Interventions for treating cavitated or dentine carious lesions

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Interventions for treating cavitated or dentine carious lesions

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the clinical and cost-effectiveness of interventions (non-selective, selective or stepwise carious tissue removal, sealing of carious lesions using sealant materials or preformed metal crowns, or NRCC) to treat carious lesions conventionally considered to require restorations (cavitated or micro-cavitated lesions, or occlusal lesions that are clinically non-cavitated but clinically/radiographically extend into dentine) in primary or permanent teeth with vital (sensitive) pulps.

BACKGROUND

Description of the condition

Dental caries is the most prevalent disease worldwide, with billions of individuals affected by the resulting burden of pain, loss of function, impaired aesthetics and speech (Marcences 2013; Kassebaum 2015). The oral microbiota are organised on dental hard tissues as biofilms and, under healthy conditions, these biofilms contain limited numbers of cariogenic bacteria (including streptococci and lactobacilli). The condition of dental caries is caused by a shift in the composition of the oral microbiota towards increased proportions of cariogenic bacteria. The mineral loss from dental hard tissues (enamel and dentine) caused by these bacteria is usually reversible, with mineral supply from dental saliva leading to remineralisation. If fermentable carbohydrates (i.e. sugars) are supplied regularly and in sufficient amount, cariogenic bacteria metabolise the carbohydrates to produce organic acids, thus decreasing the pH within the biofilms (which is why they are termed 'acidogenic' bacteria). As these acidogenic bacteria are also aciduric (i.e. acid-tolerant) while most other bacteria are not, they increasingly dominate the biofilm. This imbalance in the biofilm results in a discrepancy in the mineral loss and gain, with a resulting net mineral loss. If this continues over time, it can lead to development of a

carious lesion as the symptom of the caries disease process (Marsh 2010; Takahashi 2011). Carious lesions can range from very early, non-detectable mineral loss, that is restricted to enamel, through to lesions that extend into dentine without any surface cavitations, to cavitated lesions, which destroy the tooth tissue and can be visible as holes in the teeth.

Description of the intervention

Traditionally, all carious lesions have been treated by removing all demineralised (affected) and bacterially contaminated (infected) dentine and replacing it using restorations (based on, for example, amalgam or composite), commonly known as a 'filling'. However, the pathophysiology of the disease process means that carious lesions can be controlled by altering the factors leading to net mineral loss. This can be achieved by reducing carbohydrate intake; removing or controlling the activity of the biofilm; sealing the tooth surface from the environment; or rebalancing demineralisation and remineralisation, for example, by applying fluoride.

For carious lesions where the tooth tissue surface has become cavitated, these options are often no longer feasible, as the biofilm is sheltered and cannot be easily removed or manipulated. In such situations, invasive (restorative) options are considered to still be required in most cases, as indicated by a recent document published by the International Caries Consensus Conference Collaboration (Schwendicke 2016a). Cavitations that are clinically hard to detect (often called microcavitations) may, upon radiographic assessment, be found to penetrate into the dentine. These dentinal lesions have traditionally also been considered to require a restoration (Ricketts 1995), especially when the lesion has entered the middle third of the dentine, and hence harbours large amounts of bacteria (Bakhshandeh 2018).

There are six main strategies that we expect to be the focus of this Cochrane Review, all considered suitable for treating cavitated/dentine carious lesions that would historically have been regarded as in need of a restoration. These include cavitated lesions, microcavitated lesions and occlusal lesions, which appear clinically to be non-cavitated but clearly extend into dentine seen radiographically or clinically as grey shadowing.

- Non-selective carious tissue removal. Carious dentine and enamel are removed, usually until only sound enamel and hard dentine remain. The cavity is subsequently restored (this review does not focus on the material, e.g. amalgam, composite etc. or how this restoration is performed).
- Selective carious tissue removal. Carious dentine and enamel are removed, usually until only sound enamel and hard dentine remain at the cavity periphery, while centrally, dentine of different hardnesses (soft, leathery or firm) remains. The cavity is subsequently restored.
- Stepwise carious tissue removal. Carious dentine is removed, as the first step, as described for selective removal to soft dentine. The cavity is restored, for example using glass ionomer cement or composite material, for some months. During this time, the lesion is arrested as sealed bacteria are inactivated, dentine remineralises, becomes hardened and dried, and tertiary dentine is laid down close to the lesion. These processes result in a lower risk of pulp exposure in the second step, which is traditionally carried out as described for selective carious tissue removal to firm dentine. Note that in older studies, the second step may have been non-selective removal (Magnusson 1977).
- Sealing using sealant materials such as resins and glass ionomers, placed over the carious lesion, depriving the carious biofilm of substrate. Sealants are placed without any prior tissue preparation, although some have advocated some preparation (fissurotomy, enameloplasty). We will only include studies where sealants have been placed without any carious tissue removal; enamel may have been prepared/bevelled prior to sealing as long as no carious dentine was removed.
- The Hall Technique. A preformed metal crown is pushed over a carious primary molar tooth to seal in the carious lesion. None of the carious tooth tissue is removed and, as previously described, the biofilm cariogenic activity is reduced by being deprived of nutrients and the lesion is arrested as the bacteria become inactive.
- NRCC. The cavity shape is made cleansable, and the tooth tissue is repeatedly and frequently cleansed by the patient or carers to remove the biofilm, remineralise the lesion and prevent it progressing.

How the intervention might work

Restoration involves the removal of demineralised carious dentine and enamel (also termed 'excavation') to allow a filling, which can be made using a variety of materials, to be placed on stable or suitably supportive tooth tissue. The process of carious tissue removal can be undertaken to various degrees. All or most carious dentine can be removed with a 'non-selective' approach using a single endpoint for removal; for example, removal until hard dentine in all parts of the cavity. Alternatively, carious dentine close to the dental pulp can be left and sealed beneath the restoration, with removal until hard dentine performed in the periphery of the cavity. This has been termed 'selective carious tissue removal'. Varying endpoints are used to guide dentine removal in different areas of the cavity (e.g. hard dentine is left peripherally, while soft or leathery or firm dentine is left centrally). A combined stepwise approach can also be used to treat deep carious lesions. This approach involves selective removal to soft dentine as an initial step; the cavity is then sealed for some months until a second selective removal to firm dentine is performed (Innes 2016). As only minimal numbers of bacteria are thought to survive long-term below a restoration sealing, it is proposed that reduced dentine removal (resulting in increased residual dentine thickness and avoiding pulp exposure), may improve patient benefit with limited subsequent risk. However, it is currently unclear which of these

strategies is most suitable for carious lesions that require restoration (Bjørndal 1997; Bjørndal 2000; Paddick 2005; Schwendicke 2016b; Bjørndal 2017).

The carious process is fundamentally the same for primary and permanent teeth. However, primary teeth are more vulnerable to the process as they have slightly less mineral content, the enamel and dentine layer is thinner, the dental pulps are relatively larger and the teeth are smaller. The anatomy also affects the sequelae of dental caries; dental infection tends to manifest more quickly in primary teeth. This is because the communications between the tooth and bone, where developing infection can escape from the confine of the tooth, tend to be at the top of the roots in primary teeth rather than the base of the roots as in permanent teeth. These differences mean that primary teeth tend to require relatively less disease process to experience pain and infection. There is also some evidence that the biofilm in primary teeth may show differences; for example, in early childhood caries, concurrent candida infection is often seen (Xiao 2016).

It has also been shown that, in some cases, no removal of carious tissue is needed at all; instead, carious lesions can either be sealed or otherwise controlled (Mertz-Fairhurst 1998). Sealing places a barrier on top of the tooth surface, thereby protecting it from any further mineral loss, and isolating sealed bacteria from dietary carbohydrates, thereby inactivating them (Oong 2008). Various sealant materials are used, including resin-based and glass ionomer products. However, as these materials can be damaged by wear and tear from chewing, sealing cavitated carious lesions with them is not usually recommended currently (Schwendicke 2016a). Instead, in primary teeth, sealing can be achieved by using preformed stainless steel crowns. This approach, the Hall Technique, has no need for local anaesthesia, tooth preparation or carious tissue removal. It is not currently clear whether sealing carious tooth tissue using sealants (primary and permanent teeth) or the Hall Technique (primary teeth) results in good outcomes for teeth that have traditionally been considered required carious tissue removal and restoration (Innes 2011; Santamaría 2017).

Based on the outlined caries pathogenesis, there have been investigations into whether it might be enough to simply control biofilm activity in cavitated carious lesions by repeated and frequent removal of the biofilm through toothbrushing, using fluoride to remineralise, or using antimicrobials/remineralising agents such as silver diamine fluoride. However, this may not always be possible or work well where the biofilm is sheltered. Based on this idea, another intervention called Non-Restorative Cavity Control (NRCC) aims to remove overhanging enamel from the cavity to allow easy access to the biofilm/lesion for cleansing and removal. The lesion can then be controlled by toothbrushing using fluoridated products, provided the patient or their carers successfully adopt and carry out this behaviour. With varying results, NRCC has, so far, also been suggested for primary teeth and root surface caries only; however, it might be suitable for other carious lesions (Gruythuysen 2010; Santamaria 2014; Hansen 2017).

Why it is important to do this review

Millions of people have carious lesions treated every day; overtreatment would carry a significant burden. Dentists worldwide are faced daily with decisions about how best to treat carious lesions that were conventionally considered to be in need of restoration: when and how to remove carious tissue, how much tissue to remove, and even whether carious tissue should be removed at all. This creates large treatment variation among clinicians (Schwendicke 2016c; Innes 2017), which is not the best standard-of-care for the patient. A previous Cochrane Review evaluated operative interventions for managing carious lesions (Ricketts 2013); a number of studies have been published since that review was undertaken and methods for synthesising relevant data have advanced. Given the prevalence of the disease, its lifelong sequelae, and the high direct and indirect costs generated (Schwendicke 2013; Schwendicke 2014; Listl 2015; Schwendicke 2015), there is a great need to evaluate which currently available interventions are most suitable for managing cavitated/dentine carious lesions.

OBJECTIVES

To determine the clinical and cost-effectiveness of interventions (non-selective, selective or stepwise carious tissue removal, sealing of carious lesions using sealant materials or preformed metal crowns, or NRCC) to treat carious lesions conventionally considered to require restorations (cavitated or micro-cavitated lesions, or occlusal lesions that are clinically non-cavitated but clinically/radiographically extend into dentine) in primary or permanent teeth with vital (sensitive) pulps.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compare any of the interventions. We will include studies that have been randomised by individual or by cluster. Split-mouth studies will also be eligible for inclusion. We will exclude cross-over trials from this review as the condition, dental caries, cannot return to baseline level following the initial intervention.

We will include studies that compare the interventions described for carious lesions with each other, placebo, or no treatment. If multiple records of the same study are available, we will extract data from all time points although we will consider outcome data from the last follow-up for use to allow rates of outcome events to be pooled.

Types of participants

Participants with permanent or primary teeth, and vital pulps (i.e. not diagnosed as having irreversible pulpitis or pulp necrosis), and carious lesions conventionally considered to be in need of a restoration, i.e. cavitated lesions on x, y and z surfaces or, on occlusal surfaces, non-cavitated or micro-cavitated but radiographically extending into dentine.

We have used the description "carious lesions considered to be in need of a restoration" as we expect some, especially older, studies will not report on lesion depths or the state of the tooth surface integrity, but may state that lesions required restoration. This pragmatic approach means that although these studies may not directly inform clinical practice recommendations, inclusion of their data will contribute to the planned analysis. However, we will conduct a sensitivity analysis excluding the studies which do not fully report lesion depth or tooth surface integrity.

Types of interventions

Interventions include any comparison of conventional (non-selective), selective or stepwise carious tissue removal, sealing of carious lesions using sealant materials or preformed metal crowns, or NRCC. We will also include 'no treatment' interventions. Note that not all interventions will have been applied in all situations where restorations might have been considered the traditional 'standard'. We acknowledge that indications for each procedure differ depending on their presentation such as dentition (primary/permanent), lesion depth (shallow/ moderate versus deep lesions), clinical surface integrity (non-cavitated occlusal versus clearly and extensive cavitated proximal-occlusal) or surface extent (one-, two- or three-surfaced lesions) as well as surface location (occlusal, smooth surface, proximal, root surface). For this reason it's important to know what the pair-wise/network comparisons might look like as the different indications increase the risk of NMA not being appropriate/feasible, and even influences the pair-wise comparisons that should be made.

Thus, we plan to evaluate interventions according lesion depth, surface integrity, surface extent and location, conducting separate analyses for the primary and permanent dentition. We acknowledge that there could be studies that combine primary and permanent teeth but we will endeavour to obtain data for each dentition separately. We expect lesion depths to be heterogeneous in the ways they are measured and recorded (clinically, radiographically) and reporting, which is why, at this stage, we plan to distinguish shallow/moderate lesions from deep lesions. Shallow/moderate lesions are those that do not extend into the pulpal area or do not risk exposing the pulp during carious tissue removal, as measured subjectively, or not extending into the inner third or quarter of dentine as shown on a radiograph. We consider deep lesions as those close to the pulp, risking exposure, extending into inner third or quarter of dentine.

We have tried to list all likely competing interventions and the types of lesions, teeth and the situations around which they are likely to be used in Table 1. We will consider each of these interventions for inclusion in the network meta-analysis (NMA) but we will analyse those carried out in primary and permanent teeth separately.

The review will not evaluate different filling materials.

Types of outcome measures

Primary outcomes

- Presence or absence of major complications, which is a composite measure of any complications that result in endodontic therapy (pulp capping, pulp therapy or root-canal treatment etc. or extraction of the tooth). This includes signs or symptoms of irreversible pulpal inflammation or death (including pain) and other complications, such as pulp exposure or restoration fracture or failure or lesion progression leading to root-canal treatment or extraction. The study authors may present outcomes as single outcomes, but we will combine them as composite outcomes where appropriate. We will extract and report individual outcomes. Where included data are not presented as separate outcomes or are cross-tabulated, we will contact the study authors for further information. The following primary outcomes will therefore be included:
    - Composite outcome of major complications (including endodontic treatment or extraction);
    - Endodontic treatment;
    - Extraction of tooth.

Secondary outcomes

- Minor complications, which also is a composite measure including, for example, restoration loss treated by re-restoration, or partial restoration failure treated by repair (Innes 2007). Similar to the primary outcome, these aspects of this secondary outcome may be presented in the studies as single outcomes. They will also be extracted and reported as single outcome items, but will be put together as composite outcomes for the review where appropriate.
- Subjective evaluation of the treatments by participants, regardless of the outcome measure used.
- Efficiency (time needed for the intervention), costs or cost-effectiveness (regardless of how effectiveness was defined; note that we will also include cost-utility or cost-benefit as outcomes).
- Any safety issues (e.g. allergies) that are related to the interventions.

Search methods for identification of studies

Cochrane Oral Health's Information Specialist will conduct systematic searches for RCTs and controlled clinical trials. Due to the Cochrane Centralised Search project to identify all clinical trials on the database and add them to CENTRAL, we will only search recent months of the Embase database. Please see the searching page on the Cochrane Oral Health website for more information. We will not place any other restrictions on the language or date of publication when searching the electronic databases.

Electronic searches

Cochrane Oral Health's Information Specialist will search the following databases.

- Cochrane Oral Health's Trials Register.
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Register of Studies.
- MEDLINE Ovid (from 1946 onwards).
- Embase Ovid (previous six months to date).

The subject strategies for databases will be modelled on the search strategy designed for MEDLINE Ovid in Appendix 1. Where appropriate, this will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Box 6.4.c; Lefebvre 2011).

Searching other resources

We will search the following trials registries.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

We will not perform a separate search for adverse effects of interventions. We will consider adverse effects described in included studies only.

Data collection and analysis

The methodology for data collection and analysis is based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The authors will comply with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) document (Chandler 2013).

Selection of studies

At least two review authors will independently screen the titles and abstracts of records retrieved from the search against the inclusion criteria. We have designed the literature search to be sensitive and include controlled clinical trials; we will filter these out early in the selection process if they are not randomised. If either review author finds a record potentially eligible, we will obtain and assess full texts, again independently and in duplicate. Two review authors will decide on inclusion by consensus, or in consultation with a third review author. We will list all studies excluded after full-text assessment in the 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors will independently extract the data from each included study using a specially designed data extraction form, which we will first pilot on a small sample of studies. All review authors who are performing data extraction will pilot this form on the same paper(s) and we will compare the content of the fields. The number of papers required for training to ensure calibration will depend on the degree of agreement. We will contact study authors for clarification or missing outcome data where necessary and feasible. We will resolve any disagreements through discussion and will consult a third review author when necessary to achieve consensus.

We will extract the following data and record it in the 'Characteristics of included studies' table.

- Methods: trial design, location, number of centres, recruitment period.
- Study details: year of publication and year or study, inclusion/exclusion criteria, number randomised/analysed, study setting (e.g. school, practice).
- Population: age, sex and number of participants, baseline caries experience.
- Potentially important effect modifiers (dentition; surface location; lesion depth; surface integrity, surface extent).
- Interventions: detailed description of the interventions, including number of teeth treated per participant.
- Outcome data: details of the outcomes reported and the outcome measures, including method of assessment and timepoint(s) assessed.
- Other: funding sources, declarations/conflicts of interest.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each included study using the Cochrane domain-based, two-part tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will contact study authors for clarification or missing information concerning sequence generation where necessary and feasible. We will resolve

any disagreements through discussion, consulting a third review author to achieve consensus when necessary.

We will complete a 'Risk of bias' table for each included study. For each domain of risk of bias, we will first describe what is reported to have happened in the study. This will provide the rationale for our judgement of whether that domain is at low, high or unclear risk of bias.

We will assess the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective outcome reporting (reporting bias).
- Other bias.

Measures of treatment effect

Relative treatment effects

We will analyse dichotomous outcomes (presence or absence of complications) by calculating the log odds ratio (lOR), and back transforming the pooled effect estimate to be expressed as an odds ratio. For continuous outcomes, we will pool data with mean difference (MD), or standardised mean difference (SMD Hedges's adjusted g) if different measures are used to assess the same outcome. We will present the results from the NMA and pair-wise analyses as pooled effects for each clinically relevant comparison.

Relative treatment ranking

We will estimate the relative ranking of the different interventions according to our primary outcome using NMA. We will use mean ranks and the cumulative ranking curve (SUCRA) (Salanti 2011; Chaimani 2013), based on the mean treatment effect, to obtain a hierarchy of the competing interventions according to our primary outcome.

Unit of analysis issues

Cluster-randomised trials

Where a participant is randomised to a single intervention, and multiple lesions within a person are being evaluated, we will consider the person to be the cluster and the lesions clustered within an individual. Where a cluster is randomised to a single intervention, for example a dental clinic, and each participant within the dental clinic is allocated to this treatment and generates outcome data, then the clinic will be the cluster and the participants clustered within the clinic.

In split-mouth studies, one or more teeth are randomised to an intervention and comparator trial arm.

Studies with multiple treatment groups

We will account for the correlation between the effect sizes from multi-arm studies in the NMA. We will treat the multi-arm studies as multiple independent two-arm studies in pairwise meta-analyses.

Dealing with missing data

We will use the methods described in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing standard deviations. We will not use any other statistical methods or perform any further imputation to account for missing data (Higgins 2011c).

Assessment of heterogeneity

Clinical and methodological heterogeneity within treatment comparisons

We will assess the presence of clinical heterogeneity (according to lesion depth, surface integrity, surface extent and location) within each pairwise comparison by comparing the trial and study population characteristics across all eligible trials. We will generate descriptive statistics for trial and study population characteristics across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics. If a sufficient number of studies are included in pairwise comparison, we will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes. We will only carry out meta-analyses where there are studies of similar comparisons that report the same outcomes.

Measures and tests for heterogeneity

We will assess statistically the presence of heterogeneity within each pairwise comparison using a Chi² test, where a P value < 0.1 will indicate statistically significant heterogeneity. We will quantify heterogeneity using the I^2 statistic and its 95% confidence interval (CI) that measures the percentage of variability that cannot be attributed to random error. An I^2 statistic of: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. This is according to Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing distribution of potential effect modifiers across the different pairwise comparisons of the network. We will evaluate any clinical features that moderate the effects of the different interventions, including dentition, lesion location (surface affected), lesion extension (number of surfaces involved), lesion depth (clinically or radiographically measured) and surface integrity (cavitation status), to investigate the distribution of these across studies grouped by comparison.

Should we consider that the assumption of transitivity has not been met, for example, in terms of substantially imbalanced distributions of prespecified effect modifiers (see above), then we will not conduct an overall NMA. Instead we will consider subgrouping studies so that NMA might be possible. We will consider performing a series of independent pairwise meta-analyses if we observe heterogeneity within but not across treatment comparisons.

Assessment of statistical heterogeneity

Assumptions when estimating heterogeneity

In standard pairwise meta-analyses, we will estimate different heterogeneity variances for each pairwise comparison. In NMA, where feasible, we will attempt to model non-common heterogeneity parameters as opposed to a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

We will base our assessment of statistical heterogeneity in the entire network on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the NMA models. We will estimate a total I^2 statistic value for heterogeneity in the network (Jackson 2014).

Assessment of statistical inconsistency

We will evaluate the statistical agreement between the various sources of evidence in a network of interventions (consistency). Since different approaches may lead to different conclusions about the magnitude of inconsistency, we will use both local and global approaches.

Local approaches for evaluating inconsistency

We will use the loop-specific method to examine the consistency between direct and indirect data (Veroniki 2013). After calculating inconsistency estimates and comparing them with the direct estimates we will assess whether the inconsistency factor os incompatible with a zero null value using a 95% CI and z-test.

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network we will use the 'design-by-treatment' interaction model (Higgins 2012). After we obtain the difference between the direct and indirect estimates, we will use a 95% CI and z-test to infer whether the inconsistency factor is incompatible with a zero null value.

Assessment of reporting biases

If at least 10 studies are included in a meta-analysis, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If we identify asymmetry, we will examine possible causes. For the NMA, we will use a comparison-adjusted funnel plot to assess network-wide publication bias.

Data synthesis

Methods for direct treatment comparisons

Initially, we will perform standard pairwise meta-analyses using the random-effects model in Stata 14 where there is sufficient data for each treatment comparison (StataCorp 2015).

Methods for indirect and mixed comparisons

We will perform NMA using a multivariate approach in Stata 14. We will use the mvmeta command (White 2015), and self-programmed Stata routines available at www.mtm.uoi.gr.

Subgroup analysis and investigation of heterogeneity

If we observe important heterogeneity or inconsistency, or both, we will explore possible sources. If sufficient data are available, we will conduct a meta-regression or subgroup analysis according to lesion depth (shallow/moderate or deep). We will also investigate the impact of lesion location (occlusal, smooth surface, proximal, root surface), lesion surface integrity (non-cavitated occlusal versus clearly and extensive cavitated proximal-occlusal) and surface extent (one-, two- or three-surfaced lesions). We will analyse primary and permanent teeth separately because of their anatomical and subsequent disease sequelae manifestation differences.

Sensitivity analysis

We will conduct a sensitivity analysis to investigate the effect of including studies that have not clearly specified lesion depths, state of the tooth surface integrity but state only that the lesion is "considered to be in need of a restoration".

Presentation of results

Using GRADEpro GDT software, we will generate 'Summary of findings' tables for the main comparisons and primary outcome (major complications) as per the overall and subgroup analyses. We will consider non-selective carious tissue removal as the reference intervention. We will assess the quality of the evidence using GRADE criteria (GRADE 2013).

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Interventions

Interventions	Standard practice (yes/no)	Primary/permanent teeth	Lesion depth (deep/shallow)	Tooth surface location (occlusal/smooth surface/proximal/root surface)	Tooth surface integrity (non-cavitated/cavitatedl)	Surface extent (1/2/3 surfaced lesions)
Non-selective carious tissue removal	Yes	Primary and permanent teeth	Shallow and deep	All	Cavitated	All
Selective carious tissue removal	Yes	Primary and permanent teeth	Shallow and deep	All except root surface	Cavitated	All
Stepwise carious tissue removal	Yes	Primary and permanent teeth	Deep	All except root surface	Cavitated	All
Fissure/proximal sealing	Yes	Primary and permanent teeth	Shallow	All except root surface	Mainly non-cavitated	1 surface

Table 1. Interventions (*Continued*)

Hall technique	Yes	Primary teeth	Shallow and deep	All except root surface	Cavitated	All
Non-restorative cavity control	Yes	Primary and permanent teeth	Shallow and deep	All	Cavitated	All

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. Dental caries/
2. (caries or carious).tw.
3. ((tooth or teeth or dentin$ or dental) adj5 (decay$ or lesion$ or cavit$)).tw.
4. or/1-3
5. Dental cavity preparation/
6. "carious tissue removal".tw.
7. ((caries or carious or cavit$) adj5 (stepwise or excavation or excavator$)).tw.
8. ((caries or carious or cavit$) adj5 ((selective or partial or incomplete) adj2 remov$)).tw.
9. ((caries or carious or cavit$) adj5 ((minimal or minimum) adj2 invas$)).tw.
10. (dentin$ adj3 remov$).tw.
11. "Pit and fissure sealants"/
12. seal$.tw.
13. Crowns/
14. (crown$ or "Hall Technique").tw.
15. "non-restorative cavity control".tw.
16. or/5-15
17. 4 and 16

The above search will be combined with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

CONTRIBUTIONS OF AUTHORS

Falk Schwendicke conceived, designed and wrote the protocol.

Tanya Walsh wrote the Methods section of the protocol.

Margherita Fontana, Lars Bjørndal, Janet E Clarkson, Thomas Lamont, Colin Levey, Gerd Gostemeyer, Ruth M Santamaria and David Ricketts revised the protocol.

Nicola PT Innes helped conceive, design and write the protocol.

DECLARATIONS OF INTEREST

Falk Schwendicke: none known.

Tanya Walsh: none known. I am an Editor with Cochrane Oral Health.

Margherita Fontana: in the last 36 months, I have received grant support from the National Institutes for Health (NIH), the Delta Dental Foundation, DentaQUest, Colgate; have served as a grant reviewer for NIH, have consulted for 3M, DentaQuest and served as part of the National Scientific Advisory Committee for Delta Dental Foundation, and been a member of the Council for Scientific Affairs of the American Dental Association.

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