related factors

Breaking a root canal instrument is a stress-increasing complication. An operator may feel compelled to remove the instrument. It is critical that care be taken when attempting to remove a broken instrument. Successful removal of a degraded instrument requires knowledge, training, familiarity with techniques and instruments, perseverance and creativity. It is important to note that an experienced operator not only removes the instrument, but also avoids unnecessarily sacrificing dental material. Referral to a dental endodontist should be the approach of choice when the practitioner lacks the above competencies.

Patient-related factors

Patient factors such as mouth opening, limited accessibility of an element, fear, time constraints and motivation to retain a tooth affect the likelihood of success. A patient can be motivated by proper explanation of the complexity of the procedure and possible complications prior to treatment. This enables the practitioner to perform optimal treatment.

Removal techniques

Different success rates are reported with respect to different file-removal techniques, instruments and tools. Before a practitioner decides to proceed with the removal of a broken instrument, he or she must first have the necessary instruments, tools and skills. Every situation is different and the appropriate approach should always be chosen. Sometimes a degraded instrument is removed by chance while attempting to pass the instrument, or while flushing the canal, on the other hand, sometimes it is impossible to remove a loose fragment from the canal, all techniques and tools notwithstanding. Several techniques and tools have been described in recent years. Some are still widely used, others are only of historical interest. Some new promising techniques and tools are also described. Correct application of the instruments and tools is essential to avoid additional complications. When in doubt about skill, referral to a specialist is recommended.

Chemical solvents

The use of EDTA is recommended to soften the dentin of the canal wall around the degraded fragment. This would make the degraded fragment easier to pass through. Other chemical agents such as iodine trichloride, nitric acid, hydrochloric acid, sulfuric acid, crystals of iodine, iron chloride solution, nitrohydrochloric acid and potassium iodide solutions have been used in the past to provoke corrosion of the metal. For obvious reasons, such as irritation of the periapical tissues, these products are no longer used.

Mini tweezers

When the root canal is wide enough, a chipped fragment located in the coronal part of the root canal can be grasped and removed with mini tweezers such as the Steiglitz tweezers, Peet silver point tweezers, or endo tweezers.

Hedström files

A broken lentulo spiral is removable by turning a Hedström file next to or inside the fragment. The Hedström file can possibly be wrapped with a cotton ball for additional retention. When the Hedström file tightens into the fragment, the whole can be removed.

Wire loop

A wire loop can be made by pulling the two ends of a 0.14 mm wire through a 25-gauge needle. A narrow instrument can be used to place the loop around a free lying coronal part of the fragment. The loop is then pulled tight and the fragment can be removed. Of course, this only has a chance if the instrument is not too tight in the canal.

Hollow needle

Space around a centrally positioned fragment could be created with an edge sharpened hollow needle, this space can also be created with trepan drills or ultrasonic tips. Sometimes a so-called staging platform is created prior to this with a shortened Gates glidden drill to the coronal level of the aborted fragment. By sliding the hollow needle over the fragment and then clamping a Hedström file through the needle between the degraded fragment and the wall of the needle. In this way, the entire complex can be removed. The hollow tube should be narrow enough to fit into the canal and the lumen of the hollow needle should be large enough to fit over the coronal part of the fragment. Instead of a Hedström file, the use of superglue and synthetic resin is also described; the hollow needle is filled with glue or synthetic resin and then slid over the aborted fragment. The fragment glued into the needle can then be removed along with the needle.

Because the needles are not bendable, this technique is not applicable in curved canals. In a study by Suter et al. the hollow needle and Hedström file method allowed 9 out of 10 fragments to be removed. The technique was applied when the technique of first choice, namely, dislodging the fragment with an ultrasonic tip, was unsuccessful.

Braiding files

Placing two files next to the broken fragment sometimes succeeds in removing a fragment. This approach can be chosen when the fragment is further to apical and not visible. Thin files may break again, so the thickest possible files should be used.

Masserann instruments

The Masserann kit consists of 14 trepan drills with diameters ranging from 1.1 to 2.4 mm and two extractors; hollow needles into which a plugger can be inserted. Using a trepan sampler, the coronal part of the fragment that has been decomposed is first exposed while turning counterclockwise. Then the hollow needle is placed over the exposed part and by inserting the plugger into the tube, the coronal part is clamped and removable. The diameters of the trepanned drills are quite large so very much dentin is lost when using the Masserann kit. This leads to extreme weakening of the root. The Masserann kit is actually only usable in front teeth and in the straight roots of posterior teeth.

Extractors

The idea of the Masserann kit was further developed and new extractors were developed. The diameter of the new hollow needles is more applicable in the root canal. The Endo Extractor System from Roydent comes in sizes 80, 50 and 30. The Cancelier Extractor Kit has 4 sizes; 0.50, 0.60, 0.70 and 0.80 mm. The Instrument Removal System contains 3 extractors in sizes; 1.00, 0.80 and 0.60. The newer The Endo Rescue includes a Pointier drill that allows a staging platform to be prepared coronal to the aborted fragment and again from trepan drills, sizes 090 and 070 that prepare counterclockwise around the aborted fragment. Another new system is the Meitrac Endo Safety System which has three sizes of hollow needles. Some extractors can be taken beyond a curvature, however, it goes without saying that a trepanning drill can only be used in the straight coronal part of a canal. Sometimes the use of superglue or a synthetic resin is recommended; the adhesive is inserted into the hollow needle and pushed over the coronal part of the fragment that has been broken off. In this way, fragments that are already somewhat loose in the canal can be removed. One must be alert to the risk of clogging the canal when an adhesive is used and to weakening, ledge formation and perforation when trepan drills are used.

Canal Finder System

The original canal finder system consists of a handpiece and specially designed files that make an up and down motion with a maximum amplitude of 1-2 mm that decreases as the speed increases. Broken fragments can be passed with these instruments, and the shape of the file sometimes pulls up the broken fragment with it. There is a risk of perforation of the root and moving to apical and even extruding the aborted fragment, especially in curved canals. A clinical study in which the canal finder was used as an initial tool reported a 68% success rate. The system was recently replaced by the EndoPuls system in which stainless steel files make an up and down motion and rotate a quarter turn.

Ultrasound

Ultrasonic instruments are used in multiple ways in endodontics. Narrow diamond-coated stainless steel tips and narrow NiTi tips with an active tip can be used in the removal of degraded fragments. First, a modified Gates glidden drill is used to widen the canal coronally of the aborted fragment. The non-grinding tip of the Gates glidden drill is ground off to create a cutting instrument that is used to remove dentin down to the degraded fragment. The intention is to create a staging platform where an even wall of dentin remains around the fragment. Ultrasonic tips are then used to remove dentin around the coronal part of the fragment in a counterclock-

wise circular motion. This creates space around the fragment, loosens the instrument and sometimes turns it out of the canal all at once. In this process, care should be taken to prevent the instrument from falling into another canal. If too much pressure is applied, there is a risk of the broken fragment moving apically or breaking the ultrasound tip. To prevent breaking of the tip, it is advisable not to let it vibrate freely but only to activate it in contact with the canal wall. A Hedström file, K-file or spreader can also serve as an ultrasonic tip. The files in particular are more fragile, though, so caution is advised. Success rates for removing degraded fragments with ultrasound range from 67% to 88% and 95% in the various studies.

File Removal System

This system was developed by Yoshitsugu Terauchi. The manufacturer claims that with this system, tissue loss is minimal. Two drills are used to create the staging platform where the first drill has a non-grinding "pilot" tip. The cutting drill has a diameter of 0.45 mm. Both drills are flexible, so can also be used in curved channels. The drills rotate counterclockwise and thus can loosen or even remove the broken fragment from the canal. When this does not happen, step 2 follows. This involves using a thin ultrasonic tip to create at least 0.7 mm of space around the coronal part of the file. The tip is spoon-shaped, allowing it to prepare a groove around the broken fragment. Turning counterclockwise with the tip often loosens the fragment and sometimes turns it suddenly out of the canal. If not, step 3 follows. A double-folded NiTi wire is pushed through a hollow tube 0.45 mm in diameter. The resulting loop can be placed around the fragment. The ends of the wire are attached to a handpiece that allows the loop to be tightened or loosened. In *in vitro* studies, this system was used to remove an apically located aborted fragment in a relatively short time. The system has recently gone on sale.

Future techniques

Laser irradiation

2 new publications describe the application of the Nd:YAG laser. The laser can be used to remove dentin around the degraded fragment, then Hedström files can be used to pass the fragment and then remove it. The laser can also be used to vaporize the degraded fragment. Both applications have the advantage that the fragment can be removed in a relatively short time (less than 5 minutes). However, the techniques also have disadvantages, namely the risk of perforations in crooked or narrow roots and the heat generation in the root up to 27 degrees on the root surface. The rise in temperature can cause damage to the periodontal ligament and burning of dentin, making adhesion to the canal wall difficult. Although the study describes several ways to avoid the disadvantages, a foolproof procedure for vaporizing degraded fragments has not yet been developed.

Electrochemical solution of the fragment

Ormiga et al. introduced and tested a new method based on electrochemical solution. Two electrodes are placed in a conductive liquid. One acts as a cathode and one as an anode. The contact between the anode and the degraded fragment, and a voltage difference between the anode and cathode result in the release of metal ions into the solution. This eventually causes dissolution of the fragment in the root canal. The tip of a #20 K3 NiTi instrument was exposed to sodium fluoride and sodium chloride solutions for 8, 17 and 25 minutes and until the entire fragment (6 mm) dissolved. Optical microscopic inspection shows progressive dissolution of the fragment with increasing polarization time. The results show that this method is effective. Despite the limitations (time-consuming procedure for complete dissolution of the fragment and limited space for both electrodes in the root canal), the results are promising and further research is suggested to develop the technique before clinical application.

The tools, techniques and methods described above differ in effectiveness, price and mechanism of action. For example, the Masseranakit has a reported success rate between 48 and 55%, Hülsmann and Schinkel reported an overall success rate of 68% including passing degraded fragments with the Canal Finder. Alomairy reported a 60% success rate with the Instrument

Removal System in an ex vivo study. Higher success rates have been achieved since the introduction of ultrasound: 79% by Nagai, 91% by Nehme, 88% by Fu and 95% by Cujé et al. The combination of ultrasound with microscopic magnification has also contributed to higher success rates. Cujé et al. and Suter et al. attributed their higher success rates to the use of the surgical microscope. Today, the use of microscopic magnification, such as with a magnifying glass, is considered a prerequisite for successful removal of degraded fragments. A protocol in which several methods are used in a fixed order may also contribute to a higher success rate.

Complications of removing aborted instruments

Ledge formation is a commonly described complication. This can result in the inability to further shape and clean the canal. Weakening of the root at the ledge can be a predilection site for the development of cracks and eventually vertical root fractures. Ledges can often be filed away with microscopic magnification with taped files or with a pre-bent hand file used in a filing motion. When the ledge is apical and there is tension-free straight access, the ledge can be passed with a rotary instrument. When the ledge is very close to the apical foramen, the risk of apical transport is very high.

The instruments used to remove broken instruments can themselves break, resulting in an additional complication. Hedström files, K files and ultrasonic tips are especially vulnerable to breakage. For prevention, an ultrasonic tip should be used without irrigation and at a low power setting. At too high a power setting, too much heat generation occurs resulting in breakage of the tip and possible damage to the periodontal ligament (PDL) due to heating. Another preventive measure is the use of air cooling with ultrasound, nevertheless, with prolonged use of ultrasonic vibrating tips in the root canal, substantial heating can occur resulting in loss of the element.

It is essential to obtain straight tension-free access to the broken fragment in order to visualize it and attempt to remove it. Most removal techniques require some dentin to be removed. When working with ultrasound, it is recommended to create a staging platform. This inevitably sacrifices dentin which leads to weakening of the root. Obviously, more dentin is sacrificed the deeper into the root canal the aborted fragment is located. Besides weakening, dentin removal can also lead to perforations and stripper perforations. Especially with narrow and curved roots and with canal walls close to the furcation, one should be alert to the risk of perforation.

If too much pressure is applied to the degraded fragment, the fragment may be displaced apically or even extruded. The pressure can be applied with a removal tool or with an ultrasonic tip. It is not likely to happen when a tip is used next to the fragment, but mainly when it is on the fragment. Again, knowledge, skill and caution are required.

B. Passing the degraded fragment

Removing a broken fragment without damaging the root is not always possible. When the fragment is very deep in the root canal or beyond the bend, passing the fragment is sometimes a better choice. To some extent, this can achieve the intended purpose of root canal treatment, which is to shape, clean and fill the root canal system. Treatment in which a fragment can be passed is considered successful. There are no studies comparing the treatment outcome after removing a fragment with the treatment outcome after passing a fragment. Passing has the risk of creating a *fausse route* in which the original canal is not cleaned and a perforation occurs. To avoid the above complication, it is recommended to work with good magnification and regularly check with X-ray to ensure that no own path is created. The possibility of re-instrument rupture, ledge formation, apical displacement or even extrusion of the fragment should also be considered when passing. An attempt to pass a fragment leads to the creation of space between the fragment and the canal wall, sometimes an ultrasonic instrument can even be placed next to the fragment which still leads to the removal of the fragment. Therefore, passing the fragment is often seen as a first step of fragment removal.

C. Leaving the fragment in situ

When removal of an instrument is unsuccessful, referral to a specialist is preferred. Sometimes it may be chosen to leave the instrument in situ, especially when the fracture occurred in the final phase of treatment and the canal had already been cleaned. Also, when the instrument has broken off in the apical part of the root canal or is beyond a strong curvature in the root canal, removal is not always possible. Cleaning and filling the canal up to the broken fragment is then the alternative strategy. However, the treated element should be closely monitored. When there is persistent apical periodontitis or when apical periodontitis develops, apical surgery often offers a solution.

Surgical treatment options

If the fragment remains in the root canal and symptoms of periodontitis apicalis occur, surgical treatment can be proceeded with. Sometimes surgical follow-up treatment is chosen immediately; indeed, it has been shown that the treatment outcome in the presence of a periapical radiolucency is adversely affected by the presence of a broken instrument. In some elements, the risk of irreversible damage to nearby tissues is too great. Besides apical surgery, intentional replantation, root amputation and hemisection are also mentioned as surgical approaches to still remove the aborted fragment. The various treatment options are discussed with the patient and the most appropriate solution is chosen. When the fragment is in the apical part, it can be removed by resecting the root tip containing the aborted fragment. When the fragment is localized in the middle part of the canal, the canal should be prepared retrograde to the aborted fragment after resection. A leak-free retrograde closure should then be applied. Both approaches require disinfection as well as proper coronal and retrograde closure. There is little clinical research on the influence of the chosen retrograde filling material on treatment outcome. A recent meta-analysis concludes that MTA gives better results than amalgam. A difference in treatment outcome between MTA and IRM could not be demonstrated. In conclusion, technological developments such as the operating microscope, new ultrasound tips and biocompatible filling materials have contributed to a better treatment outcome after apical surgery.

Conclusion

1. Instrument rupture can result in metal fragments obstructing the root canal. Apical to the obstruction, the root canal is no longer accessible for chemo-mechanical cleaning. The degree of infection of this untreated root canal section may adversely affect the outcome of root canal treatment. However, there is as yet no convincing evidence that removing fragments from an endodontic file improves prognosis.
2. There is not yet convincing clinical evidence on the optimal strategy for broken instruments. Factors that influence the approach to be chosen include: anatomical characteristics of the root canal in which the instrument is broken, the stage of treatment at which the fracture occurred, the expertise of the practitioner, available resources, possible complications, strategic value of the tooth and the presence or absence of periapical pathology. Clinical experience and knowledge of the influence of the factors mentioned above as well as the ability to make a considered choice are essential.

Considerations

Quality of evidence

Not applicable. The literature review is based on a recent review in which the evidence was not classified according to GRADE.

Patient values and preferences

It goes without saying that prevention of instrument rupture is of utmost importance. When it does occur, the patient benefits from a careful consideration of the various treatment options with the associated risks of additional damage or complications. When instrument rupture does occur unexpectedly, the patient should be informed.

Professional perspective

The primary objective is to achieve the intended goal of root canal treatment, which is to reduce bacterial infection in order to have no more pathological reaction. The choice of whether or not to remove a broken fragment is determined by the condition of the root canal apical to the broken fragment and the position of the broken fragment: when the instrument broke in the apical one-third beyond the bend and the canal contents consisted of vital pulpal tissue, it is recommended to leave the broken fragment in situ. When the instrument breaks in the early stages of treatment, and the root canal is still filled with necrotic infected material, removal is indicated. When the broken fragment can be visualized with microscopic magnification, in other words, if it is located before the curvature in the root canal, removal is often possible without much tissue sacrifice. For instruments in infected canals that cannot be reached, the risk of tissue loss and extreme weakening of the root must be weighed against leaving the instrument in situ and the persistent infection.

Costs

A referral to a dental endodontist for removal of the broken instrument involves more cost to the patient than leaving it in situ. This cost, as well as the other consequences of the treatment choice, should be discussed with the patient.

Recommendations

Inform the patient of a complication that has occurred.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to informing the patient after the occurrence of a complication.

Consider the following factors when deciding whether or not to remove or have removed the aborted instrument:

- position of the aborted fragment;
- cleaning degree of the root canal;
- available resources;
- risk of complications and
- Presence of periapical lesion.

In the following conditions, consider leaving the aborted instrument in situ:

- No periapical radiolucency is visible on the solo recording at the root where the instrument fracture occurred.
- The root canal apical to the aborted instrument is sufficiently clean by thorough irrigation prior to instrument fracture.
- The fragment is not accessible (located in the apical part of the root canal or beyond the bend).

In all other conditions, removal of the aborted instrument should be considered. This should include the risk of complications; if the aborted instrument is not in the coronal part of the root

canal, removal of the fragment will involve tissue loss to make the fragment accessible

If the practitioner does not feel competent in removing broken instruments or does not have the necessary tools, the practitioner should refer the patient to a dental endodontist.

[unchanged after update 2022/3]

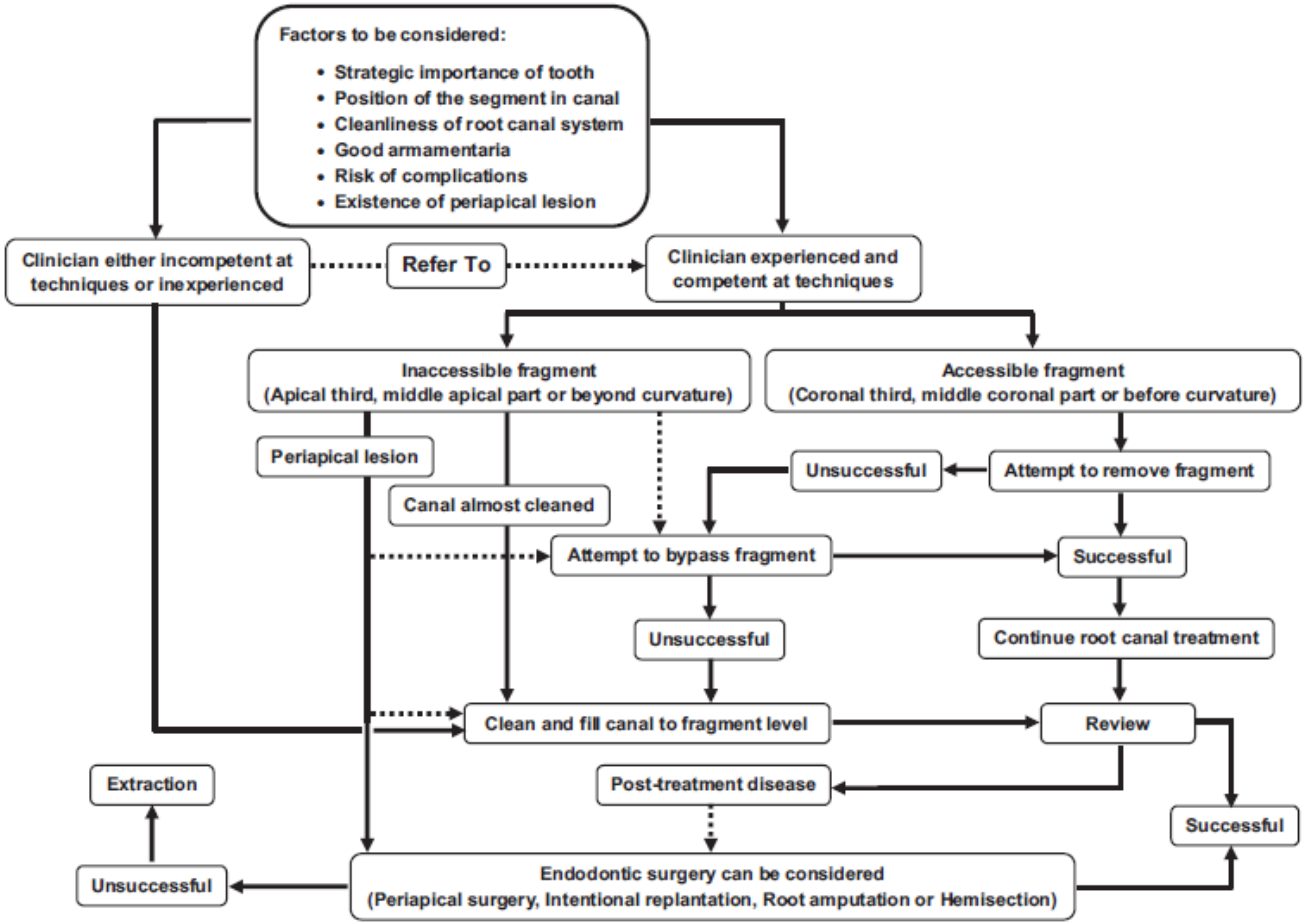
Rational

The guideline working group places great importance on avoiding harm from repairing complications.

Literature

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Appendix 11.1. Decision tree Management of intracanal fractured instruments (dashed lines indicate preferred approaches).



2. What is the effect of perforation on treatment outcome? How to avoid perforations? How to handle a perforation?

Introduction

Root perforations occur due to complications or pathology such as resorption and caries. The literature shows that 47% of iatrogenic perforations occur during root canal treatment and 53% during the restorative procedure. During root canal treatment, perforation may occur during fabrication of the endodontic opening or during canal preparation due to incorrect insertion direction. Preparation of post space is a common cause of perforation during the restorative procedure. In maxillary teeth, perforation occurs almost three times more frequently compared to mandible teeth. One study found that 4.2% of extracted endodontically treated elements were removed because of iatrogenic perforation. Infection due to non-leakage closure of the perforation leads to inflammatory symptoms. Apical displacement of the gingival epithelium toward the perforation leads to periodontal attachment loss.

The goal of a repair is preservation of the tooth by maintaining a healthy periodontium adjacent to the perforation. In recent years, various materials have been studied and recommended for closing root perforations, namely amalgam, plaster, gutta-percha, "indium foil" glass ionomer, "zinc ethoxybenzoic acid cement" and IRM. The probability of successfully closing a perforation has increased since bioceramic materials such as MTA have been used. However, there are few clinical studies on the success of repaired root perforations and it is not known which treatment is most effective in the occurrence of a root perforation.

Method of literature analysis

No *systematic* literature search was conducted. Instead, a recently published systematic review was used (Siew et al., 2015). No systematic review was available on perforation prevention.

Summary of literature

The review used looked at the treatment outcome of perforation repair and mainly preoperative factors affecting the degree of success. Of the 32 studies found, 17 could be included.

The studies used were published between 1974 and 2014, with the majority dating from after 2000. There are several possible explanations why most of the studies are from after 2000. Most likely, it was only considered a real treatment option from then on. The introduction of the operating microscope as an important tool is another explanation and finally, the advent of MTA as a repair material is also an important explanation.

12 of the studies took place in university clinics. Treatment was mainly performed by endodontists or endodontists in training. Some studies included a variety of operators, including oral surgeons, dental students, general practitioners and general practitioners with an affinity for endodontics. In 2 studies, the type of operator was not mentioned. The extent to which outcomes differed according to the type of practitioner was not analyzed by the reviewers.

The average evaluation period ranged from 12 months to 30 years. Treatment outcome was assessed in different ways: 2 studies scored per root rather than per tooth. Most studies had two possible treatment outcomes: success or failure. Some studies added the category of uncertain treatment outcome. The only article on surgically repaired perforations had four possible treatment outcomes (complete healing, partial healing, uncertain healing, and failure). The treatment outcome was determined both clinically and radiographically in all but 1 study.

Almost all studies evaluated a nonsurgical approach. This is obvious because when a perforation occurs, an immediate attempt is made to repair it. Studies that directly compared a non-surgical and a surgical approach are lacking.

For non-surgical repairs, gutta-percha was mainly used until 1990. The more recent studies exclusively describe the use of MTA. A number of other studies report a wide variety of filling materials used (MTA, gutta-percha, Optibond with tetric flow, zinc ethoxybenzoic acid cement, IRM, glass ionomer, amalgam and EBA). In some studies, the material used was not mentioned.

Chances of success

An average success rate could be calculated from 10 studies. The success rate was 72.5% (CI 61.9%-81%) for all repair materials used. The 7 articles in which only MTA was used report a success rate ranging from 57.1% to 100%, meta-analysis of 5 studies (2 studies with 100% success were excluded) report a mean success rate of 80.9% (CI 67.1%-89.8%) for repairs with MTA. The 8.5% difference in success rate is not significant given that the aforementioned confidence intervals overlap significantly. It should be noted that this difference cannot simply be attributed to repair materials other than MTA. Numerous other factors may have played a role. The following preoperative, potential prognostic factors were evaluated:

- Gender;
- number of roots;
- incisives & cuspidates versus (pre-) molars;
- mandibula versus maxilla;
- size of the perforation;
- primary treatment versus re-treatment;
- Presence versus absence of signs and symptoms;
- Presence versus absence of radiolucency immediately adjacent to the perforation;
- Presence versus absence of apical periodontitis;
- time elapsed after recovery perforation (immediate versus < 1 month versus > 1 month) and
- Location of perforation (on versus above versus below bone).

3, sometimes 4, studies with up to 188 repaired perforations could be used to combine the effects of possible potential prognostic factors (Table 12-1).

Table 12-1 Effect of potential prognostic factor on probability of success

Potential prognostic factor	Odds ratio (95% BI).
Gender	
- male	1
- female	1.33(0.64-2.76)
Number of roots	
- 1	1
->1	1,07 (0,48-2,42)
Teeth	
- incisors, cuspidatand	1
- (pre-) molars	1,35 (0,48-3,79)
Position in the jaw	
- mandibula	1
- maxilla	2,22 (1,04-4,76)†
Size of perforation	
-<1 mm	1
-1-3 mm	1,25 (0,44-3,57)
->3 mm	0,58 (0,16-2,06)
Nature of treatment	
-primary treatment	1
-re-treatment	1,26 (0,39-4,09)*
Signs and symptoms	
- present	1

- absent	1,62 (0,77-3,40)*
Radiolucency naast perforation	
- present	1
- absent	2,57 (1,15-5,75)†*
Aperiodontitis	
-absent	1
-present	1,02 (0,45-2,31)
Time elapsed after recovery perforation	
-immediately	1
- < 1 month	1,28 (0,20-8,36)
- > 1 month	0,88 (0,15-5,03)
Location of perforation	
- at	1
- above	2,63 (0,31-21,92)
- below bone	1,63 (0,66-4,04)

Note: †significantly increased probability of success; * inconsistency of outcomes

Of the 11 potential preoperative factors related to nonsurgical repair, two significantly increased the probability of success:

- maxillary teeth have a significantly higher success rate than mandible teeth. This can be explained in two ways: better blood flow and therefore higher healing potential, more overlap on X-rays and therefore higher false negative interpretation of the X-ray image.
- Dental elements without preoperative radiolucency around the perforation have a higher success rate than elements with a radiolucency, although it should be noted that the outcomes in the studies were not consistent among themselves. A lower success rate with preoperative radiolucency around the perforation defect is explained by a long-standing perforation and infection of the perforation.

Two factors, namely a location of the perforation above or below bone level, i.e. not *at* bone level, and absence of signs and symptoms, while showing a reasonably increased probability of success (OR>1.50), are not statistically significant.

Quality of evidence success factors

In the systematic review, the included studies were not assessed for methodological quality. Therefore, to assess the quality of evidence, only the following factor criteria were assessed: circumstantial evidence, imprecision, inconsistency and publication bias.

Exploratory phase 1 cohort studies in which no explicit hypothesis(s) is(are) tested (all included studies included for Table 12-1 were used belong to this category) start as reasonable quality of evidence. It can then be downgraded for any of the aforementioned criteria. For indirect evidence, none of the potential prognostic factors were downgraded, although this can be considered due to the circumstance that the evaluation period was short so there is no certainty regarding longer-term success. For all factors except the two that were significant, one was downgraded for imprecision. For the factor radiolucency around perforation defect and the factor signs and symptoms were discounted by one for inconsistency. Publication bias was not detected.

Conclusions

Undetermined GRADE	<i>Success due to non-surgical repair</i> Non-surgical repair of root perforations has a favorable treatment outcome, with an overall success rate of 73% for all repair materials. When using MTA as a repair material, this success rate may be higher. Siew et al., 2015
Fair to low GRADE	<i>Success due to location of dentition</i> Elements in the maxilla are more likely to be successful than elements in the mandibula. Siew et al., 2015
Low to very low GRADE	<i>Success due to absence of preoperative radiolucency, location of perforation and absence of signs and symptoms</i> Absence of preoperative radiolucency around the perforation defect may give a greater chance of success. Location of perforation below bone level and absence of signs and symptoms may give a greater chance of success. Siew et al., 2015

Considerations

Quality of evidence

It ranges from fair to very low.

Patient perspective

For patients, retention of a tooth is usually preferable.

Costs

These are not relevant to the recommendation.

Professional perspective

The success of a repair is determined by the degree of closure of the perforation defect and the biocompatibility of the material used. MTA seems to be a suitable material for closing perforations because of its biocompatibility and induction of bone formation. In most studies, MTA has been evaluated and also shows a higher although not significant success rate. Other materials such as composite, IRM or super-EBA cement showed chronic inflammatory reaction in direct connection with the material. In addition, the material properties of MTA are not adversely affected by the presence of moisture, which is the case with the other materials. This makes MTA or a similar bioceramic material the material of choice for root perforation repair.

The nonsurgical approach is the most commonly chosen and obvious approach. No comparative studies have been done so we are basing ourselves on the most commonly used. For a successful repair, cleaning and a hermetic seal must be achieved. When both conditions are met, the treatment outcome for a repaired perforation is similar to that of root canal treatment for elements without perforation, regardless of the location of the perforation. However, 1 study found that a perforation in the vicinity of the alveolar bone level gives a higher probability of periodontal breakdown and pocket formation.

Recommendation

Non-surgical repair of a root perforation using MTA material is preferred. The defect to be repaired should be cleaned. When the perforation is above bone level, composite or glass ionomer cement is the material of choice.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to repairing complications and the correct choice of material.

Inform the patient of a complication that has occurred.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to informing the patient after the occurrence of a complication.

Knowledge gaps

Collectively collecting treatment data and the pre- and postoperative status of repaired root perforations may make enough information available in the near future for a more evidence-based recommendation for the treatment of root perforations.

Literature

Siew K, Lee AH, Cheung GS. Treatment Outcome of Repaired Root Perforation: A Systematic Review and Meta-analysis. J Endod. 2015 Nov;41(11):1795-804.

3. How to handle a sodium hypochlorite accident?

A sodium hypochlorite solution ranging from 0.5 to 5.25% is the most commonly used disinfectant. It is a strong oxidizing agent that has a high pH (11-12) in unbuffered form. It is a powerful disinfectant with a broad antimicrobial spectrum through oxidation, hydrolysis and osmosis. An added value of this agent is that it dissolves organic tissue. In addition, at the concentration used, it is little irritant to periapical tissues and does not damage root dentin. Sodium hypochlorite will decompose into Na⁺ and Cl⁻ ions on contact with organic tissue, since the pH also drops rapidly, the end product is harmless. However, if sodium hypochlorite (NaOCl) is pressed accidentally, under pressure, into the periapical tissue, an acute, severe, severe reaction follows, accompanied by a great deal of pain and swelling and sometimes subcutaneous bleeding. From: Thoden van Velzen, *Endodontology*

Method of literature analysis

A systematic literature search was performed in PubMed dated January 19, 2016. Using the search strategy: "Sodium Hypochlorite/adverse effects"[Majr], several publications were found. For this section, the study group selected the article "Guidelines for management of sodium hypochlorite extrusion injuries. This is a recent guideline (2014) that includes the remaining studies found in PubMed.

Summary of literature

Risk Factors

In order to prevent a sodium hypochlorite incident, the risk factors are described first. Often an iatrogenically altered canal configuration is the cause of sodium hypochlorite perforation. These include perforations in the pulp chamber wall or base, perforations in the canal wall or apical overpreparation. Also, resorption defects are a risk factor for sodium hypochlorite perforation. Improper irrigation technique has also been cited as a cause; when the flushing needle becomes stuck in the root canal, there is no longer an opportunity for passive reflux of the fluid. The literature seems to indicate that bone density around the apex affects the likelihood of jacking through: Sodium hypochlorite fractures are more common in the maxilla than in the mandible and more common in women than in men. When the apex is surrounded by only a thin layer of bone or exclusively by soft tissue, even extrusion of a small amount of fluid will lead to symptoms.

Sodium hypochlorite accidents can be divided into mild, moderate and severe categories, for each of the categories, immediate treatment, early treatment and late treatment can be described.

Anamnesis The occurrence of a sodium hypochlorite incident is easily recognized; during irrigation of the root canal, an acute, violent reaction occurs accompanied by a great deal of pain and acute swelling. It is recommended that the degree of pain be recorded using a Visual Analogue Scale in order to demonstrate at a later time that the pain is decreasing. A medical history may reveal additional risk factors such as increased bleeding tendency or risk of infection.

Additional oral examination

Sodium hypochlorite dissolves organic tissue and causes hemolysis. This allows it to be absorbed by superficial blood vessels and spread into soft tissue. This leads to swelling and subcutaneous bleeding (ecchymosis). The degree of swelling and bleeding is recorded; a comparison is made with the contralateral side to determine a percentage increase in facial size. The hematoma may be localized or diffuse in nature. A check of the airway and respiratory and swallowing function is performed. Sensory and motor functions of the N. facialis and N. trigeminal nerve are also tested and reported.

Intra-oral examination

Intra-oral swelling and hematoma are also noted. One should be especially alert for swelling of the oral floor and adjacent structures. There may be ulceration or necrosis of nearby soft tissues. The extent of ulceration or necrosis is accurately recorded, as well as sensory disturbances and percussion and palpation sensitivity of the affected dentition and surrounding tissues. Based on the foregoing investigation, the severity of the accident can be determined.

Table 12-2 Summary of findings during history and clinical examination and corresponding category

Symptoms	Degree of severity		
	Mild	Moderate	Seriously
Pain (VAS)	0-3	4-6	7+
Swelling	<30%	30-50%	>50%
Ecchymosis	Local	Diffuse	Diffuse
Ulceration	No ulceration	Intra oral ulceration	Intra-oral ulceration
Necrosis	No necrosis		Intra-oral necrosis Airway obstruction Neurovascular damage
Follow-up treatment	AP/TE	Consultation or referral to MKA surgeon	Referral to MKA surgeon

Immediate, early and late treatment of mild, moderate and severe sodium hypochlorite accidents
Immediate treatment takes place in the first 24 hours after the accident. Explaining to the patient and prescribing painkillers are top priority.

For mild damage, a commonly available analgesic such as paracetamol is preferred; to control swelling, an NSAID may be chosen. Additionally, application of cold compresses or a cold pack can counteract swelling. An intra-oral radiograph or OPT should be performed to determine the cause of extrusion and may be helpful in further management.

For moderate damage, an opiate may be prescribed in connection with severe pain. Consultation with an MKA surgeon is also recommended.

In cases of severe damage, immediate referral to an MKA department is indicated. In addition to adequate analgesia with opiates, intravenous administration of steroids is required. Intravenous administration of antibiotics should be considered to reduce the risk of secondary infection, especially in immunosuppressed patients. Additional imaging techniques such as T2 weighted MRI or CT are used to determine the effect on surrounding tissues.

Early treatment occurs in the first week after the accident and serves to stabilize the patient prior to any completion of root canal treatment. Application of warm compresses is recommended to stimulate local circulation. The patient should be seen with regularity to treat worsening symptoms in a timely manner. Daily contact is recommended. If the treated tooth should be considered lost due to perforation, for example, extraction can take place during this period.

With moderate damage, additional antibiotic prescribing may be chosen at signs of infection.

In the severe accidents, the same early treatment takes place, but incision and drainage of necrotic tissue is sometimes required. Regular monitoring is indicated to recognize airway obstruction early to treat.

Late treatment occurs when the soft tissues already show healing. If preservation of the tooth is possible, root canal treatment should be completed, taking all possible precautions. With moderate damage, similar late treatment takes place. Sometimes soft tissue lesions arise from loss of fatty tissue in cosmetic areas. These can be treated with fillers, implants or Coleman fat transfer.

Severe lesions may require additional therapy to treat cosmetic defects, motor and sensory nerve damage, and neuropathic pain.

Conclusions

Prevention of sodium hypochlorite accidents is based on proper assessment of potentially present risk factors. When a sodium hypochlorite incident occurs, an assessment of the degree of damage is necessary, as a different approach is indicated for severe damage. Various treatment options are discussed in the literature.

Considerations

Quality of evidence

Not applicable because the literature review is based on a recent guideline, not a review of the studies included therein.

Patient

Perspective It goes without saying that prevention of a sodium hypochlorite incident is of paramount importance. When it does occur, the patient benefits from optimal mitigation of collateral damage.

Professional perspective

The decision to use sodium hypochlorite as a channel disinfectant is based on numerous scientific publications. Because the severity of damage increases with the concentration of the solution used, the required concentration is questioned in several articles. In the context of press-through risk, the lowest effective concentration would be preferable. After occurrence of a sodium hypochlorite incident, accessibility of the health care provider as well as frequent monitoring of the patient is of great importance. In order to record the severity of the damage and monitor the course, light photos can be taken after the accident occurs and at each subsequent checkup.

Cost

It is irrelevant to make recommendations that could reduce costs, other than avoiding sodium hypochlorite accidents.

Recommendations

Accident prevention with sodium hypochlorite:

- Identify risk factors such as perforations and resorptions.
- Avoid jamming the irrigation needle in the root canal.

[unchanged after update 2022/3]

Rational

The guideline working group attaches great importance to the avoidance of sodium hypochlorite injury.

Treatment in the same session in which accident occurred

In mild damage (mild pain, swelling <30%, local hematoma, no ulcerations or necrosis; see Table 12-2), the general practitioner or dental endodontist should:

- Explaining to the patient.
- Prescribe analgesics, preferably an NSAID to control swelling.

- To be cooled by application of cold compresses or a cold pack to control swelling.
- Perform an intra-oral x-ray or OPT to determine the cause of jacking and use in further management.

For moderate or severe damage (moderate or severe pain, swelling >30%, diffuse hematoma, intraoral ulcerations, necrosis, airway obstruction, or neurovascular damage; see Table 12-2) patient should be referred to the MKA surgeon.

Follow-up treatment in the first week after the accident

For mild damage (mild pain, swelling <30%, local hematoma, no ulcerations or necrosis), the general practitioner or dental endodontist should:

- Recommend using warm compresses to stimulate blood flow.
- Perform regular monitoring to identify any deterioration in the patient's condition in a timely manner.

Longer-term follow-up treatment

With mild damage (mild pain, swelling <30%, local hematoma, no ulcerations or necrosis) or after referral back by the MKA surgeon, the general practitioner or dental endodontist should complete the root canal treatment.

Also when completing root canal treatment, use sodium hypochlorite as a root canal irrigant. In some cases, physiological saline may be chosen as a root canal irrigant in consultation with the patient, even though it may adversely affect the treatment outcome.

[unchanged after update 2022/3]

Rationale initial and follow-up treatment (in the first week and longer term)

The guideline working group attaches great importance to distinguishing between mild and moderate or severe damage on the one hand, verifying the correct estimation of the damage level, and completing root canal treatment in the usual manner to optimize the treatment outcome.

Literature

Farook SA, Shah V, Lenouvel D, Sheikh O, Sadiq Z, Cascarini L, Webb R. Guidelines for management of sodium hypochlorite extrusion injuries. Br Dent J. 2014 Dec;217(12):679-84.

Farook SA, Shah V, Lenouvel D, Sheikh O, Sadiq Z, Cascarini L, Webb R. Corrigendum. Practice article (BDJ 2014; 217: 679-684). Guidelines for management of sodium hypochlorite extrusion injuries. Br Dent J. 2015 Feb;218(4):230.

13. Knowledge gaps

There are insufficient randomized, controlled studies in which different methods for disinfection and filling of the root canal of teeth with necrotic pulp have been evaluated for their effect on relief of symptoms, prevention of reinfection, and preservation of the tooth.

Large prospective cohort studies examining what factors influence root canal treatment failure, in terms of persistence or development of a periapical lesion, are lacking.

Collectively collecting treatment data and the pre- and postoperative status of repaired root perforations may make enough information available in the near future for a more evidence-based recommendation for the treatment of root perforations.

The diagnostic accuracy of CBCT has not yet been sufficiently compared with that of conventional, intra-oral X-rays. A good reference standard is indispensable in this regard.

A possible research approach could be, when one imaging technique has a negative result and the other indicates periapical pathology, to take a biopsy during surgical apical endodontic treatment and examine it histologically (source: Petersson et al., 2012).

Phase 1 and 2 prognostic studies are needed to determine the extent to which one or more of the following factors significantly affect the success rate of orthograde (re)treatment:

- Size of the periapical lesion;
- expertise of the practitioner (endodontist vs. general practitioner);
- systemic diseases such as diabetes mellitus, and age;
- presence of broken instruments in the channel or other blockages;
- presence of perforations, and the influence of their locations, size and time;
- Presence and type of a root tip;
- procedures during root canal re-treatment: removal of the old root canal filling, type of mechanical preparation, irrigation and filling, and
- type of element (single-channel elements versus multi-channel elements).

Collectively registering data on endodontic treatment in general and specialty practice can facilitate these Phase 1 and Phase 2 prognostic studies.

In light of minimally invasive endodontology, further research on the success rate of pulpotomy is desirable. Pulpotomy as an alternative to pulpectomy is promising. After all, this treatment costs less, provides more preservation of the structure, is simpler and gives less after pain.

Future scientific research should focus on exploring methods that clarify whether vital but affected pulpae can be preserved or should be removed and replaced with filling material.

More large, longitudinal studies are needed to quantify the risks to general health when apical periodontitis remains untreated.

14. Implementation

Starting questions

1. How can the implementation of this directive be promoted?
2. Are there viable indicators for promoting the quality of endodontic diagnosis and treatment?

How can implementation of the guideline promote endodontic diagnosis and treatment?

The working group does not consider it its task to specify exactly how this directive should be implemented. However, in this brief contribution it wishes to make a number of suggestions to promote implementation.

The following activities have already been undertaken or are underway to promote the implementation of the guideline on endodontic treatment and diagnostics:

- The relevant scientific association (NVvE) is distributing the guideline to all its members.
- The NVvE will review the content of the guideline at least every five years and assess whether partial or total updating is necessary.

The guideline working group proposes the following activities to promote the implementation of the guideline on endodontic diagnosis and treatment:

- Put discussion of the guideline on the agenda at upcoming annual scientific meetings of the NVvE in order to identify "starting problems" with the guideline and enable adjustment.
- Development of patient education materials to support the guideline.
- At the local level - where relevant - transpose parts of the guideline into protocols.
- Publication of key recommendations in the *Dutch Journal of Dentistry* and in the digital newsletter *The Channel*.
- Have the guideline included in the dental practice guideline database.

Are there viable indicators for promoting the quality of endodontic diagnosis and treatment?

The guideline working group established potential structure indicators based on identified core recommendations. Structure indicators do not require the establishment and maintenance of records. Structure indicators can be answered yes/no. Suggested structure indicators are:

- Is the cold test and electrical test *always used* to determine the sensibility, and indirectly vitality, of the pulp?
- [*update 2022/3*] Is occlusal reduction used for the purpose of pain relief?
- Are antibiotics still prescribed for the purpose of pain relief?

The working group recommends that the NVvE Board of Trustees consider the possibilities of having these indicators applied in dental practice.

Appendix starting questions

1. **[H3]** How accurate (sensitivity, specificity, positive and negative predictive value) are the various methods for determining pulpal sensitivity and vitality? Methods: thermal testing, electrical testing, percussion, pulse oximetry and laser Doppler flowmetry.
2. **[H3]** What is the predictive value of methods or markers for the outcome of treatment aimed at keeping the pulp vital, healthy and asymptomatic? Methods/markers: bleeding of the pulp, preoperative pain of mild intensity, thermal testing, electrical testing, percussion, and color and hardness of dentin around the affected pulp (depth of caries lesion).
1. **[H4]** How accurate (sensitivity, specificity, positive and negative predictive value) is a digital X-ray image compared with a conventional X-ray image for detecting changes in periapical tissue?
2. **[H4]** How accurate (sensitivity, specificity, positive and negative predictive value) is a CBCT compared with a periapical X-ray image for detecting changes in periapical tissue?
3. **[H4]** How accurate (sensitivity, specificity, positive and negative predictive value) is color Doppler ultrasound compared to X-ray for detecting changes in periapical tissue?
4. **[H4]** How accurate (sensitivity, specificity, positive and negative predictive value) are color Doppler ultrasound, CBCT and periapical radiographs for determining the nature of the condition (including degree of inflammation, presence of cyst or granuloma, or healing with scar tissue)?
5. **[H4]** How accurate (sensitivity, specificity, positive and negative predictive value) is subtraction radiography compared with an X-ray image for detecting minor bone lesions?
6. **[H4]** Is there a relationship between the width and shape of the paradontal ligament and the vitality of the pulp?
7. **[H4]** [update 2022/3] How accurate (sensitivity, specificity) is CBCT in detecting vertical root fractures in (permanent) elements with canal filling compared to a reference standard (direct visualization by surgical exploration, extraction or orthograde re-treatment)?
8. **[H4]** [update 2022/3] How accurate is CBCT (sensitivity, specificity) in detecting an extra canal in permanent teeth with no root anomalies and no calcification compared to reference standard (micro-CT or 'staining & clearing' or root sectioning)?
1. **[H5]** Is there a difference in effect between stepwise, partial or complete removal of carious dentin?
2. **[H5]** Is there any difference in effect between MTA *versus* other materials and among other materials (Biodentine, glass ionomer cement and calcium hydroxide) in *indirect* pulp capping?
3. **[H5]** Is there a difference in effect between direct pulpal overdenture *versus* partial or complete pulpotomy?
4. **[H5]** Is there any difference in effect between calcium hydroxide, MTA or other materials in *direct* pulp capping?
5. **[H5]** [update 2022/3] Is there any difference in effect between calcium hydroxide, MTA or other materials in *pulpotomy*?
6. **[H5]** Is there a difference in effect between pulpotomy, partial and total pulpectomy?
7. **[H5]** Is there a difference in effect between single-session pulpectomy versus two-session pulpectomy?
8. **[H5]** Is there a difference in effect between occlusal reduction versus no occlusal reduction?

1. **[H6]** In patients with permanent, immature teeth with pulpal necrosis, what is the survival, healing and root development of regenerative endodontic treatment?
 2. **[H6]** In patients with permanent, mature or immature teeth with pulpal necrosis, what is the clinical and/or radiographic success of regenerative endodontic treatment compared with conventional nonsurgical endodontic treatment?
 3. **[H6]** Does the cause of pulpal necrosis (trauma, dens evaginatus and caries) of permanent teeth with immature roots in patients treated with a regenerative procedure affect the outcomes of this procedure?
 4. **[H6]** In patients with permanent, immature teeth with pulpal necrosis, what is the clinical and/or radiographic success of regenerative endodontic treatment in one session compared with regenerative endodontic treatment in a second session?
 5. **[H6]** In patients with permanent, immature teeth with pulpal necrosis receiving regenerative endodontic treatment, what is the effect of using calcium hydroxide *versus* antibiotics as an intra-canal medication on root canal calcification?
-
1. **[H7]** Is there any difference in effect of irrigating with sodium hypochlorite (different concentrations) *versus* chlorhexidine (different concentrations)?
 2. **[H7]** Is there a difference in effect of irrigating with 0.2% chlorhexidine *versus* saline?
 3. **[H7]** Is there difference in effect of irrigating with 1% sodium hypochlorite with additional irrigation of chlorhexidine 2% *versus* saline?
 4. **[H7]** Does the use of lasers in combination with chemo-mechanical cleaning of infected root canals add value?
 5. **[H7]** Is there a difference in effect of irrigating with negative pressure *versus* irrigating with positive pressure?
 6. **[H7]** Is there a difference in effect of irrigating with 1% sodium hypochlorite *versus* a passive ultrasound protocol prescribing 1% sodium hypochlorite, 17% EDTA, and 2% chlorhexidine?
 7. **[H7]** Is there a difference in effect of irrigating with Er,Cr:YSGG *versus* 3% sodium hypochlorite?
 8. **[H7]** Is there a difference in effect of conventional irrigation and ultrasonic (activated) irrigation on postoperative pain intensity and/or pain incidence?
 9. **[H7]** [update 2022/3] Is there difference in effect of *reciprocal versus rotational motion*?
 10. **[H7]** [update 2022/3] Is there a difference in effect of "bioceramic" and resin-based sealers?
 11. **[H7]** Is there a difference in the effect of treating in one session *versus* treating in two sessions?
 12. **[H7]** [update 2022/3] Is there a difference in endotoxin levels in infected root canals before and after application of calcium hydroxide medication?
 13. **[H7]** Does the preoperative status of a tooth with necrotic pulp, with or without periodontitis apicalis, have a significant effect on periapical healing?
 14. **[H7]** Is there difference in effect of adequate *versus* inadequate root canal filling and coronal restoration procedures ?
 15. **[H7]** Is there a difference in effect of administration of systemic antibiotics *versus* no antibiotics/placebo?
 16. **[H7]** Is there a difference in effect of calcium hydroxide paste with 2% chlorhexidine gel *versus* 2% chlorhexidine gel *versus* calcium hydroxide paste *versus* no disinfectant as an intracanal medication?

17. **[H7]** Is there a difference in effect (on postoperative pain) between 5.25% sodium hypochlorite versus 2% chlorhexidine gel as an intracanal medication?
 18. **[H7]** *update 2022/3* Is there difference in effect of retained vs. nonretained apical patency? ("apical patency") ?
1. **[H8]** What is the effect of the number of treatment sessions, instrumentation, disinfection protocol or root filling material on the outcome of *orthograde* re-treatment?
 2. **[H8]** Are there effective methods for preventing or treating postoperative complications after re-treatment?
1. **[H9]** Is removal of the contents of the pulpal chamber in symptomatic pulpitis or symptomatic apical periodontitis as effective in terms of symptom relief as total removal of the contents of the root canal system?
 2. **[H9]** Is there a difference in effect on pain between oral antibiotics and placebo or pain medication in patients with irreversible pulpitis?
 3. **[H9]** Is there a difference in effect on pain, flare-up and swelling between systemic antibiotics and placebo, whether or not combined with surgical intervention, whether or not combined with pain medication, in patients with symptomatic apical periodontitis or acute apical abscess?
 4. **[H9]** *update 2022/3* Is there a difference in effect on pain, flare-up and swelling between inclusion of an intravenous drug and not inclusion of intravenous drug?
 5. **[H9]** *update 2022/3* Is there a difference in effect on postoperative pain between refrigerated and nonrefrigerated irrigants in patients with irreversible pulpitis or pulpal necrosis?
 6. **[H9]** *update 2022/3* What is the *relative* efficacy and safety of oral analgesics given postoperatively (i.e., after nonsurgical endodontic treatment) to patients with irreversible pulpitis or pulpal necrosis?
 7. **[H9]** *update 2022/3* What is the *relative* efficacy and safety of oral premedication on postoperative pain in patients with irreversible pulpitis?
 8. **[H9]** *update 2022/3* What is the *relative* effectiveness of local anesthetics for molars and premolars in the mandible, in terms of success of *inferior alveolar nerve* blockade, in patients with irreversible pulpitis? How safe are these local anesthetics?
1. **[H10]** What factors influence the survival of a tooth that has undergone root canal treatment?
 2. **[H10]** What factors are associated with change in periapical status, insofar as the initial PAI score is ≥ 2 ?
 3. **[H10]** What is the relative effect of root canal filling and coronal restoration on the outcome periodontitis apicalis?
 4. **[H10]** What are causes of failure of restorations with different types of fiber-reinforced posts combined with a synthetic resin cement or "passive" posts with a traditional cement (zinc phosphate or glass ionomer cement)?
 5. **[H10]** What is the effect of the amount of remaining coronal dentin and placement of prefabricated or an individual fiber-reinforced post on the survival of endodontically treated teeth?
 6. **[H10]** Is there a difference in effect between restorations with a cast post structure, or with prefabricated posts or a restoration with composite without a post?
 7. **[H10]** Is there a difference in effect between indirect restoration (metal-ceramic crown) with marker compared with adhesive composite?
 8. **[H10]** Is there a difference in effect between restorations with metal posts compared to restorations with fiber-reinforced posts?
 9. **[H10]** Is there a difference in effect between restoration with post and crown compared to restoration with a crown only?

10. **[H10]** Is there a difference in effect between direct posterior composite and indirect posterior composite restorations for excessive tissue loss of a molar?
 11. **[H10]** [*update 2022/3*] Is there a difference in effect between an endocrown and a conventional crown in the case of damaged endodontically treated teeth?
 12. **[H10]** [*update 2022/3*] Is there a difference in effect between a cotton wool or Teflon as an 'endodontic space maintainer'?
-
1. **[H11]** Can pulpitis or periodontitis apicalis cause systemic disease?
-
1. **[H12]** [*update 2022/3*] What are risk factors for instrument breakage?
 2. **[H12]** What is the effect of instrument breakage on treatment outcome? How to handle instrument breakage?
 3. **[H12]** How does perforation affect treatment outcome? How to avoid perforations? How to act in the event of a perforation?
 4. **[H12]** How to handle a sodium hypochlorite accident?

Appendix members sounding board group

- Drs. L. Cornet
- Drs. F. Dommering
- Drs. R. Fletterman
- Drs. R. Gravemaker*
- Drs. M. de Groot
- Drs. M. Kollenhof
- Drs. I. Reekers
- Drs. T. Broekman-Teggelaar
- Drs. D. van Waaijen*

*involved in updating the directive in 2022/3

Appendix literature search patient perspective

Pubmed January 20, 2017.

Search strategy: ("Attitude to Health"[MAJR] OR "Patient Participation"[MAJR] OR preference*[tiab] OR "Patient Preference"[MAJR]) AND (root canal therapy).

Relevant studies

J Endod. 2012 Oct;38(10):1322-5. doi: 10.1016/j.joen.2012.06.038. Epub 2012 Aug 15.

Patient preferences regarding 1-visit versus 2-visit root canal therapy.

Vela KC(1), Walton RE, Trope M, Windschitl P, Caplan DJ.

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INTRODUCTION: Patient preferences should be taken into account by clinicians when treatment planning. The purposes of this study were to describe the number of visits patients preferred when undergoing root canal therapy (RCT) and to assess whether their preferences were related to hypothetical treatment success rates.

METHODS: Self-administered questionnaires were mailed to 351 consecutive patients scheduled for initial RCT appointments in the University of Iowa College of Dentistry's graduate or faculty endodontic clinic. The questionnaires ascertained demographic information; preferences for 1-visit versus 2-visit RCT given different hypothetical success rate scenarios for the 2 approaches, as well as patient dental history. Univariate frequency distributions were generated, and relationships between hypothetical success rates and patient preferences were evaluated.

RESULTS: Questionnaires were returned by 124 patients (35% response rate). Given equal success rates, 78% of respondents preferred 1-visit RCT, compared with 7% who preferred 2-visit RCT and 16% who would follow their dentist's recommendation. As success rates for 2-visit RCT went from equal to 5% better to 10% better to 20% better compared with 1-visit RCT, the proportion of respondents who preferred 2-visit RCT increased from 7% to 34% to 46% to 65%, respectively. Regardless of success rates, approximately 5% of respondents said they would prefer 2-visit

RCT, and 20% would do whatever their dentist recommended.

CONCLUSIONS: Although most respondents preferred 1-visit RCT regardless of success rates, many would prefer 2-visit RCT if its success rate were greater than that of 1-visit RCT. This finding confirms the importance of discussing success rates and considering patients' wishes when treatment planning.

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Root canal treatment and special needs patients.

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AIM: To identify current trends of root canal treatment for patients with special needs.

METHODOLOGY: A postal questionnaire was sent to General Dentists in Victoria, Australia and Endodontists and Special Needs Dentists across Australia to determine the extent of root canal treatment performed on special needs patients.

RESULTS: Over a four-month period, 1120 questionnaires were distributed with an overall response rate of 63.9% (n = 716). Response rates were 63.2% (n = 655), 68.5% (n = 50) and 100.0% (n = 11) among General Dentists, Endodontists and Special Needs Dentists, respectively. Endodontists (95.7%) and Special Needs Dentists (100.0%) performed significantly more root canal treatment on adult patients with special needs compared with 51.2% of General Dentists, (P < 0.001 and P = 0.001 respectively; Fisher's exact test). The most common reasons for not undertaking root canal treatment included limited cooperation, poor oral hygiene and uncontrolled movement. Amongst General Dentists, 75.7% opted for extraction in preference to root canal treatment. Significantly, more specialist practitioners performed root canal treatment utilizing conscious sedation (P < 0.001) and general anesthesia (P = 0.003). Most specialist practitioners

(69.1%) had undertaken single-visit root canal treatment on special needs patients compared with only 29.7% of General Dentists (P < 0.001).

CONCLUSIONS: Root canal treatment in special needs patients was more likely to be carried out by specialist dental practitioners who were more likely to utilize a pharmacological approach for behavior guidance and to perform single-visit root canal treatment compared with General Dentists. A multidisciplinary approach for special needs patients who require root canal treatment provides an opportunity for these patients to retain their dentition.

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PMID: 24871933 [PubMed - indexed for MEDLINE].

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Quality of life and satisfaction of patients after nonsurgical primary root canal treatment provided by undergraduate students, graduate students and endodontic specialists.

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AIM: (i) To assess the impact of primary root canal treatment on the perceived quality of life amongst a cohort of Jordanian patients, (ii) to assess this cohort's satisfaction of their primary root canal treatment, and (iii) to evaluate the association of the level of training and experience of clinicians with these two parameters.

METHODOLOGY: A systematic random sample of 302 subjects was selected from patients who attended undergraduate, graduate and specialty clinics of Jordan University of Science and

Technology. Participants were interviewed before and two weeks after completion of root canal treatment. The study instrument included the Oral Health Impact Profile questionnaire (Dugas et al. 2002) and seven semantic differential scales. Data analyses included descriptive statistics and

nonparametric analyses.

RESULTS: More than 90% of subjects reported improvements in the sense of taste, pain, eating, altering food temperature, self-consciousness, waking up during sleep, interruption of meals, difficulty to relax and difficulty to sleep after root canal treatment. There was no significant difference in terms of improvement amongst patients treated by specialists, graduate students or undergraduate students. The overall semantic differential score of intraoperative pain, pleasantness, chewing ability and general satisfaction was about 8. Satisfaction of root canal treatment by specialists was higher in terms of time involved, intraoperative pain, pleasantness and general satisfaction than those treatments by undergraduate students. Patients treated by specialist were least satisfied with the treatment cost compared to those patients treated by graduate or undergraduate students.

CONCLUSIONS: The impact of root canal treatment on the quality of life was apparent. Satisfaction with root canal treatment approximates 8 on the semantic differential scale with preference for specialists over dental students.

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A survey of patients' preferences for the treatment of teeth with apical periodontitis.

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INTRODUCTION: This research aimed to investigate the preference of patients in Toronto, Canada for management of a tooth affected by painful apical periodontitis when considering its retention via root canal treatment (RCT) and its extraction followed by no replacement, replacement with an implant-supported crown, fixed, or removable partial prostheses.

METHODS: Data were collected through a mail-out survey of the University of Toronto Faculty of Dentistry patients, which was complemented by a convenience sample of patients in 10 community practices in Toronto (n = 1000, response rate = 43%). Participants were asked to select their general preference for anterior and posterior teeth with apical periodontitis between saving the tooth or extraction and their specific preference for tooth retention via RCT or extraction. By using bivariate and logistic regression analyses, we applied the Gelberg-Andersen Behavioral Model for Vulnerable Populations to the preference questions to understand the influential factors ($P \leq .05$).

RESULTS: Participants' specific preference for tooth retention via RCT was slightly but significantly lower than their general preference (anterior tooth, 93.7% versus 97.2%; posterior tooth,

83.8% versus 89.6%; $P < .005$). Higher annual income, previous RCT, functional dentition, good/excellent self-rated oral health, and regular dental visits were associated with higher preferences for tooth retention in response to different questions.

CONCLUSIONS: The high preference for retaining a tooth in general was moderated by the specific consideration of RCT to retain the tooth. When RCT and extraction are viable options, patients should be advised about the treatment options in an impartial manner and encouraged to communicate their preferences.

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J Endod. 2014 Jun;40(6):784-9. doi: 10.1016/j.joen.2014.01.045. Epub 2014 Mar 29.

Clinical decision making for a tooth with apical periodontitis: the patients' preferred level of participation.

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INTRODUCTION: To effectively engage patients in clinical decisions regarding the management of teeth with apical periodontitis (AP), there is a need to explore patients' perspectives on the decision-making process. This study surveyed patients for their preferred level of participation in making treatment decisions for a tooth with AP.

METHODS: Data were collected through a mail-out survey of 800 University of Toronto Faculty of Dentistry patients, complemented by a convenience sample of 200 patients from 10 community practices. The Control Preferences Scale was used to evaluate the patients' preferences for active, collaborative, or passive participation in treatment decisions for a tooth with AP. Using bivariate and logistic regression analyses, the Gelberg-Andersen Behavioral Model for Vulnerable Populations was applied to the Control Preferences Scale questions to understand the influential factors ($P \leq .05$).

RESULTS: Among 434 of 1,000 respondents, 44%, 40%, and 16% preferred an active, collaborative, and passive participation, respectively. Logistic regression showed a significant association ($P \leq .025$) between participants' higher education and preference for active participation compared with a collaborative role. Also, immigrant status was significantly associated with preference for passive participation ($P = .025$).

CONCLUSIONS: The majority of patients valued an active or collaborative participation in deciding treatment for a tooth with AP. This pattern implied a preference for a patient-centered practice mode that emphasizes patient autonomy in decision making.

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Community Dent Oral Epidemiol. 2004 Feb;32(1):55-66.

Utilities of dentin regeneration among insured and uninsured adults.

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OBJECTIVES: This population-based study measured utilities (preferences measured under conditions of uncertainty) of dentin regeneration (DR), a potential new therapy, root canal therapy (RCT), and extraction (EXT).

METHODS: A representative sample of dentate adults (aged 18-69 years) was randomly selected from the Detroit area. A computer program was used to administer the standard gamble (SG) method and record utility score (US) for treatment options of a tooth with reversible pulpitis using the SG method. For the SG method, two anchor states were used: filled tooth with full oral health and filled tooth with severe and continuous pain leading to EXT. Additional data were obtained using a self-administered questionnaire.

RESULTS: Out of the 807 adults who resided in 446 screened and selected households, a final sample of 630 adults who resided in 368 households were interviewed. The mean US for DR with 75 and 95% success rates were 72.5 and 86.2 (on a 0-100 scale), respectively. The US for RCT and immediate EXT were 75.6 and 31.3, respectively. Eleven per cent of the adults valued DR with 95% success probability higher than a simple filling with full oral health for life. There were no statistically significant differences in the average US of DR between insured and uninsured adults. Factors such as gender, race, education, income and insurance status, experiences with EXTs or root canal treatment, regularity of dental visits, quality of life, and quality of oral health were not significantly associated with the scores of DR. There was, however, a small but significant interaction between race and dental insurance, and race and gender.

CONCLUSION: This population-based study found that DR was highly preferred to other standard treatment options.

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DOI: 10.1111/j.1600-0528.2004.00127.x

PMID: 14961841 [PubMed - indexed for MEDLINE].

J Dent Educ. 2006 Feb;70(2):133-41.

A chairside aid for shared decision making in dentistry: a randomized controlled trial.

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The concept of shared decision making (SDM) is an important emerging trend in clinical medicine but has received little or no attention in the dental literature. Decision aids can play a useful role in SDM by helping patients and clinicians choose among reasonable alternative treatment options. The purpose of this study was to develop and test an Endodontic Decision Board (EndoDB) for chairside use to help clarify treatment alternatives, benefits, risks, prognosis, and costs when root canal therapy or extraction of a tooth was indicated. The hypothesis was that the use of the EndoDB would lead to improved patient knowledge, greater satisfaction with the decision-making process, and no difference in anxiety when compared to the standard discussion and informed consent process (usual care). The EndoDB was tested in a randomized controlled

trial in a postgraduate endodontics clinic. After treatment discussion, a brief questionnaire was completed by the patient to measure knowledge, satisfaction, and anxiety. Patients in the EndoDB group (n=32) demonstrated a small, but statistically significant, increase in knowledge (t-test; difference=+0.37; p=0.03) compared to the usual care group (n=35). There was no difference between groups in the measures of satisfaction or anxiety (Mann-Whitney U-test; p>0.05). Decision aids may emerge as a useful tool to facilitate SDM and evidence-based clinical practice.

PMID: 16478927 [PubMed - indexed for MEDLINE].

J Eval Clin Pract. 2007 Feb;13(1):102-8.

Racial differences in treatment preferences: oral health as an example.

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RATIONALE, AIMS AND OBJECTIVES: Recent analyses from the Florida Dental Care Study found that response to a hypothetical scenario at baseline strongly predicted: (a) tooth loss during follow-up; and (b) subsequent receipt of either a dental extraction or Root Canal Therapy (RCT). The scenario ('CHOICE') required choosing either to: (1) extract the tooth before even knowing the cost of treatments; (2) extract, but after knowing the cost of all treatments; or (3) have RCT despite knowing costs.

OBJECTIVE: The purpose of this study was to identify factors associated with CHOICE and quantify their effects.

METHODS: As part of the baseline phase of the study, 873 subjects with at least one tooth and who were 45 years or older participated for an interview and dental examination. A multinomial multivariable regression of CHOICE quantified effects due to hypothesized predictors.

RESULTS: CHOICE was strongly associated with race (African-Americans were significantly less likely to choose RCT). Results from the multivariable regression suggest that the race effect could be explained by racial differences in patient preference, treatment acceptability and ability to afford treatment.

CONCLUSIONS: There were substantial racial differences in treatment preference even in this hypothetical scenario where racial differences in patient-provider interaction and clinical factors were not relevant. Certain predisposing and enabling variables explained these racial differences in treatment preference.

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PMID: 17286731 [PubMed - indexed for MEDLINE].

Int Endod J. 2002 Oct;35(10):812-9.

Patients' attitudes to rubber dam.

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AIM: The aims of this study were to record patients' views of their experience of RD use in an objective manner, and to evaluate the influence of some personal and clinical factors on patients' opinion.

METHODOLOGY: A questionnaire was designed which was then distributed to patients receiving dental treatment under RD by (a) final-year dental students at Birmingham Dental School, and (b) general dental practitioners. Patients completed the confidential questionnaire anonymously after treatment, outside the treatment room. After 100 correctly completed forms were collected from group (a) and 106 from group (b), data were entered into a database and subsequently analyzed using SPSS. Analyses were confined to simple cross-tabulations of the patients' responses and potential associated factors, with chi-square analysis and appropriate follow-up comparisons wherever necessary.

RESULTS: In both groups, the majority of patients said they would prefer RD to be used at their next appointment, and most had a positive opinion of the experience. No statistically significant association between age, sex, procedure, application time or duration of use and preference for rubber dam was found. Prolonged RD use showed some association with a negative opinion of the experience of RD. Compared with the dentists, students took longer to apply rubber dam and it was in place for longer. Fewer student patients preferred RD next time, and were less positive about its use than the dentists' patients.

CONCLUSIONS: Further evidence is presented that (i) Patients generally are not averse to RD. (ii) Placement of rubber dam does not take long. (iii) Operator experience improves patient compliance.

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64. Ned Tijdschr Tandheelkd. 2007 Jul;114(7):296-9.

[Post-academic dental specialties 13. What are anxious dental patients most afraid of?].

[Article in Dutch]

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What are the dental stimuli and situations that are experienced as more or less fear provoking by anxious dental patients? To investigate this question, 81 highly anxious patients, who were referred to a center of special dental care were presented with a list of 76 potentially fear-provoking objects and situations.

The results showed that invasive dental procedures are considered as most terrifying by anxious patients, and that stimuli related to the dental office (dental chair), the dental team (dentist) and their equipment (protecting clothes) are considered as least fear provoking. Root canal treatments were rated as most fear provoking. The results emphasize the importance of assessing the whole range of potentially terrifying stimuli for each anxious patient. Only in this way an approach focused on the extinction of patients' dental fear can be successful.

Appendix

Evidence profile 1

Biodentine compared to glass ionomer cement for indirect pulp capping in patients with reversible pulpitis

Bibliography: Hashem et al. Clinical and Radiographic Assessment of the Efficacy of Calcium Silicate Indirect Pulp Capping: A Randomized Controlled Clinical Trial. Journal of Dental Research 2015, Vol. 94(4) 562-568.

Outcomes	Nº of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with glass ionomer cement	Risk difference with Biodentine
clinical success follow up: mean 12 months	72 (1 RCT)	⊕⊕○○ LOW ^{1,2}	RR 1.00 (0.81 to 1.23)	833 per 1,000	0 fewer per 1,000 (158 fewer to 192 more)

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Unclear concealment of allocation. Operator unblinded.
2. Wide confidence interval. Less than 300 events.

Evidence profile 2

Mineral trioxide aggregate compared to calcium hydroxide cement for indirect pulp capping

Bibliography: Leye Benoist et al. Evaluation of mineral trioxide aggregate (MTA) versus calcium hydroxide cement (Dycal) in the formation of a dentin bridge: a randomized controlled trial. International Dental Journal 2012; 62: 33-39

Outcomes	Nº of par (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with calcium hydroxide cement	Risk difference with mineral trioxide aggregate
clinical success follow up: mean 6 months	60 (1 RCT)	⊕⊕○○ LOW ^{1,2}	RR 1.23 (0.96 to 1.57)	733 per 1,000	169 more per 1,000 (29 fewer to 418 more)
radiological success follow up: mean 6 months	60 (1 RCT)	⊕⊕○○ LOW ^{1,2}	-	The mean radiological success was 0 mm	MD 0.014 mm higher (0.03 lower to 0.06 higher)

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Inadequate sequence generation and concealment of allocation. single blind.
2. Wide confidence interval crosses no effect.

Evidence profile 3

Pulpotomy compared to Pulpectomy in permanent molars with irreversible pulpitis

Bibliography: Asgary 2013; Asgary 2014; Asgary 2015

Outcomes	Nº of par (studies) Follow-up	Quality of the evi- dence (GRADE)	Relative effec (95% CI)	Anticipated absolute effects	
				Risk with Pulpectomy	Risk diffe- rence with Pulpotomy
Pain intensity post-operative (PI) assessed with: NRS numerical rating scale) Scale from: 0 (no pain) to 9 (worst pain) follow up: mean 7 days	407 (1 RCT)	⊕⊕○○ LOW 1,2,3,4	-	The mean pain intensi- ty post- operative was 1.26 points	MD 0.59 points lower (0.58 high- er to 0.6 higher)
% clinical success assessed with: subjective & objective signs & symptoms follow up: mean 12 months	342 (1 RCT)	⊕⊕○○ LOW 1,2,3	RR 0.993 (0.963 to 1.024)	983 per 1,000	7 fewer per 1,000 (36 fewer to 24 more)
% clinical success (clinical success 24 mo) assessed with: subjective & objective signs & symptoms follow up: mean 24 months	332 (1 RCT)	⊕⊕○○ LOW 1,2,3,5	RR 1,000 (0.971 to 1.030)	982 per 1,000	0 fewer per 1,000 (28 fewer to 29 more)
% radiographic success assessed with: radiograph follow up: mean 12 months	342 (1 RCT)	⊕⊕⊕○ MODERATE 2,3,5,6	RR 1,312 (1,180 to 1,459)	703 per 1,000	219 more per 1,000 (127 more to 323 more)
% radiographic success assessed with: radiograph follow up: mean 24 months	332 (1 RCT)	⊕⊕○○ LOW 2,3,5,6,7	RR 1.083 (0.982 to 1.195)	795 per 1,000	66 more per 1,000 (14 fewer to 155 more)
clinical success assessed with: subjective & objective signs & symptoms follow up: mean 60 months	271 (1 RCT)	⊕○○○ VERY LOW 1,2,3,5,7,8	RR 1.026 (0.901 to 1.168)	761 per 1,000	20 more per 1,000 (75 fewer to 128 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Pulpotomy compared to Pulpectomy in permanent molars with irreversible pulpitis

Bibliography: Asgary 2013; Asgary 2014; Asgary 2015

Outcomes	Nº of par (studies) Follow- up	Quality of the evi- dence (GRADE)	Relative effec (95% CI)	Anticipated absolute effects	
				Risk with Pulpectomy	Risk diffe- rence with Pulpotomy

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Detection bias due to knowledge of the allocated interventions by outcome assessors. I have some doubts about the randomization procedure. The authors do not mention the specific type of randomization. In multicenter trials it is common to use balanced randomization (most commonly permuted blocks within center) to ensure similar proportions of treatment assignments across centers. I assume this method has been used. As far as the statistical analysis is concerned, the authors do not report whether or not differences in outcome occurred between centers.
2. not applicable (1 study)
3. Concrete information on the composition of calcium-enriched mixture cement is lacking. During hand instrumentation, canals were frequently irrigated with adequate amount of sterile normal saline solution. In the Netherlands the usual procedure is irrigating with NaOCl.
4. It is assumed that a mean difference of at least 1.0 is clinically relevant using a 10-points NRS-scale
5. It is assumed that an absolute effect of 100 per 1,000 more is clinically relevant.
6. Assessment by independent experienced endodontists and oral radiologists
7. Therefore confidence interval crosses thresholf for clinical relevance
8. Not downgraded by two levels although percentage of drop-outs is more than 30%, but the number of dropouts is equal in both groups. Therefore it is assumed that no additional bias was introduced.

Evidence profile 4

Penicillin combined with partial or total pulpectomy compared to no penicillin combined with partial or complete pulpectomy for symptomatic apical periodontitis or acute apical abscess

Bibliography: Cope A, Francis N, Wood F, Mann MK, Chestnutt IG. Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD010136.

Outcomes	Nº of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative eff (95% CI)	Anticipated absolute effects	
				Risk with no penicillin combined with partial or complete pulpectomy	Risk difference with penicillin combined with partial or total pulpectomy
Pain at 24 hours Assessed with: short ordinal numerical scale Scale from: 0 to 3 follow up: mean 24 hours	61 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	-	The mean pain at 24 hours was 0	MD 0.03 lower (0.53 lower to 0.47 higher)
pain at 48 hours assessed with: short ordinal numerical scale Scale from: 0 to 3 follow up: mean 48 hours	61 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	-	The mean pain at 48 hours was 0	MD 0.32 higher (0.22 lower to 0.86 higher)
pain at 72 hours assessed with: short ordinal numerical scale Scale from: 0 to 3 follow up: mean 72 hours	61 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	-	The mean pain at 72 hours was 0	MD 0.08 higher (0.38 lower to 0.54 higher)
swelling at 24 hr assessed with: different scales follow up: mean 24 hours	62 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	-	-	SMD 0.27 SD higher (0.23 lower to 0.78 higher)
swelling at 48 hr assessed with: different scales follow up: mean 48 hours	61 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	-	-	SMD 0.04 SD higher (0.47 lower to 0.55 higher)
swelling at 72 hr assessed with: different scales follow up: mean 72 hours	61 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	-	-	SMD 0.02 SD higher (0.49 lower to 0.52 higher)

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardized mean difference.

Penicillin combined with partial or total pulpectomy compared to no penicillin combined with partial or complete pulpectomy for symptomatic apical periodontitis or acute apical abscess

Bibliography: Cope A, Francis N, Wood F, Mann MK, Chestnutt IG. Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD010136.

Outcomes	Nº of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative eff (95% CI)	Anticipated absolute effects	
				Risk with no penicillin combined with partial or complete pulpectomy	Risk difference with penicillin combined with partial or total pulpectomy

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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- a. Rates of withdrawal were in excess of 20% across groups, with higher rates of withdrawal from the placebo than the penicillin group in one trial. The other trial was unclear regarding reporting drop-outs.
 - b. Interventions differed in two trials (partial and/or total pulpectomy; pain medication regimen)
 - c. Less than 400 patients.