Minimum Intervention (MI) in Dentistry

Evidence based Compendium – Database Plus+ handbook

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Minimum Intervention (MI) in Dentistry
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Preface
Evidence-based medicine has been described as integration of the best available evidence into daily clinical practice under consideration of individual clinical expertise by the care provider (Sackett et al. 1996). Before the best available evidence can be integrated it needs to be found, however, within the ever-increasing volume of scientific studies. Finding it is the purpose of systematic reviews. According to the Cochrane Collaboration, systematic reviews establish where the effects of healthcare vary and where they are consistent. In order to achieve the goal, explicit systematic methods are applied to reduce the chance effect and limit systematic error/bias and thus, provide more reliable results (Antman et al. 1992 and Oxman et al. 1993). Limiting bias by identifying studies of high internal validity is important. Egger et al. (2003) have shown that inadequate allocation concealment during the randomization process, alone, in clinical trials may lead to a 54% overestimation of the true result, as a direct impact of selection bias! The efficacy and patient benefit of any clinical procedure based on such overestimation has to be regarded as unfit for use in clinical practice and its advocacy or even use for patient treatment should be condemned as unethical. Having best available evidence for integration in daily clinical practice is particularly important when applying Minimum Intervention (MI) in dentistry. MI as an oral health care philosophy is still new and promises patients the highly desirable benefits of information regarding the risk of disease onset when still healthy, earliest disease detection as soon as an ailment occurs and the subsequent option of the least invasive, thus most patient-friendly, treatment. To find and present the best available evidence in MI is the aim of this handbook accompanying the ‘MI Compendium-PLUS+ database’. This first edition includes published systematic reviews with meta-analyses covering the remineralising effect of Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP); the anti-cariogenic properties of conventional glass ionomer cements (GIC) as fissure sealants and restorative material and the longevity of restorations placed in accordance with the Atraumatic restorative treatment (ART) approach.

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CHAPTER 1

Introduction to minimum intervention in dentistry

This chapter is an updated modification of the publication by Mickenautsch S. An introduction to minimum intervention dentistry. Singapore Dent J 2005; 27: 1-6.
Introduction
Minimum (or minimal) intervention dentistry (MI) can be defined as a philosophy of professional care concerned with the first occurrence, earliest detection, and earliest possible cure of disease on micro (molecular) levels, followed by minimally-invasive and patient-friendly treatment to repair irreversible damage caused by such disease\(^1\).

Based on MI understanding, tooth caries is considered to be a multifactor disease resulting in lesions of the tooth hard tissues\(^2\). The disease starts with a disturbance of the oral mineral balance between remineralization and demineralization on the tooth surface. Such changes occur on micro (molecular) levels first. The reasons are an increase in bacterial metabolism and subsequent increase in acid production, as well as an increase in bacteria numbers. Contributing factors are an increased intake in frequency and amount of carbohydrates (sucrose) and the absence of fluoride, as well as reduced saliva flow, buffering capacity and pH\(^2\). In addition, modifying factors such as changes in lifestyle, general medical conditions, socioeconomic circumstances, and patient compliance also play a role\(^3\). The caries disease process starts with an oral imbalance and progresses into reversible symptoms (non-cavitated lesions) first, but extends into irreversible symptoms (cavitated lesions) with subsequent loss of tooth structure and aesthetic, masticatory, phonetic, and biological functions. The period of transition from lesion to cavity depends on its location on the tooth. For example, an interproximal lesion may take up to 4 years to become a cavity and take another 4 years to reach the pulp\(^4,5\).

On the other hand, cavitation in occlusal pits and fissures often manifests quicker because of masticatory forces pushing plaque deeper into fissures and putting pressure on the demineralized enamel\(^5\). Hence, the decision as to when and how to treat caries depends to some extent on its location on the tooth surface. Furthermore, the transition from lesion to a small cavity and from a small to a large cavity evolves gradually and into various sizes, each with its own spectrum of treatment requirements.

Disease risk assessment and early diagnosis
The goal of MI is to stop disease first and then to restore lost structure and function. To be able to stop tooth caries as early as possible, present caries risk and caries activity should be established. Caries risk may be assessed from a number of predictors such as baseline caries prevalence, Streptococcus mutans levels, salivary buffering capacity and flow rate, as well as fissure retentiveness. Caries activity can be determined from the speed at which carious lesions progress\(^3\). Earliest caries detection, traditionally by use of mirror and light, as well as bitewing radiographs, can now be aided by new developments in dental magnification and imaging, laser fluorescence or quantitative light-induced fluorescence\(^3,6-8\).
Long before cavitation occurs, caries disease starts as a result of exposure to risk factors such as increased sugar consumption and eating frequency, or the breakdown of protective saliva properties. These changes can be measured using chair side tests for saliva buffering capacity, pH, viscosity, and flow, as well as tests for oral bacteria levels. Furthermore, information on dietary habits and absence or presence of fluoride may assist in detecting further caries risk. A patient interview within a relaxed atmosphere may help to establish information on disease modifying factors (medical conditions, lifestyle, socioeconomic background, oral hygiene habits), as well as a patient’s possible compliance level with future health interventions\textsuperscript{3,9-11}. All of this information completes a comprehensive diagnosis of the disease. Specific software programmes have been developed to summarize measured factors and to provide individual caries risk profiles for patients\textsuperscript{12}. Quantified risk profiles may assist in motivating patients to collaborate within the frame of an individual treatment plan. Such a plan may include adjustments in modifying and contributing factors, as well as antibacterial intervention.

**Disease control and early treatment**

Any intervention, whether first-time or secondary, i.e. restoration-replacement, needs to first heal the caries lesion and control the disease. Without disease control, any replacement will fail because of continued disease activity. MI treatment on micro or molecular levels starts, e.g. with fighting the bacterial activities and healing reversible carious lesions. Bacterial activities may be controlled using a wide range of treatment methods, which may involve the use of chlorhexidine, diammine silver fluoride, triclosan, or cavity seal by chemical material adhesion\textsuperscript{13-17}. After disease control, the loss of minerals from tooth hard tissues needs to be addressed and the oral balance between de- and remineralization processes on the tooth surface regained. This may be done through “external remineralization” (on the tooth surface) and in cavity walls through “internal remineralization” (Hien Ngo, Dental School, University of Adelaide, South Australia; oral communication, September 2004). In general, remineralization depends on the presence of water, a pH higher than 6.5, and the availability of minerals such as calcium and phosphate. Remineralization of the tooth surface relies on an increase in saliva flow, which can be aided by an increase in fluid intake and the use of sugar-free chewing gum. Efficient oral hygiene and diet adjustments help to reduce acidic conditions and adjust the pH to neutral levels by reducing the substrate availability for bacterial metabolism. Mineral availability can be supported by the use of dentifrice containing casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) and fluoride\textsuperscript{2,18}. Remineralization within cavity walls relies mainly on the use of a therapeutic biomimetic filling material like glass ionomer cement (GIC). GICs are hydrophilic and provide a good seal (by chemical adhesion) and a constant mineral and fluoride release\textsuperscript{2,19}. During this
period of caries treatment, repeated patient recalls for diagnostic measurements, monitoring, and patient motivation may be required. Treatment should continue until the bacterial infection is controlled and reversible carious lesions are healed. Once “absence of disease” is achieved, the irreversible loss of structure and function can be addressed using minimally-invasive, patient-friendly treatment options.

Minimally-invasive treatment
Minimally-invasive treatment in dentistry is not new and was pioneered in the early 1970s with the application of diammine silver fluoride\textsuperscript{20}. This was followed by the development of the preventive resin restoration (PRR)\textsuperscript{21} in the 1980s and the atraumatic restorative treatment (ART) approach\textsuperscript{22} and chemo-mechanical caries removal concepts\textsuperscript{23} in the 1990s. These ultraconservative treatment concepts are applied with the intention to preserve as much tooth tissue as possible and to offer more patient-friendly care to fearful patients. Minimally-invasive, long-term repair of tooth cavities may comprise aspects in preparation to gain cavity access using air-abrasion, laser treatment, or sono-abrasion\textsuperscript{24–26} and excavation of infected carious tooth tissue through selective caries removal or laser treatment\textsuperscript{24,26}, as well as cavity restoration by applying ART, PRR, or sandwich restoration treatment protocols\textsuperscript{1,21,22,27}. In comparison to the traditional treatment modality using amalgam, MI restorations are usually smaller and its procedures considered being relatively painless, often without the need for local anesthetics. However, if needed, local anesthetic can be administered less invasively by using computer-controlled local anesthetic delivery systems\textsuperscript{28}. Failed restorations are repaired rather than replaced\textsuperscript{2}.

Benefits of MI
The benefit for patients from MI lies in better oral health through disease healing, not merely symptom relief. Furthermore, MI may assist in reducing widespread patient dental anxieties, which are usually caused by conventional, highly invasive dental procedures\textsuperscript{29–34}. Health care funders, who have been reluctant to pay for MI services, should reconsider rewarding dentists for early caries detection and disease healing, rather than paying only for treating the end results of caries such as cavitation, pulp death, and tooth loss. Such a paradigm shift is important, since MI knowledge and clinical skills amongst dental practitioners worldwide is increasing\textsuperscript{35}. The benefit of MI for dentists as practice builders is demonstrated by the responses to a questionnaire administered within a pilot study amongst 118 randomly selected members of the South African public. Fifty percent of the respondents said that they visited the dentist only when they had a problem. However, 90% said they would go more often if dental treatment were less threatening and less invasive. Almost 90% of respondents disliked aspects related to highly invasive
treatment, such as drilling or injections, the most (S. Mickenautsch, unpublished data, 2004).

Conclusion
MI has the potential for dentists to apply a more conservative approach to caries treatment and simultaneously offer patients a more friendly and health orientated treatment option. MI based caries treatment in daily dental practice has been suggested to rely on clinical applications such as:

*Disease risk assessment by chair-side testing of*
- Streptococcus mutans level;
- Saliva flow, -pH and buffer capacity.

*Early disease diagnosis by use of*
- Dental magnification and imaging;
- Laser fluorescence;
- Quantitative light-induced fluorescence.

*Minimally-invasive treatment by application of*
- Air-abrasion;
- Atraumatic restorative treatment;
- Casein phosphopeptide-amorphous calcium phosphate;
- Chemo-mechanical caries removal;
- Chlorhexidine;
- Computer-controlled local anesthetic delivery systems;
- Diammine silver fluoride;
- Glass-ionomer cements;
- Laser;
- Sono-abrasion;
- Sugar-free chewing gum;
- Topical fluoride;
- Triclosan.

Further MI applications are currently under development or already pioneered. As the clinical implementation of MI is still new, there is a need for the best available evidence and its continuous update in order to show its efficacy in daily dental practice.
References


CHAPTER 2

Adopting minimum intervention in dentistry:
Diffusion, bias and the role of scientific evidence

This chapter is an updated modification of the publication by Mickenautsch S. Adopting MI: Diffusion, bias and the role of scientific evidence. Int Dent SA 2009; 11: 16-26.
Introduction

Since the beginning of this millennium information about clinical procedures and the benefits of minimum intervention are increasingly disseminated\(^1\)\(^-\)\(^8\). As with any innovation, the wide adoption of minimum intervention by the dental profession is reliant upon factors related to the process of diffusion\(^9\). This chapter aims to highlight the roles that *Research bias* and *Scientific evidence* can play in this process.

Minimum intervention

Minimum Intervention (MI) in dentistry aims to empower patients, through information, skills and motivation, to take charge of their own oral health in order to be in need of only minimum intervention from the dental profession (Hien Ngo, National University of Singapore; oral communication, September 2004). Although the focus of MI in dentistry has so far been on caries-related topics\(^10\), the approach follows the 3-step philosophy of:

1. Disease risk assessment;
2. Early disease detection;

Such philosophy is applicable to any type of disease\(^2\). MI enables the healthcare provider to advise healthy patients about their risks regarding possible future ailments\(^11\). Such risks may be due to aspects related to a patient’s lifestyle or to other factors with the potential to have an impact upon health\(^12\). These aspects are then quantitatively assessed to determine the basis on which addressing the identified risk factors through targeted prevention are possible\(^13\). Patients with manifest disease are helped by as early as possible identification of such manifestation\(^14\)-\(^16\). As disease at an early stage is often relatively contained, treatment can consequently be simple, very conservative and minimally-invasive\(^1\).

Laboratory findings, clinical considerations and protocols, materials and technologies for all three steps of MI in dentistry have been reported elsewhere\(^3\)-\(^6\),\(^17\). Patients benefit from MI because MI focuses on the cause of disease instead of on merely addressing disease symptoms\(^7\). A further benefit is MI’s patient-friendly nature, due to its range of minimally-invasive treatment options. MI treatment is considered to be atraumatic, since patients experience less discomfort and pain than traditional treatment options incur\(^8\).

Experience and expectation of pain and discomfort during dental treatment has been associated with dental fear\(^18\). A study investigating the dental fear levels of children and adults during, e.g. atraumatic restorative treatment (ART), in comparison to those receiving traditional restorative treatment using high-speed drilling, found patients treated with ART to
be significantly less fearful than the others\textsuperscript{19}. Patients with low levels of dental fear are more cooperative during treatment than those with high fear levels\textsuperscript{20}. Positive patient attitude and cooperation resulting from reduction of fear during treatment sessions benefits the healthcare provider, as a direct correlation between dental fear and operator stress in daily dental practice has been observed\textsuperscript{21}.

These MI benefits: (i) Treatment of disease causes instead of mere symptoms; (ii) Reduction of patient discomfort and (iii) Reduction of operator stress are reasons for adopting MI into daily dental practice.

**Diffusion of innovation**

Despite its stated benefits the still new philosophy of MI faces, as most innovations commonly do, the process of diffusion. Rogers\textsuperscript{9} (2003) defined “innovation” as an idea, practice or object that is perceived as new, and “diffusion” as the process through which innovation spreads. Diffusion comprises: (i) the innovation itself; (ii) the type and availability of channels through which the innovation is communicated to others; (iii) time and (iv) the prevailing social system\textsuperscript{9}.

The social system constitutes the community of potential adopters of innovation, categorized as follows: the innovators themselves, early adopters, early majority, late majority and laggards\textsuperscript{9}. Rogers (2003) estimated the percentage distribution of these groups as being 2.5%, 3.5%, 34%, 34% and 16%, respectively\textsuperscript{9}. Except for the innovators themselves, these adopter groups’ responses to innovation can vary between adoption, non-adoption or rejection\textsuperscript{22}. An innovation is considered self-sustaining once it has been accepted by 10-20% of all potential adopters\textsuperscript{9}.

**Research bias**

One of the factors governing the response to an innovation by potential adopters is insecurity concerning uncertainties about the advantages of new ideas, practices or objects as compared to those of current ones\textsuperscript{22}. Skepticism regarding claims of superiority of new ideas, practices or objects is justified if these are based on studies containing high degrees of research bias, also known as systematic error. Bias has been defined as “any process at any stage of inference tending to produce results that differ systematically from the true values”\textsuperscript{23}.

The most important types of bias in clinical studies are selection-, performance-, detection- and attrition bias (Table 1)\textsuperscript{24}. Bias may affect studies by causing either an over- or under estimation of the treatment effect of an investigated clinical procedure. This may lead to a situation where a new ineffective treatment procedure is presented as effective or an effective
treatment is presented as ineffective. The overestimation of a treatment effect through bias has been observed to be the most common\textsuperscript{25}, thus providing the rationale for late adopters to doubt superiority claims of any innovation at the onset. Schulz et al. (1995) reported a 41% treatment effect overestimation due to selection bias alone\textsuperscript{26}. Such overestimation would mean that a study comparing the treatment effect of a new clinical procedure against a standard one would report a Risk ratio (RR) of 0.82 while the true RR would be 1.13. The term “Risk” (R) describes the number of patients having an event (e.g. remaining ill after treatment) (n_{ill}) divided by the total number of patients treated (n_{total})\textsuperscript{27}.

\[ R = \frac{n_{ill}}{n_{total}} \]

If the effect of treatment with a new procedure is compared with the effect of a conventional standard procedure, a “Risk ratio” (RR) can be calculated by dividing the patient Risk of remaining ill after treatment with the new procedure (R_{new}) by the patient Risk of remaining ill after treatment with the standard procedure (R_{old})\textsuperscript{28}.

\[ RR = \frac{R_{new}}{R_{old}} \]

The so calculated RR indicates whether treatment with the new procedure, in comparison to treatment with the standard procedure, increases or decreases the risk (or chance) that patients may remain ill\textsuperscript{28}. A presented RR of 0.82 would imply that the new procedure has reduced the chance of remaining ill by 18%. (A risk ratio of 1.00 would indicate no difference in risk between the two procedures.) However, in a case of a 41% overestimation through bias, a real RR of 1.13 would mean that the new procedure has in fact increased by 13% the chance of patients’ remaining ill! If such new clinical procedure were to be adopted into daily practice on the basis of the biased overestimated results, then 13 out of 100 patients treated with the new procedure would have been worse off than they would have been if treated with the standard procedure.

Negative experiences of early adopters of an apparently ineffective innovation, as shown in the example above, would in time lead to its rejection. Early adopters have been described as interacting more frequently with peers than late adopters\textsuperscript{9}. Therefore, negative experiences of an innovation by early adopters would be communicated to other adopter groups and this would prevent further diffusion. In that case, the critical mass of 10-20% of adopters\textsuperscript{29} would not be reached and the innovation would thus remain unsustainable.

**Evidence and diffusion**

To avoid negative feedback from early adopters during the diffusion process, an innovation needs to be based on low-bias research because high internal validity of research provides the prerequisite for the successful generalization and adoption of the innovation\textsuperscript{24}. Bias
reduction in clinical studies that focus on treatment is realized through a range of
interventions (Table 2) to be considered while planning and conducting a clinical study\textsuperscript{24,29,30}. In addition, it has been acknowledged that various study designs contain various degrees of bias\textsuperscript{31-33}. For that reason an ‘evidence hierarchy’ of study designs has been established (Table 3)\textsuperscript{31-33}. It also has been recommended that once a study is conducted, its reporting should follow guidelines in order to assure recognition of study quality\textsuperscript{34}. Such guidelines include the CONSORT statement for randomized control trials\textsuperscript{35} and the STROBE statement.

**Table 1. Types of bias in clinical trials**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Description</th>
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<tr>
<td>Selection bias</td>
<td>New clinical procedures are usually tested in clinical trials consisting of 2 groups of patients: One group, forming the control group, is treated with a conventional, most commonly used procedure being considered as “currently accepted standard of care”. A second group (test group) is treated with the new procedure. At the end of the study the success (or failure) rates of both procedures are compared. Selection bias occurs when patients are selected into the 2 groups with known or unknown different characteristics. For example, if patients in the test group have conditions, which favor the success of treatment and which are lacking in patients of the control group then the new clinical procedure cannot be credited with the treatment success\textsuperscript{43}.</td>
</tr>
<tr>
<td>Performance bias</td>
<td>Similar to selection bias, performance bias leads to wrong study results if the characteristics of patients in one group of a clinical study support or hinder the treatment effect of a clinical procedure. However, unlike in selection bias, performance bias is induced through active intervention, by deviation from the study protocol, e.g. through additional treatment during the study in preference to one group only\textsuperscript{44}.</td>
</tr>
<tr>
<td>Detection bias</td>
<td>Detection bias is created if the outcomes of both test- and control group are assessed differently. In other words, if the outcome of one group is assessed more favorably than the other\textsuperscript{44}.</td>
</tr>
<tr>
<td>Attrition bias</td>
<td>Attrition bias occurs when patients allocated to either test- or control group are excluded from the outcomes assessment. For example, if patients in the control group are excluded for whom the standard clinical procedure lead to a treatment success. In such case the overall success rate of the standard treatment would be comparable lower than the new clinical procedure, thus falsely indicating that the later is superior\textsuperscript{24}.</td>
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</table>
for observational studies, such as Cohort and case control studies\textsuperscript{36}. Studies with low bias are identified through systematic reviews, using explicit, systematic methods designed to limit bias and the chance effects\textsuperscript{37}. Where possible the results of the identified studies are statistically combined, using meta-analysis and thus providing more precise estimates of healthcare effects\textsuperscript{37}.

Despite the value of low-bias evidence, it has been shown that on its own this is not sufficient to facilitate diffusion of innovation\textsuperscript{38}. Nevertheless, diffusion of innovation is more likely if the evidence supporting it is regarded as being strong\textsuperscript{38,39}. Furthermore, it has been observed that clinicians do recognize a hierarchy of evidence and most frequently regard randomized control trials (RCT) as the “gold standard”\textsuperscript{38}. Locock et al. (1999) described RCTs as providing the only form of evidence that may convince clinicians to adopt change\textsuperscript{40}. Therefore strong evidence is an important prerequisite for achieving wider adoption of an innovation.

**Table 2. Bias-reducing interventions**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Intervention</th>
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<tbody>
<tr>
<td><strong>Selection bias</strong></td>
<td><em>(a) Selection of study subjects using a random allocation sequence</em></td>
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<tr>
<td></td>
<td>*(b) Concealment of allocation sequence from investigators\textsuperscript{24}</td>
</tr>
<tr>
<td><strong>Performance bias</strong></td>
<td>Blinding (masking) of study subjects and care providers as to the differences per test- or control group\textsuperscript{24}</td>
</tr>
<tr>
<td><strong>Detection bias</strong></td>
<td>Blinding (masking) of study assessors as to the differences per test or control group\textsuperscript{24}</td>
</tr>
<tr>
<td><strong>Attrition bias</strong></td>
<td>Inclusion of all randomized study subjects into the analysis regardless of their adherence to the study protocol, thus following “intention-to-treat” principle\textsuperscript{29,30}</td>
</tr>
</tbody>
</table>

Once strong positive evidence regarding an innovation is available, further aspects of diffusion need to be considered. These aspects are related to complex factors of adopter behavior. According to Morris et al. (1989), they may include past educational and professional experiences, work environment and professional and personal aspirations\textsuperscript{41}. Fitzgerald et al. (2002) add further considerations related to whether the innovation threatens the established skill base and, consequently, the status and professional position of potential adopters, and to the impact of financial incentives which may facilitate or inhibit adoption of
an innovation. The latter may be further reinforced by perceptions of potential adopters as to whether the innovation offers advantages that the current methods do not.

### Table 3. Evidence hierarchy

<table>
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<th>Study Design</th>
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<tr>
<td><strong>Highest</strong></td>
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<tr>
<td>Quantitative systematic reviews (with meta-analysis)</td>
</tr>
<tr>
<td>Qualitative systematic reviews</td>
</tr>
<tr>
<td>Randomized control trials (RCT)</td>
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<tr>
<td>COHORT studies</td>
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<tr>
<td>Case control trials</td>
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<td>Case series or reports</td>
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<tr>
<td><strong>Lowest</strong></td>
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<td>Narrative reviews</td>
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</table>

### MI Evidence

The need for strong (low-bias) evidence as an important prerequisite for wide adoption of innovation<sup>38-40</sup> applies also to MI. The Cochrane library (online: [www.cochrane.org](http://www.cochrane.org)) and Midentistry’s compendium database (online: [www.midentistry.com/compendium.html](http://www.midentistry.com/compendium.html)) are known sources for evidence generated through systematic reviews and meta-analyses and cover aspects of disease risk assessment; early disease detection and minimally invasive treatment. The MI Compendium database follows Cochrane recommendations and guidelines regarding the conduct of systematic reviews and meta-analysis but focuses exclusively on MI topics, including disease treatment and etiology, prognosis and diagnosis.

### Conclusions

Minimum intervention (MI) in dentistry focuses on causes of disease and allows for ultraconservative treatment that is more patient-friendly than traditional dentistry. Successful diffusion of MI requires substantiation of its beneficial claims through low-bias evidence. Such evidence provides the first step for a wider adoption, which furthermore depends on complex factors of adopter behavior.
References


CHAPTER 3

Systematic Reviews

All reviews are updated modification of the original journal articles and are re-printed based on permission of the journals in which they were originally published.
Absence of carious lesions at margins of glass-ionomer and amalgam restorations: a meta-analysis


ABSTRACT. Aim To report on the absence of carious lesions at margins of glass ionomer cement (GIC) and amalgam restorations. Methods Six Anglophone and 1 Lusophone databases were searched for articles up to 5 January 2008. Inclusion criteria for articles were: (i) titles/abstracts relevant to topic; (ii) published in English, Portuguese or Spanish language; (iii) reporting on a randomised controlled trial. Exclusion criteria were: (i) insufficient random allocation of study subjects; (ii) operator and subject not blinded, where appropriate; (iii) not all entered subjects accounted for at trial conclusion; (iv) subjects of both groups not followed up the same way. Articles were accepted only if they complied with all the criteria. Ten articles complied with the inclusion criteria and were selected for review. From these 4 were rejected and 6 articles reporting on 8 separate studies accepted. Due to aspects of heterogeneity, studies were sub-grouped before meta-analysis. Results Significantly less carious lesions were observed on single-surface GIC restorations in permanent teeth after 6 years as compared to amalgam restorations (OR 2.64 - CI 95% 1.39 - 5.03, p = 0.003). No studies investigating multiple-surface restorations on permanent teeth were identified. Studies investigating carious lesions at margins of restorations in primary teeth showed no difference between both materials after 3 and 8 years. Conclusions Carious lesions at margins of single-surface GIC restorations are less common than with amalgam fillings after 6 years in permanent teeth. No difference was observed in primary teeth. More trials are needed in order to confirm these results.

Key words: Glass ionomer cement; Amalgam; Caries; Meta-analysis.

Introduction

Caries lesions associated with the margins of tooth restorations have previously been defined as recurrent or secondary caries [Mjör, 2005]. In recent years it has been suggested that placing a filling does not cure caries and that the "recurrence" of lesions on restoration margins results from neglecting to treat caries as disease before placing a restoration [White and Eakle, 2000]. Part of the treatment of caries is to encourage remineralisation in the cavity walls [Tyas et al., 2000]. Ten Cate and van Duinen [1995] have shown, in-situ, a hyper-remineralisation effect in demineralised tooth tissues bordering glass ionomer cement (GIC) type restorations. In contrast, tissues bordering amalgam showed further extensive demineralisation. The significant remineralisation potential of GIC has been ascribed to the release of fluoride ions, facilitated by a hydrophilic environment [Asmussen et al., 2002]. In addition, the release of strontium by GIC and its diffusion into demineralised tooth tissue, thus further aiding remineralisation, has been observed [Ngo et al., 2006]. Several trials have compared the clinical success rates of GIC and amalgam restorations in vivo [Taifour et al., 2002; Rahimtoola and van Amerongen, 2002; Taifour et al., 2003; Mandari et al., 2003; Qvist et al., 2006; Frencken et al, 2007]. During these trials marginal integrity, anatomical form, material loss at surface and carious lesions at the restoration margins were assessed. Qvist et al. [1990] established that carious lesions were the main cause of failures of amalgam restorations in permanent teeth. In contrast, it has been suggested that carious lesions are rarely the cause of GIC restoration failures [Mjör, 2005].

So far no meta-analysis has been conducted to this topic. One narrative review, lacking a systematic methodology for literature search and article inclusion- and exclusion criteria, concluded that the effect of fluoride release of materials, such as GIC,
remains clinically unproven [Wiegand et al., 2007]. In addition, one systematic review was unable to identify conclusive evidence for or against a treatment effect of secondary caries inhibition by GIC [Randall and Wilson, 1999]. This systematic review was of qualitative nature and did not include a meta-analysis.

The aim of this meta-analysis was to report on the combined results of trials comparing the absence of carious lesions at margins of GIC and amalgam restorations. The objectives were to determine absence of carious lesions in single and multiple-surface restorations (GIC versus amalgam) in: (a) permanent teeth and (b) primary teeth.

**Materials & Methods**

*Data collection*

Six Anglophone databases: Biomed Central, Cochrane Library, Directory Of Open Access Journals, PubMed, Science-Direct, Research Findings Electronic Register –ReFeR and one Lusophone database: Literatura Latino-Americana e Caribenha em Ciências da Saúde – LILACS were systematically searched for articles reporting on clinical trials up to 5 January 2008. The string of search terms: “Dental Caries OR Dental Caries Susceptibility OR Root Caries OR Tooth Demineralization AND Glass Ionomer Cements OR Cermet Cements AND Cariostatic Agents OR Dental Caries OR Cariostatic Agents AND Dental Amalgam OR silver mercury amalgam” was used to search the Anglophone databases and “ionomer$ and amalg$ and cariosta$” was used to search LILACS. Articles were selected for review from the search results on the basis of their compliance with the inclusion criteria: (i) titles/abstracts relevant to topic; (ii) published in English, Portuguese or Spanish; (iii) reporting on a randomized or quasi-randomized control trial. Where only a relevant title without a listed abstract was available, a full copy of the article was assessed for inclusion.

*Article review*

Only articles, which complied with the inclusion criteria were reviewed further. Articles were reviewed independently by 6 reviewers for compliance with the exclusion criteria shown in Table 1 [Sutherland, 2001]. Disagreements were resolved by discussion and consensus. Articles were accepted for meta-analysis only if they complied with all the criteria. Where several articles had reported on the same trial, the article covering the longest period in accordance with the exclusion criteria was accepted. If one article reported more than one outcome, these were analysed as separate trials.
Table 1. Exclusion criteria for trials

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insufficient random allocation of study subjects.</td>
</tr>
<tr>
<td>2.</td>
<td>Operator and subject not blinded, where appropriate.</td>
</tr>
<tr>
<td>3.</td>
<td>Not all entered subjects accounted for at the end of the trial.</td>
</tr>
<tr>
<td>4.</td>
<td>Subjects of both, study and control group, not followed up the same way.</td>
</tr>
</tbody>
</table>

Data extraction from accepted trials

The outcome measure of this meta-analysis was the absence of carious lesions at the margin of restorations. Two reviewers (VY and SM) independently extracted data from the accepted articles, using a pilot-tested data-extraction form that included information contained in Table 2. Where possible, missing data were calculated from information given in the text or tables of included trials, in order to complete a 2x2 table used to enter per-trial data for meta analyses. In addition, authors of articles were contacted in order to obtain missing information. Disagreements between reviewers during data extraction were resolved through discussion and consensus. It was anticipated that some of the studies eligible for inclusion would be split-mouth in design (quasi-randomized trials). The split-mouth study design is commonly used in dentistry to test interventions and has the advantage of enabling an individual to serve as both subject and control. In this study design one or more pairs of teeth (e.g. primary molars) form the unit of randomization. These pairs are, strictly speaking, not independent and should be analysed as “paired data” on a per-child basis. However, as in a similar review [Ahovuo-Saloranta et al., 2004], in order to prevent exclusion of data, split-mouth trials were included and the pairs were analyzed independently.

Quality of studies

The quality assessment of the accepted trials was undertaken independently by two reviewers (VY and SM). Trials not included in this review were used to pilot the process. Subsequently quality assessment rating scored by both reviewers was derived by consensus within the review group. Four main quality criteria were examined:

(1) Generation of randomization sequence (allocation), recorded as:
(A) Adequate - e.g. computer-generated random numbers, table of random numbers;
(B) Unclear;
(C) Inadequate - e.g. case record number, date of birth, date of administration, alternation.

(2) Allocation concealment, recorded as:
(A) Adequate - e.g. central randomization, sequentially numbered sealed opaque envelopes;
(B) Unclear;
(C) Inadequate - e.g. open allocation schedule, unsealed or non-opaque envelopes.

(3) Blind outcome assessment, recorded as:
(A) Yes;
(B) Unclear;
(C) No;
(D) Not used/possible.

(4) Completeness of follow-up (clear explanation for withdrawals and loss-to-follow-up in each treatment group) assessed as:
(A) Yes, drop outs less than 30%;
(B) Yes, drop outs more than 30%;
(C) No explanation.
### Table 2. Some characteristics of trials comparing caries on margins of GIC and amalgam restorations.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>Study design</th>
<th>Age of subjects (in years)</th>
<th>No. Restorations</th>
<th>Dentition</th>
<th>Cavity type</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frencken et al. [2007]</td>
<td>Syria</td>
<td>Parallel group</td>
<td>13.8</td>
<td>GIC: 487, Amalgam: 403</td>
<td>Permanent</td>
<td>Single-surface</td>
<td>6.3 years</td>
</tr>
<tr>
<td>Taifour et al. [2002 (Study 1)]</td>
<td>Syria</td>
<td>Parallel group</td>
<td>6-7</td>
<td>GIC: 441, Amalgam: 326</td>
<td>Primary</td>
<td>Single-surface</td>
<td>3 years</td>
</tr>
<tr>
<td>Taifour et al. [2002 (Study 2)]</td>
<td>Syria</td>
<td>Parallel group</td>
<td>6-7</td>
<td>GIC: 610, Amalgam: 425</td>
<td>Primary</td>
<td>Multiple-surface</td>
<td></td>
</tr>
<tr>
<td>Östlund et al. [1992]</td>
<td>Sweden</td>
<td>Parallel group</td>
<td>4-6</td>
<td>GIC: 25, Amalgam: 25</td>
<td>Primary</td>
<td>Multiple-surface</td>
<td>3 years</td>
</tr>
<tr>
<td>Welbury et al. [1991]</td>
<td>United Kingdom</td>
<td>Split-mouth</td>
<td>No information</td>
<td>GIC: 99, Amalgam: 99</td>
<td>Primary</td>
<td>Single/ Multiple -surface</td>
<td>22.7 – 26.3 months</td>
</tr>
<tr>
<td>Qvist et al. [2004 (Study 1)]</td>
<td>Denmark</td>
<td>Parallel group</td>
<td>2.8 - 13.5</td>
<td>GIC: 131, Amalgam: 87</td>
<td>Primary</td>
<td>Single-surface</td>
<td>8 years</td>
</tr>
<tr>
<td>Qvist et al. [2004 (Study 2)]</td>
<td>Denmark</td>
<td>Parallel group</td>
<td>2.8 - 13.5</td>
<td>GIC: 384, Amalgam: 456</td>
<td>Primary</td>
<td>Multiple-surface</td>
<td></td>
</tr>
</tbody>
</table>
Results
Only articles published in the English language were identified during the literature search. From the initial search results, 10 articles complied with the inclusion criteria and were selected for further review. From these, 4 articles were excluded: 2 articles [Mjör and Jokstad, 1993; Phantumvanit et al., 1996] did not report how subjects were allocated to either the study or the control group; 1 article reported on 4 treatment- and restoration groups: amalgam restoration after hand-excavation; GIC restoration after hand-excavation; amalgam restoration after drilling; GIC restoration after drilling. However, this article did not report on the number of carious teeth for each group and was thus excluded [Rahimtoola and van Amerongen, 2002]. One further article was an older report [Taifour et al., 2003] of the same trial [Frencken et al., 2007].

Six articles reporting on 8 separate studies were accepted [Welbury et al., 1991; Östlund et al., 1992; Taifour et al., 2002; Mandari et al., 2003; Qvist et al., 2004; Frencken et al., 2007]. The main characteristics of the accepted studies are described in Table 2.

Table 3 provides information about quality aspects assessed for these studies. Details about loss-to-follow-ups were reported in all accepted studies. Treatment allocation was rated A (Adequate) in one study [Welbury et al., 1991], B (Unclear) in three [Östlund et al., 1992; Taifour et al., 2002; Frencken et al., 2007] and C (Inadequate) in the remaining two [Welbury et al., 1991; Qvist et al., 2004].

Table 3. Quality Assessment of Accepted Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Allocation Concomitant</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Drop-outs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frencken et al. [2007]</td>
<td>Randomized</td>
<td>B - Unclear</td>
<td>B - Unclear</td>
<td>D - Not Possible</td>
<td>A 84/681 (12.3%) patients</td>
</tr>
<tr>
<td>Mandari et al. [2003]</td>
<td>Quasi-randomized</td>
<td>C - Inadequate</td>
<td>B - Unclear</td>
<td>D - Not Possible</td>
<td>A 38/152 (25%) - patients</td>
</tr>
<tr>
<td>Taifour et al. [2002]</td>
<td>Randomized</td>
<td>B - Unclear</td>
<td>B - Unclear</td>
<td>D - Not Possible</td>
<td>A 185/835 (22.1%) - restorations</td>
</tr>
<tr>
<td>Östlund et al. [1992]</td>
<td>Randomized</td>
<td>B - Unclear</td>
<td>B - Unclear</td>
<td>D - Not Possible</td>
<td>C No explanation</td>
</tr>
<tr>
<td>Welbury et al. [1991]</td>
<td>Quasi-randomized</td>
<td>A - By use of random permuted block design</td>
<td>B - Unclear</td>
<td>D - Not Possible</td>
<td>A 12/88 (13.6%) - patients</td>
</tr>
<tr>
<td>Qvist et al. [2004] - Study 1 &amp; 2</td>
<td>Randomized</td>
<td>C - Alteration</td>
<td>B - Unclear</td>
<td>D - Not Possible</td>
<td>A (7%) - restorations</td>
</tr>
</tbody>
</table>
Absence of carious lesions in single- and multiple-surface restorations (GIC versus amalgam) in permanent teeth

Data from two studies [Mandari et al., 2003; Frencken et al., 2007] were used to investigate this objective. Figure 1 shows that margins of single-surface GIC restorations in permanent teeth had significantly less carious lesions (p = 0.003) after 6 years than did similar teeth restored with amalgam (OR = 2.64; CI 95% 1.39 – 5.03). No trials covering multiple-surface restorations in permanent teeth were identified.

**Figure 1.** Caries on margins of single-surface GIC and amalgam restorations on permanent teeth after 6 years. Odds ratios (OR) and 95% confidence intervals (CI) per study and combined.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>GIC</th>
<th>n</th>
<th>Amalgam</th>
<th>n</th>
<th>OR (fixed) 95% CI</th>
<th>Weight (%)</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandari et al.</td>
<td>170/273</td>
<td>146/262</td>
<td>21.92</td>
<td>0.31 [1.77, 21.74]</td>
<td>23.88</td>
<td>1.47 [0.74, 3.23]</td>
<td></td>
</tr>
<tr>
<td>Frencken et al.</td>
<td>376/497</td>
<td>338/505</td>
<td>18.68</td>
<td>1.74 [0.94, 3.3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (OR, CI)</td>
<td>646</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: CH² = 3.08, df = 1 (P = 0.08); P = 67.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.31 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; N = total number of restorations; n = number of restorations with caries absent.

**Figure 2.** Caries on margins of multiple-surface GIC and amalgam restorations on primary teeth after 3 years. Odds ratios (OR) and 95% confidence intervals (CI) per study and combined.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>GIC</th>
<th>n</th>
<th>Amalgam</th>
<th>n</th>
<th>OR (fixed) 95% CI</th>
<th>Weight (%)</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talhouk et al. (2)</td>
<td>607/473</td>
<td>320/301</td>
<td>22.10</td>
<td>2.04 [1.22, 3.34]</td>
<td>6.90</td>
<td>1.13 (0.13, 9.09)</td>
<td></td>
</tr>
<tr>
<td>Dentice et al.</td>
<td>26/26</td>
<td>24/24</td>
<td>8.90</td>
<td>8.12 (0.13, 9.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (OR, CI)</td>
<td>633</td>
<td>324</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: CH² = 0.07, df = 1 (P = 0.00); P = 9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.93 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; N = total number of restorations; n = number of restorations with caries absent.
Absence of carious lesions in single- and multiple-surface restorations (GIC versus amalgam) in primary teeth

Information on carious lesions in multiple-surface GIC and amalgam restorations 3 years after placement are shown in Figure 2. The difference between the numbers of carious lesions of both materials was not statistically significant (p = 0.10). This implies that both materials were equally effective in terms of their caries-preventive effects. When data from the 8-year follow-up study by Qvist et al. [2004 (Study 2)] were added to the meta-analysis, the result, however, favored GIC (OR = 2.35; CI 95% 1.18 – 4.71) and was statistically significant (p = 0.02).

For single-surface restorations in primary teeth, the data from the studies by Taifour et al. [2002 (Study 1)] and Qvist et al. [2004 (Study 1)] were pooled, even though the follow-up periods were 3 and 8 years respectively. The results showed no statistically significant difference (p = 0.24) between both materials (OR = 1.78; CI 95% 0.67 – 4.72) and need to be considered with caution, since these studies did not comply with the criteria for homogeneity. On an individual basis, the study by Taifour et al. [2002 (Study 1)] showed an odds ratio of 2.88 (CI 95% 0.88 – 9.44) and the study by Qvist et al. [2004 (Study 1)] 0.39 (CI 95% 0.04 – 3.82). A further study by Welbury et al. [1991] showed no statistically significant difference (p = 0.33) between GIC and amalgam after 22.7 – 26.3 months (OR = 1.64; CI 95% 0.61 – 4.43) in primary teeth.

Discussion

This meta-analysis investigated the absence of carious lesions at margins of GIC restorations in comparison to amalgam restorations. A general lack of randomized control trials complying with all criteria was identified. Despite the systematic literature search in 7 databases and 3 different languages, only 6 articles, reporting on 8 separate studies, were accepted. Moreover, clinical heterogeneity between the studies meant that even fewer trials could be pooled together for meta-analyses. The studies were grouped according to type of dentition, cavity type and follow-up period (Table 2). The decision to sub-group the studies into these categories was justified by the consideration that survival rates of restorations in primary teeth, as well as for large cavities, are lower than in permanent teeth and small cavities, and that restoration survival is associated with the time factor [van’t Hof et al., 2006]. It has to be noted that appraisal for clinical heterogeneity between studies did not include assessment of differences in the types of caries removal applied before GIC restorations were placed or in the types of GIC material used. Hand-excavation of infected dentine, following the Atraumatic Restorative Treatment (ART) approach, was used in 3 studies [Taifour et al., 2002 (Study 1); Taifour et al., 2002 (Study 2); Frencken et al., 2007]. In one study hand-excavation was aided by use of chemo-mechanical agents [Mandari et al., 2003] and 2 studies did not specify how caries was removed for GIC restorations [Welbury et al., 1991; Östlund et al., 1992]. Caries
removal by hand-excision has been reported to remove soft infected dentine, but not the harder, demineralised affected dentine [Tyas et al., 2000]. Thus, hand-excavation could be assumed to result in greater susceptibility to recurrent caries than caries removal by drilling, where more affected tooth material is generally removed. However, contrary to such an assumption, all studies [Taifour et al., 2002 (Study 1); Taifour et al., 2002 (Study 2); Frencken et al., 2007] in which hand-excavation was applied showed less caries on GIC restoration margins than were found on margins of amalgam restorations placed after drilling. Low-strength GIC material was used in 5 studies [Welbury et al., 1991; Östlund et al., 1992; Mandari et al., 2003; Qvist et al., 2004 (Study 1); Qvist et al., 2004 (Study 2)] and high-strength GIC in the others [Taifour et al., 2002 (Study 1); Taifour et al., 2002 (Study 2); Frencken et al., 2007]. It has been suggested that both types of GIC material show distinctly different physical characteristics [Frencken et al., 2004]. However, these characteristics are more likely to impact on the marginal integrity, anatomic form and material loss at the surface of GIC restorations.

The results of the meta-analysis indicate that carious lesions are less observed on the margins of GIC, than amalgam restorations in single-surface restorations of permanent teeth. It is thought that the continued fluoride release from the GIC material is protective, and hence the tooth may remain caries-free even in the presence of a marginal defect. In the case of amalgam, the protective effect is purely mechanical and the tooth is at higher caries risk. The combined odds ratio for single-surface restorations in permanent teeth, of 2.64 (CI 95% 1.39 – 5.03), suggests that teeth restored with GIC are more than twice as likely to remain free of carious lesions as those filled with amalgam (Figure 1).

In the primary dentition, the results for multiple-surface restorations after 3 years (Figure 2), as well as the results of the study by Qvist et al. [2004 (Study 2)] after 8 years, suggests that none of the materials is superior. The results of the 2 studies investigating carious lesions at margins of single-surface restorations in primary teeth (Taifour et al. [2002 (Study 1), Qvist et al. [2004 (Study 1)], as well as the study by Welbury et al. [1991] do also show no difference. The reason for this is unclear. It can be assumed that factors like the larger restoration surface, as well as the greater difficulties involved in placing restorations in children than in adults may outweigh any caries-preventive properties of GIC in comparison to amalgam. In addition, none of the accepted studies reported on fluoride exposure of subjects. It can be assumed that if subjects were exposed to external fluoride sources that this may have increased caries resistance of teeth restored with amalgam, thus confounded the caries-preventive effect of GIC as suggested by Hara et al. [2006].
Conclusion

Despite the limitations of this meta-analysis, due to the low number of randomized control trials it can be concluded that absence of carious lesions at margins of single-surface GIC restorations is higher than on amalgam fillings of permanent teeth after 6 years. This result is in line with in-situ and in-vitro observations of the characteristics of GIC [Wesenberg and Hals, 1980; Tsanidis and Koulourides, 1992; ten Cate and van Duinen, 1995; Tam et al., 1997; Knight et al., 2007; Takeuti et al., 2007]. Results for both multiple- and single-surface restorations in primary teeth show no difference between both materials. More clinical trials are needed in order to confirm these findings.

References


Caries-preventive effect of glass ionomer and resin-based fissure sealants on permanent teeth: a meta analysis

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Abstract: The purpose of this quantitative systematic review was to appraise the evidence on the caries-preventive effect of glass ionomer cement (GIC) in relation to resin-based fissure sealants. Nine English and two Portuguese databases were searched (15 January 2008). Randomized clinical trials and systematic reviews were considered for inclusion. Trial exclusion criteria were: drop-out rates > 33%; no randomization; baseline differences in groups not statistically adjusted; and no clinically important outcomes were presented. Two authors reviewed the articles independently. The outcome measure for the caries-preventive effect was caries absence on sealed teeth. Of the 112 identified articles, 25 were selected for review. Of these, 14 were excluded and 11 accepted (8 trials; 3 systematic reviews). The accepted reviews provided no evidence of superiority of either sealant material. Six trials were included for meta-analysis. The pooled odds ratio was 0.96, 95% CI 0.62-1.49, indicating no difference in the caries-preventive effect of GIC and resin-based fissure sealant material. This systematic review with meta-analysis found no evidence that either material was superior to the other in the prevention of dental caries. Thus, both materials appear equally suitable for clinical application as a fissure sealant material. (J Oral Sci 51, 373-382, 2009)

Keywords: glass ionomer cement; resin composite; fissure sealing; meta-analysis.

Introduction

Pits and fissures of posterior molar teeth are considered to be highly susceptible to the adhesion of microorganisms and, consequently, caries. Therefore, a significant amount of tooth decay occurs at these sites. Fissure sealants are used to prevent occlusal caries with 71% percent of occlusal decay preventable after a once-off fissure sealant application (1). The evidence for the efficacy and cost-effectiveness of sealants in reducing occlusal caries in molars has been highlighted in a number of articles in highly rated journals (1-5). The most commonly used sealant material is resin composite (6-8). Its caries-preventive effect relies on the sealing of pits and fissures through micro-retention, created through tags after enamel acid etching. However, these are easily destroyed by saliva contamination, which reduces micro-retention and consequently, the caries-preventive effect (9). Under the generally wet conditions in the oral cavity, Glass Ionomer Cement (GIC) offers an alternative. Owing to its hydrophilic properties, GIC is not as moisture-sensitive as hydrophobic resin (10). It has been suggested that the ‘gold standard’ in caries prevention through sealant administration should not be based on physical (material retention on the tooth surface) but rather, on biological outcomes (11). Such biological outcomes are measured in relation to the absence of caries in pits and fissures after sealant application. So far, three systematic reviews (2,11,12) including appraisals on the effectiveness of GIC fissure sealant have been published. One of these, by Mejare et al. (12), did not include a direct comparison between GIC and resin-based sealants. Two other systematic reviews (2,11) have compared the effect of GIC with that of resin based fissure sealants. One of these was a Cochrane Systematic Review (2) that used strict inclusion criteria, which resulted in a large number of
trials being excluded from the final analysis. The systematic review by Beiruti et al. (11) excluded studies lacking sufficient reported statistics for calculation of relative and attributable risk. In all these three systematic reviews, only English databases were searched and English articles reviewed. Additionally, the inconclusive findings reported in each of these reviews were based on the authors’ assessment of each included trial using a PICOS (patient; intervention; controls; outcome; study authors’ conclusions) format and a narrative synthesis of the included articles. However, the disadvantage of a narrative synthesis in systematic reviews is that bias may be introduced if the outcomes of some studies are inappropriately stressed over others (13). The advantages of a meta-analysis over narrative synthesis are that it provides the chance to detect a treatment effect as statistically significant (p<0.05) and to improve the estimation of a treatment effect by quantifying its outcome, thus making its estimation more precise (13). Therefore, whilst methodological weaknesses limit what can be inferred in terms of efficacy, the cumulative weight of evidence (as highlighted, where possible, in a meta-analysis) provides a more objective assessment of a systematic analysis of the literature. The inconclusive findings reported in the three published systematic reviews may reflect the opposite should a meta-analysis of trials that report on the same outcome be added. Indeed, this has been shown to be the case in a number of systematic reviews where the individual studies had varied outcomes but the cumulative weight of the evidence (done by pooling together the results of trials with similar outcomes) were found to be conclusive for that particular outcome (14-16). Due to the lack of a conclusive quantitative analysis in past reviews, the aim of this systematic review is not only to extend the evidence search and review to non-English clinical trials, but also to conduct a meta-analysis in order to quantitatively appraise the current evidence regarding the caries-preventing effect of GIC in comparison to that of resin-based fissure sealants for the first time.

Materials and methods

Search strategy

The literature search covered nine Anglophone databases: Biomed Central, Cochrane Oral Health Reviews, Cochrane Library, Directory Of Open Access Journals, Expanded Academic ASAP PLUS, Meta Register Of Controlled Trials - mRCT, PubMed, Science-Direct, Research Findings Electronic Register –ReFeR and two Lusophone databases: Bibliografia Brasileira Em Odontologia – BBO, Literatura Latino-Americana E Caribenha Em Ciências Da Saúde – LILACS. In order to search databases, strings of search terms were constructed, consisting of relevant text words and Boolean links. The string of English search terms: “(GIC sealant* OR Glass ionomer cement sealant) AND (caries OR tooth decay)” was used to search the Anglophone databases and the string of Portuguese search terms: “SELANTE [Palavras]”
and “CIMENTOS DE IONOMEROS DE VIDRO” [Palavras] and “CARIE” [Palavras] was used to search the Lusophone databases. All publications listed in the databases until 15 January 2008 were included in the search.

Table 1. Exclusion criteria for trials and literature reviews

<table>
<thead>
<tr>
<th>Trials</th>
<th>Literature reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drop-out rate &gt;33%</td>
<td>Focus on population or intervention not clearly stated in title and abstract</td>
</tr>
<tr>
<td>Patients and clinicians not ‘blinded’ where possible and appropriate</td>
<td>Article methodology describes no clear inclusion and exclusion criteria for reviewed publications</td>
</tr>
<tr>
<td>Baseline differences among groups not statistically adjusted</td>
<td>Article methodology describes no clear search strategy, key words and databases used and includes no study-by-study critique table or discussion of study qualities</td>
</tr>
<tr>
<td>Clinically important outcomes for patients not assessed.</td>
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<tr>
<td>No in-vivo or in-situ study design</td>
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<tr>
<td>No randomization/ quasi-randomization method reported</td>
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</table>

Inclusion and exclusion criteria

Both clinical trials and systematic reviews by other authors were eligible for inclusion. Publications were included from the search results on the basis that their titles and abstracts were in accordance with broad inclusion criteria: (i) titles/abstracts were relevant to the review objective; and (ii) the article was published in English, German, Portuguese or Spanish. Where only a relevant title without a listed abstract was available, a full copy of the publication was assessed for inclusion. In accordance with published recommendations (17), included articles were reviewed independently by two reviewers. Disagreements were resolved through discussion and consensus. After review, articles were accepted only if they complied with all the exclusion criteria described in Table 1. In cases of multiple reports regarding the same trial, the report covering the longest period and lacking the exclusion criteria was accepted. For the systematic reviews, only a descriptive analysis was attempted.

Data extraction from accepted trials

The outcome measure of the caries preventive effect was the caries absence on sealed teeth. Two reviewers (VY and SM) independently extracted data from the accepted articles, using a
pilot-tested data-extraction form that included information contained in Table 2. Whereever possible, missing data was calculated from information given in tables and text of trials in order to complete the 2x2 table for meta analysis. Disagreements between reviewers during data extraction were resolved through discussion and consensus. It was anticipated that the majority of studies eligible for inclusion would be split-mouth in design. The split-mouth study design is commonly used in dentistry to test interventions and has the advantage of having an individual serve as both the experiment and control. In this study design, one or more pairs of teeth (e.g. primary molars) form the unit of randomization. Strictly, these pairs are not independent and should be analysed as “paired data” on a patient basis. However, similar to other reviews where split-mouth trials are included (2), it was decided to analyze the pairs independently as it would have meant that most trials considered for inclusion here would have been excluded.

Quality of trials
The quality assessment of the included trials was undertaken independently by two reviewers (VY and SM). The quality assessment process was piloted using trials not included in this review and subsequently; quality assessment rating scored by both the reviewers was derived by consensus within the review group. Four main quality criteria were examined:

1. Generation of randomization sequence (Allocation), recorded as:
   (A) Adequate - e.g. computer generated random numbers, table of random numbers.
   (B) Unclear.
   (C) Inadequate - e.g. case record number, date of birth, date of administration, alternation.

2. Allocation concealment, recorded as:
   (A) Adequate - e.g. central randomization, sequentially numbered sealed opaque envelopes.
   (B) Unclear.
   (C) Inadequate - e.g. open allocation schedule, unsealed or non-opaque envelopes.

3. Blind outcome assessment, recorded as:
   (A) Yes.
   (B) Unclear.
   (C) No.
   (D) Not used/possible.
(4) Completeness of follow up (clear explanation for withdrawals and loss-to-follow-up in each treatment group) assessed as:

(A) Yes, drop outs less than 30%.

(B) Yes, drop outs more than 30%.

(C) No explanation.
# Table 2. Details of accepted trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Test material</th>
<th>Control material</th>
<th>Participants / teeth</th>
<th>Age (years)</th>
<th>Tooth</th>
<th>Application</th>
<th>Follow-up Period (years)</th>
<th>Drop-out (%)</th>
<th>Caries preventive Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovadino JR, et al. (32)</td>
<td>RCT (SM)</td>
<td>Chelon Fil</td>
<td>Delton</td>
<td>22 children</td>
<td>6-11</td>
<td>1st permanent molars</td>
<td>Single</td>
<td>1</td>
<td>31.8% children (7/22) lost</td>
<td>GIC – 80% total retention</td>
</tr>
<tr>
<td>Tostes M (33)</td>
<td>RCT (SM)</td>
<td>1. Ketac Cem 2. Fluoroshield 3. Fluor varnish</td>
<td>No treatment</td>
<td>25 children</td>
<td>6-8</td>
<td>1st permanent molars</td>
<td>Single</td>
<td>2</td>
<td>12% children (3/25) lost</td>
<td>GIC – 100% partially or total lost Resin – 63.7% partially or total lost</td>
</tr>
<tr>
<td>Karlzen-Reuterving G &amp; van Dijken JWV (34)</td>
<td>RCT (SM)</td>
<td>Fuji III</td>
<td>Delton</td>
<td>47 (26 girls; 21 boys) 148 1st molars</td>
<td>7</td>
<td>1st molar</td>
<td>Single</td>
<td>3</td>
<td>4.3% children (2/47) lost</td>
<td>GIC-72.2% partially lost; 98% total loss Resin- 20.8% partially lost; 0% total loss</td>
</tr>
<tr>
<td>Arrow P, et al. (35)</td>
<td>RCT (SM)</td>
<td>Ketac Fil</td>
<td>Delton</td>
<td>465 pairs of molars in 465 children</td>
<td>7</td>
<td>1st molar</td>
<td>Single</td>
<td>3.64</td>
<td>10.8% (50/465) children drop-out &gt;60% of both sealants lost 62% GIC lost at 44 months 100% resin lost at 44 months 31% (71/231) children lost at 2 years; GIC- 93% (274/295) lost Resin-18% (55/295) lost</td>
<td>Carious teeth: 1.5% (6/415) RR=0.19 (CI 0.09-0.4)</td>
</tr>
<tr>
<td>Williams B, et al. (36) (Only 2 year results reviewed)</td>
<td>RCT (SM)</td>
<td>Fuji III</td>
<td>Delton</td>
<td>860 sealants placed in 228 children</td>
<td>6-8</td>
<td>1st molar</td>
<td>Single</td>
<td>2</td>
<td>14% (73/512) lost at 2 years. At 24 months, 96% GIC F/S lost</td>
<td>1. DFS –for 1st molars reduced by 52%; mean DMFS for whole mouth reduced by 51.3% compared to control</td>
</tr>
<tr>
<td>Songpaisan Y, et al. (31) (Part 1)</td>
<td>RCT (PG)</td>
<td>1. Fuji III</td>
<td>1. No treatment</td>
<td>512 children with ≥3 1st molars assigned to 4 groups (Control: 2</td>
<td>7-8</td>
<td>1st molar</td>
<td>Single and repeated for GIC if missing at 6 months; Topical</td>
<td>2</td>
<td>14% (73/512) lost at 2 years. At 24 months, 96% GIC F/S lost</td>
<td>1. DFS –for 1st molars reduced by 52%; mean DMFS for whole mouth reduced by 51.3% compared to control</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Participants</td>
<td>Results</td>
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<tr>
<td>Songpaisan Y, et al. (31) (Part 2)</td>
<td>Fuji III 1. No treatment</td>
<td>752 children with ≥3 1st molars assigned to 4 groups (Control; 3 Test)</td>
<td>1. DFS –for 1st molars reduced by 31%; mean DMFS for whole mouth not significant when compared to control</td>
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<tr>
<td></td>
<td>Fuji III 2. No treatment</td>
<td></td>
<td>2. DFS –for 1st molars reduced by 20%; mean DMFS for whole mouth not significant when compared to control</td>
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<td></td>
<td>Fuji III 2. Single</td>
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<td>3. DFS –for 1st molars reduced by 15% of Resin F/S lost.</td>
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<tr>
<td></td>
<td>Delton (LC) 3. No Treatment</td>
<td></td>
<td>Resin based sealants performed significantly better than GIC sealants when mean DFS scores were compared at 2 years</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12-13 Molar teeth</td>
<td>11% (81/752) lost at 2 years. At 2 years, 99% of GIC F/S lost; 15% of Resin F/S lost.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>2. DFS –for 1st molars reduced by 20%; mean DMFS for whole mouth not significant when compared to control</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3. DFS –for 1st molars reduced by 93%; mean DMFS for whole mouth significantly lower than control</td>
</tr>
<tr>
<td>Kervanto-Seppälä S et al. (38)</td>
<td>Fuji III Chemical cure Delton (LC)</td>
<td>599 children who received sealants on 2nd molars</td>
<td>GIC = single / Resin = defective sealants resealed</td>
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<td></td>
<td></td>
<td>12-16 yrs 2nd molars</td>
<td>20%</td>
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<td>At 3 years, 24% (21/86) lost to follow-up. At 3 years, 0% GIC F/S intact; 70% Resin FS intact.</td>
</tr>
<tr>
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<td>At 3 years, caries present in 13.8% of GIC F/S teeth; Caries preventive effect of resin fissure sealant 74.1% (95%CI 43.4-88.13%) and rate difference 3.2% (95%CI 1.44-4.98%). Relative Risk for GIC sealed surfaces having dentin caries 3.9 (95%CI 1.77-8.42)</td>
</tr>
<tr>
<td>Rock WP, et al. (37)</td>
<td>GIC (Baseline) Resin (Fluoro-shield –contains F –Light Cure)</td>
<td>86 children received GIC F/S on one side of mouth and Resin F/S on contra-lateral side</td>
<td>At 3 years, 24% (21/86) lost to follow-up. At 3 years, 0% GIC F/S intact; 70% Resin FS intact.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-8 1st molar single</td>
<td>At 3 years, caries present in 3.2% of Resin Filled teeth. Statistically significant.</td>
</tr>
</tbody>
</table>

GIC = glass ionomer cement; RMGIC = resin modified glass ionomer cement; RCT = randomized-control trial; SM = split-mouth; PG = parallel group; LC = light cured; F/S = fissure sealant; RR = relative risk
**Meta-analysis**

The caries absence and caries presence in sealed teeth were treated as dichotomous data. Trials were assessed for their clinical and methodological heterogeneity following Cochrane guidelines (13). Trials were considered homogenous, if they did not differ substantially in the following clinical and methodological aspects: age of patients; follow-up period; type of sealant material used; frequency of sealant material application; as well as measured outcome. Only trials considered to be clinically and methodologically homogenous were included for meta-analysis, for which the fixed effects model of the meta-analysis software, RevMan 4.2 was used. The differences in the caries preventive effect were computed on the basis of odds ratios (OR) from each trial and the respective 95% confidence interval (CI). Studies were assigned a Mantel-Haenszel weight in direct proportion to their sample size.

**Results**

From the initial search results, 112 articles were identified, 25 of which were selected for review. Independent review of these 25 articles resulted in further exclusion of 2 reviews (8,18) and 12 trials (19-30). Table 3 provides information on the reasons for exclusion. Four trials (19,20,23,29) were excluded because the dropout rates of participants were greater than 33%. The trial by Boksman et al. (21) was abandoned 6 months into the 3-year trial period, because only 1.7% of the GIC fissure sealants placed were available for evaluation.

Eight trials (31-38) and three literature review articles (2,11,12), were accepted and thus formed the basis for the evaluation of evidence regarding the caries-preventive effect of GIC versus that of resin-based fissure sealants.

**Description of accepted reviews**

Three literature reviews (2,11,12) were accepted. The Cochrane systematic review (2) sought to evaluate the caries preventive effect of resin and GIC cements in trials comparing these two interventions with each other or with a placebo (or no treatment). The strict inclusion and exclusion criteria meant that 40 of the 56 studies included for review were excluded, e.g. split-mouth trials, in which the authors did not present data in a paired way were excluded in this review without the attempt to calculate the missing data from available information. These criteria added to the strength of methodological rigor of this review but resulted in similar findings in the review presented by Mejâre et al. (12): although there was evidence regarding the effectiveness of resin sealants, the evidence related to GIC based sealants was perceived to be less convincing or incomplete.
Moreover, the results from the comparison of resin sealants and GIC sealants were conflicting, as two of the assessed trials (23,31) were in favor of resin, while one trial (35) reported that GIC fissure sealants performed significantly better at 44 months after placement. As the results of these trials differed substantially, the authors did not attempt a meta-analysis.

The second review by Mejáre et al. (12) did not include trials comparing one type of fissure sealant material with another. Therefore, trials that pitted GIC fissure sealants against resin-based sealants for a variety of outcome measures were excluded. All of the 13 studies assessed in the review by Mejáre et al. (12) contained control groups that did not receive any intervention (i.e., fissure sealant caries preventive effect per tooth/child was compared to ‘no treatment’). Of these studies, none was graded as providing “high value” evidence; only 2 were graded as offering “moderate” evidence and most were rated as having “limited value”.

The main outcome measures were relative risk reduction (the number of decayed occlusal surfaces in the controls minus the number of decayed surfaces in the sealed teeth, divided by the number of decayed surfaces in the controls) or prevented fraction (caries increment in the

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reason for Exclusion</th>
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<tbody>
<tr>
<td>Forss H &amp; Halme E (20)</td>
<td>Drop-out rate = 42%</td>
</tr>
<tr>
<td>Mejare I &amp; Mjor IA (21)</td>
<td>No randomization method described; Adult drop-out rate = 38% (no information on drop-out rate for children)</td>
</tr>
<tr>
<td>Boksman L et al. (22)</td>
<td>Drop-out rate = 98.3% of sealants; Trial abandoned at 6 months</td>
</tr>
<tr>
<td>Herle GP et al. (23)</td>
<td>No randomized controlled, in-vivo or in-situ study</td>
</tr>
<tr>
<td>Poulsen S et al. (24)</td>
<td>Drop-out rate = 35.2%</td>
</tr>
<tr>
<td>Yip H-K &amp; Smales RJ (19)</td>
<td>Article methodology describes no clear search strategy, key words and databases used, no clear inclusion and exclusion criteria for reviewed publications and includes no study-by-study critique table or discussion of study qualities</td>
</tr>
<tr>
<td>Simonsen RJ (8)</td>
<td>Article methodology describes no clear search strategy, key words and databases used, no clear inclusion and exclusion criteria for reviewed publications and includes no study-by-study critique table or discussion of study qualities</td>
</tr>
<tr>
<td>Basting RT et al. (25)</td>
<td>No randomized controlled, in-vivo or in-situ study</td>
</tr>
<tr>
<td>Navarro MFL et al. (26)</td>
<td>Groups not comparable (GIC group has high caries experience; Resin group has low caries experience); No randomization method stated; No adjustment of baseline differences in groups</td>
</tr>
<tr>
<td>Ganesh &amp; Shobha (27)</td>
<td>No randomized controlled, in-vivo or in-situ study</td>
</tr>
<tr>
<td>Kantovitz KR et al. (28)</td>
<td>No randomized controlled, in-vivo or in-situ study</td>
</tr>
<tr>
<td>Delfino CS et al. (29)</td>
<td>No randomized controlled, in-vivo or in-situ study</td>
</tr>
<tr>
<td>Beirutl N et al. (30)</td>
<td>Drop out rate greater than 50% after 5 years</td>
</tr>
<tr>
<td>Poulsen S et al. (31)</td>
<td>This study was part of a larger study involving 386 children who participated in a randomized-control trial comparing GIC (Fuji III) and a resin sealant (Delton) for caries preventive effect and retention of sealant material. The authors undertook a secondary data analysis of a portion of the children (n=153) with 364 site pairs and a set of bitewings and analysed the data, comparing the caries preventive effect of the sealants using clinical and radiological diagnostic criteria for caries detection. The sample was thus conveniently selected (only children with bitewing x-rays) and was a secondary analysis of a portion of the participants (n=153). Therefore true randomization was lacking and the study was excluded.</td>
</tr>
</tbody>
</table>
control minus caries increment in the sealed group, divided by the caries increment in the controls). The relative risk reductions reported were variable; ranging between 4% and 93% for all of the studies assessed. A meta-analysis, reporting on the caries-preventive effect of a single application of resin-based fissure sealants on the occlusal surfaces of 1st molars, showed that the relative risk of developing caries in a fissure-sealed tooth in relation to an untreated control was 0.67 (95% Confidence interval: 0.55-0.83), which corresponded to a relative risk reduction of 33%. Only 2 of the 13 studies in the Mejäre et al. (12) review dealt specifically with GIC-type fissure sealants (31,39). Both trials reported significant caries preventive effects for GIC sealants but the strength of the evidence was rated as being of limited value. Consequently the authors' concluded that the evidence regarding use of GIC fissure sealants was incomplete.

The systematic review by Beiruti et al. (11) was critical of the Cochrane (2) and Mejäre et al. (12) reviews, as the former excluded many trials and the latter only considered trials in which the control groups did not receive an intervention. Beiruti et al. (11) also limited their search to Medline and PubMed database entries to December 2004 and analyzed articles published in English only (94 publications identified but 12 analyzed). Of these, only randomized-control trials (RCT) were analyzed, from which a relative risk (RR) or an attributable risk (AR) could be calculated as an outcome measure for a caries-preventive effect. The GIC materials were categorized as medium viscosity, low-viscosity, and low-viscosity resin-modified (cavity liner). The resin-based materials were grouped into ‘auto-cured’ and ‘light-cured’. Although such methodology was conceived as being more appropriate for reviewing trials comparing GIC and resin based sealants, the conclusions reached were similar to that regarding the Cochrane Review: that no evidence is provided regarding the relative superiority of resin-based or GIC sealants materials in preventing caries development in pits and fissures over time.

Description of accepted trials

Of the 8 clinical trials (31-38) included in this systematic review (Table 2), 7 followed a split-mouth study design (32-38) and 1 was a parallel-group study (31). In the split-mouth trials, the unit of randomization was the tooth. The split-mouth trials reported significantly different follow-up periods and sample sizes. All teeth under investigation were 1st permanent molars in children 6 to 11 years old, except in the trial by Kervanto-Seppälä et al. (38). In this trial, the caries-preventive effect of GIC versus resin sealants was investigated in the 2nd molars only, of children aged 12-16 years. In all split-mouth studies except the trial by Tostes (33), the interventions were randomly allocated to tooth surfaces within each pair of teeth per patient (either 1 or 2 pairs of molar teeth). In contrast, the trial by Tostes (33) randomized the teeth of
each child in order to receive 3 interventions, with the fourth selected molar serving as a control (Table 2).

With the exception of the Kervanto-Seppälä et al. (38) trial, where children were clinic attendees, all the other trials (31-37) covered children recruited from local schools. All the trials provided a clear description of the interventions given (Table 2) but only 2 trials (31,35) provided information on baseline caries prevalence in the form of DMFT/dmft scores: DMFT 1.81 +/- 1.84 for 12-13 year olds (31) and dmft 1.64 +/- 2.45 for the mean age 7 years (35). Two trials (31,36) reported a fluoride concentration ranging from 0.1- to 0.7 ppm in the water supply. Five trials (32-35,38) provided no information about the water fluoride concentration. Only three trials (31,36,38) gave information about inter/intra-examiner reliability by means of kappa scores and none of the included trials examined the effect of potential confounders on their reported results. Only 2-year data was accepted of one trial, which also reported on 4-year results. The 2-year data was chosen due to the high dropout rate (49%) after 4 years (36).

**Quality of accepted trials**

Table 4 provides information about quality aspects assessed for included studies. Only one study (31) could be regarded as a randomized controlled trial with a parallel group design. All the others were split-mouth studies, which are regarded as quasi-randomized. Details about loss-to-follow-ups were reported in all included studies. Treatment allocation was rated A (Adequate) (36,37) in two trials, B (Unclear) in five (32-34) and C (Inadequate) in the remaining two (35,38).

**Studies that compared GIC with Resin Sealants**

Of the 8 accepted trials (31-38) that compared the caries-preventive effect of GIC and resin sealants, 4 trials were found in favor of resin sealants (31,36-38), 3 trials (32-34) found that both were effective, and 1 trial (35) favored GIC over resin sealants.

The Songpaisan et al. trial (31) compared GIC, resin and 0.5% hydrofluoric acid against a control group receiving no treatment. However, resin was applied only in children aged 12-13 years, whereas the other interventions were placed in children 7-8 years old and 12-13 years old. Although each intervention was only compared against the control group, data presented in tables in this trial enabled this research team to compare resin and GIC sealants. It was found that resin sealants performed significantly better than GIC sealants when mean DFS scores were compared at 24 months (Table 2).
The Kervanto-Seppälä et al. (38) trial studied 2nd permanent molars only, and the GIC sealant was applied only once in a 3-year follow-up period, while the resin sealants were resealed during annual evaluations, in the event of being defective or lost.

The trials by Lovadino et al. (32) and Arrow et al. (35) reported significantly greater retention rates for GIC sealants when compared to resin sealants. However, all the other trials reported exactly the opposite; i.e., significantly lower retention rates for GIC sealants. Tostes (33) found no statistically significant difference in the caries preventive effect between the intervention and control groups after 2 years.
Table 4. Quality Assessment of Accepted Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Allocation</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Drop-outs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovadino JR et al. (33)</td>
<td>Quasi-randomized</td>
<td>B- Unclear</td>
<td>B- Unclear</td>
<td>D - Not possible</td>
<td>B 7/22 (31.8%)</td>
</tr>
<tr>
<td>Tostes M (34)</td>
<td>Quasi-randomized</td>
<td>B-Unclear</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 3/25 (12%)</td>
</tr>
<tr>
<td>Karlzen-Reuterving G &amp; van Dijken JWV (35)</td>
<td>Quasi-randomized</td>
<td>B-Unclear</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 2/47 (4.3%)</td>
</tr>
<tr>
<td>Arrow P et al. (36)</td>
<td>Quasi-randomized</td>
<td>C- By use of month of birth</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 50/465 (10.8%)</td>
</tr>
<tr>
<td>Williams B et al. (37) (2 year results)</td>
<td>Quasi-randomized</td>
<td>A- By use of computer generated random numbers</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>B 71/157 (31%)</td>
</tr>
<tr>
<td>Songpaisan Y, et al. (32) (Part 1)</td>
<td>Randomized</td>
<td>B-Unclear</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 73/512 (14%)</td>
</tr>
<tr>
<td>Songpaisan Y, et al. (32) (Part 2)</td>
<td>Randomized</td>
<td>B-Unclear</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 81/752 (11%)</td>
</tr>
<tr>
<td>Kerrvanto- Seppälä S et al. (39)</td>
<td>Quasi-randomized</td>
<td>C- By use of birthday</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 20%</td>
</tr>
<tr>
<td>Rock WP et al. (38)</td>
<td>Quasi-randomized</td>
<td>A- By use of random number tables</td>
<td>B-Unclear</td>
<td>D- Not Possible</td>
<td>A 21/86 (24%)</td>
</tr>
</tbody>
</table>
The assessment for clinical and methodological heterogeneity between trials showed that the two trials (31,38) differed substantially from the others. The Songpaisan et al. (31) trial had DMFT/DFS increment as the outcome measure. The Kerrvanto-Seppälä et al. (38) trial used repeated application of the resin-based sealant material throughout the investigation and included older children (aged 12-16 years). Therefore, neither trial was included in the meta-analysis.

All six of the other trials (32-37) used split-mouth design, had caries incidence on sealed teeth as the outcome measure, used single material application during the investigation, included children aged between 6 to 11 years and compared a low – viscosity GIC against a resin-based sealant material. These trials were consequently included for meta-analysis. Data was not presented in a paired way in 3 trials (34,36,37). However, it was possible to calculate the missing data from information provided in the tables (36,37) and in the results section of these articles (34). The result of the meta-analysis is shown in Figure 1. The pooled odds ratio (0.96, 95% CI 0.62-1.49) suggests that neither material is more effective in preventing dental caries in pits and fissures.

**Discussion**

This meta-analysis was the first to include non-English databases in its systematic literature search to the topic of caries preventive effect of GIC-based fissure sealants in comparison to resin-based materials. Although no publications in the German and Spanish languages were identified, five Portuguese articles (24,25,28,32,33) were included for review and two were

---

**Figure 1.** Caries preventive effect of GIC and resin based fissure sealants.

CI = confidence interval; OR = odds ratio  
N= total number of sealants; n = number of sealants with caries absent  

<table>
<thead>
<tr>
<th>Study of sub-category</th>
<th>GIC material (%)</th>
<th>Resin-based material (%)</th>
<th>OR (fixed) 95% CI</th>
<th>Weight</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpom, F. et al.</td>
<td>412/412</td>
<td>292/412</td>
<td>1.50 (0.95-2.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koop, D.et al.</td>
<td>72/72</td>
<td>68/74</td>
<td>2.00 (1.28-3.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landen, J.R. et al.</td>
<td>15/15</td>
<td>15/15</td>
<td>0.80 (0.48-1.32)</td>
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<td></td>
</tr>
<tr>
<td>Roch, J. et al.</td>
<td>68/68</td>
<td>68/68</td>
<td>1.00 (0.64-1.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trossel H. et al.</td>
<td>21/22</td>
<td>21/22</td>
<td>2.00 (0.54-7.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilamowski, E. et al.</td>
<td>26/26</td>
<td>26/26</td>
<td>1.00 (0.64-1.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>557</td>
<td>557</td>
<td>1.00 (0.48-2.25)</td>
<td></td>
<td></td>
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</tbody>
</table>

Test for heterogeneity: CH²= 32.21, df= 5 (P<0.0001), I²=57.6%
Test for overall effect: Z= 1.16 (P<0.07)
accepted (32,33). However, despite this broader approach, other aspects in the methodology might have contributed to limitations in its results: (i) not all relevant publications were listed in the selected databases (ii) not all relevant publications were published in English, German, Portuguese or Spanish; (iii) the chosen strings of search terms may not have been broad enough to have captured all articles listed in the databases. Thus, some relevant studies may not have been identified.

In the three accepted reviews included (2,11,12), methodological issues have been highlighted as being an important determinant in decisions to include or exclude trials. The split-mouth study design is commonly used in dentistry to test interventions and includes the advantage of having an individual serve as both experimental subject and control. However, Mejáre et al. (12) have cautioned against this study design as “randomized”, as the common practice of including children with at least one pair of caries-free molars results in exclusion of caries-active children. An obvious selection bias is thus created, as not all children will have the same chance to participate. Mejáre et al. (12) have rightfully suggested that the split-mouth trial design should therefore be regarded as “quasi-randomized”. Thus, reviews where inclusion criteria include only randomized-control trials should, in theory, exclude trials that use the split-mouth study design. Additionally, in order to reduce selection bias, trials that seek to assess the caries-preventive effect of fissure sealants should aim to recruit children soon after the eruption of their first molars.

Previous publications (2,12,40) have highlighted a number of factors that could potentially affect the caries-preventive effect of fissure sealants. Only some of the trials have reported on these factors. They include: (a) baseline caries prevalence in the study population (31,35); (b) number of applications of sealant material – single or repeated (31-37); (c) type of sealant material (27-37); (d) follow-up period (31-37); (e) type of tooth and location in jaw (31-37); (f) fluoride content of drinking water (31,36,37); (g) operator factors (31,36); (h) role of other simultaneous preventive measures, e.g., topical fluoride application (none); and (i) frequency of eating sugary snacks (none). The appropriateness of some of the outcomes reported, especially in the GIC trials, should be noted, as these sealants are effective long after being regarded as “lost” or “partially lost” (31,36). This lower/poor retention rate has been reported in many systematic reviews (2,9,12,41). It has been hypothesized that although the GIC sealants appear clinically as “partially” or “totally” lost, the opening of the fissures remain sealed and the effectiveness of GIC is attributable to the isolation of bacteria from nutrients in the substrate below early carious lesions that have been sealed, the release of fluoride into the dentin or a combination of both factors (41).
In contrast, resin-based sealants have been shown to lose almost all of their protective effect once their retention is lost (36). Hence, the measured outcome of interest when comparing GIC and resin-based sealants should be caries incidence/increment, rather than retention. Resin and GIC sealants both demonstrated a caries-preventive effect, as confirmed in previous systematic reviews (2,11,12). The result of this meta-analysis is in agreement with these previous findings. It is important to note that all accepted trials investigated only obsolete low-viscosity GIC materials and were restricted to 2-3 years. New, high-viscosity GIC materials have been introduced for sealing pits and fissures (29). Clinical application of these materials for sealing fissures differs from the application of low-viscosity GICs. While the latter are applied onto pits and fissures in thin consistency, using a hand instrument, a gloved index finger coated with petroleum jelly (42) is used with pressure to apply high-viscosity glass-ionomer materials. This procedure may achieve deeper fissure penetration of the GIC material than is achieved through the application of thin low-viscosity GIC with a hand instrument. Such deeper fissure penetration of the material may support its higher retention in pits and fissures. Van’t Hof et al. (43) showed in a meta-analysis a full retention rate of 72% of high-viscosity GIC fissure sealants, as compared to 50% of low-viscous GIC material, after 3 years. Beiruti et al. (29) reported a four times higher chance of preventing caries in pits and fissures when using high-viscosity GIC applied through finger pressure, than in using resin-based fissure sealants, after 5 years. These results are in contrast to those presented in this meta-analysis and may be indications of the effectiveness of GIC-based fissure sealants in the future. Further high-quality randomized control trials are needed in order to confirm such initial findings.

GIC and resin based sealants exhibited significant caries preventive effects. This systematic review with meta-analysis found no evidence that either material was superior to the other in the prevention of dental caries. Therefore, both materials appear to be equally suitable for clinical application as fissure sealant materials. Further high-quality randomized control trials are needed in order to investigate the caries-preventive effect of high-viscosity GIC compared to resin-based fissure sealant material.

Acknowledgment
The authors thank Dr Richard Niederman for his advice and guidance in writing this report.
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33. Tostes M (1997) Prevenção de cárie de sulcos e fissuras em dentes permanentes com diferentes materiais contendo fluoreto. RBO 54, 368-371


Atraumatic restorative treatment versus amalgam restoration longevity: a systematic review

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Abstract The aim was to report on the longevity of restorations placed using the atraumatic restorative treatment (ART) approach compared with that of equivalent placed amalgam restorations. Five databases were systematically searched for articles up to 16 March 2009. Inclusion criteria: (1) titles/abstracts relevant to the topic; (2) published in English; (3) reporting on 2-arm longitudinal in vivo trials; (4) minimum follow-up period of 12 months. Exclusion criteria: (1) insufficient random or quasi-random allocation of study subjects; (2) not all entered subjects accounted for at trial conclusion; (3) subjects of both groups not followed up in the same way. Fourteen from the initial search of 164 articles complied with these criteria and were selected for review. From these, seven were rejected and seven articles reporting on 27 separate datasets, accepted. Only identified homogeneous datasets were combined for meta-analysis. From the 27 separate computable dichotomous datasets, four yielded a statistically significant improvement of longevity of ART versus amalgam restorations: posterior class V, 28% over 6.3 years; posterior class I, 6% after 2.3 years and 9% after 4.3 years; posterior class II, 61% after 2.3 years. Studies investigating restorations placed in the primary dentition showed no significant differences between the groups after 12 and 24 months. In the permanent dentition, the longevity of ART restorations is equal to or greater than that of equivalent amalgam restorations for up to 6.3 years and is site-dependent.

No difference was observed in primary teeth. More trials are needed in order to confirm these results.

Keywords Atraumatic restorative treatment · Amalgam · Longevity · Systematic review · Meta-analysis · Glass ionomer cement

Introduction

Atraumatic restorative treatment (ART) is a minimally invasive procedure that involves removing markedly softened carious enamel and dentine using only hand instruments and then restoring the resulting cavity with an adhesive restorative material [1]. Although developed for use in the less industrialized parts of the world, ART has now been accepted as part of the minimum intervention philosophy in developed countries [2–7]. At present, the restorative material of choice for ART is high-viscosity glass ionomer cement (GIC) [8]. GIC is ideally suited to managing dental caries according to the principles of minimally invasive dentistry as it can be applied in the very early stages of caries development or in the larger cavity. Additionally, it simplifies the restorative process and enables the dentine-pulp complex to react against the carious process [9]. During the ART procedure, the histological zone of caries-infected dentine is removed with hand instruments, and, upon application of GIC, a seal is created between the GIC and the remaining enamel margin, and caries-affected dentine lining the cavity surfaces. The glass ionomer adheres to this enamel and dentine primarily
via calcium bonds to the mineral content of the tooth structure [10]. This adherence provides an adaptive seal and as the material slowly leaches fluoride ions into the adjacent tooth tissue, GICs are capable of halting or slowing the progression of carious lesions [11]. Amalgam has been used successfully as a universal posterior restorative material for over a century [12]. However, much controversy still exists regarding the use of amalgam in dentistry; mainly because of its mercury content [13]. The search for a suitable replacement for this material continues. Its operative advantages of being relatively simple to place, its intrinsic strength and the longevity of the final restoration has led to amalgam being considered the “gold standard” against which all new materials are measured for outcomes such as the effectiveness and durability of the restoration.

To date, only one meta-analysis comparing the success rate of ART and amalgam restorations has been published [14]. This focused on single-surface restorations in permanent teeth only and is based on a systematic literature search in PubMed/Medline up to the 1st of September 2003. The meta-analysis found no difference in the survival results between both types of restoration over the first 3 years. No systematic review has been published in the literature comparing the longevity of single- and multiple-surface ART versus amalgam restorations in permanent and primary dentition over longer time periods than 3 years. This systematic review sought to answer the question as to whether, in tooth cavities of the same size, type of dentition and follow-up period, ART restorations are as successful as conventional amalgam fillings. Therefore, the aim of this quantitative systematic review was to analyze trials comparing the longevity of ART, versus amalgam fillings, in the permanent or primary dentition in single- or multi-surface cavities, with follow-up periods from more than 1 to exceeding 3 years.

**Materials and methods**

**Data collection**

Five databases: Biomed Central, Cochrane Library, Directory of Open Access Journals, PubMed and Science-Direct were systematically searched for articles reporting on clinical trials up to 16 March 2009. The terms “ART”, “ART approach”, and “ART technique” yielded 43,111, 3,282 and 2,147 articles respectively, in PubMed. In order to optimize the search breadth and specificity of the databases, excluding many 1-arm longitudinal studies not involving amalgam and non-ART studies using GIC, the final text search term “atraumatic restorative treatment” was used. Articles were selected for review from the search results on the basis of their compliance with the inclusion criteria:
1. Titles/abstracts relevant to topic;
2. Published in English;
3. 2-arm longitudinal in-vivo trial;
4. Minimum follow-up period 12 months.

Where only a relevant title without a listed abstract was available, a full copy of the article was assessed for inclusion. The references of included articles were checked for additional studies suitable for inclusion.

**Article review**

Only articles that complied with the inclusion criteria were reviewed further. Full copies of articles were reviewed independently by 2 reviewers (VY and SM) for compliance with the exclusion criteria [15]:

1. No random or quasi-random allocation of study subjects;
2. Not all entered subjects accounted for at the end of the trial;
3. Subjects of both groups not followed up in the same way.

For the purpose of this review atraumatic restorative treatment (ART) was defined as a tooth restoration procedure including caries removal by hand instruments, using spoon excavators, and cavity restoration with a high-viscosity glass ionomer cement (GIC). Therefore, articles reporting on treatment procedures, which differed from this definition were excluded. Articles were also excluded if no computable data were reported for both the control- and the test group. Where several articles had reported on the same trial over similar time periods, the one covering the trial most comprehensively in accordance with the inclusion/exclusion criteria was accepted. Disagreements between reviewers were resolved by discussion and consensus.

**Data extraction from accepted trials**

The outcome measure was restoration longevity measured according to the dichotomous success/failure rates of tooth restorations. Two reviewers (VY and SM) independently extracted data from the accepted articles. Individual dichotomous datasets for the control and test group were extracted from each article, including the number of successful restorations (n) and total number of evaluated restorations (N). Where possible, missing data were calculated from information given in the text or tables. In addition, authors of articles were contacted in order to obtain missing information. Disagreements between reviewers during
data extraction were resolved through discussion and consensus. It was anticipated that some of the studies eligible for inclusion would be split-mouth in design (quasi-randomized trials). The split-mouth study design is commonly used in dentistry to test interventions and has the advantage of enabling an individual to serve as both subject and control. In this study design one or more pairs of teeth (e.g. primary molars) form the unit of randomization. These pairs are, strictly speaking, not independent and should be analysed as “paired data” on a per-patient basis. However, as in other similar reviews [16], in order to prevent exclusion of data, split-mouth trials were included and the pairs were analysed independently.

Quality of studies

The quality assessment of the accepted trials was undertaken independently by two reviewers (VY and SM) following Cochrane guidelines [17]. Trials not included in this review were used to pilot the process. Subsequently, quality assessment rating scored by both reviewers was derived by consensus. The following quality criteria were examined:

1. Generation of randomization sequence (allocation), recorded as:
   (A) Adequate - e.g. computer-generated random numbers, table of random numbers;
   (B) Unclear – unclear or not reported;
   (C) Inadequate - e.g. case record number, date of birth, date of administration, alternation not reported.

2. Allocation concealment, recorded as:
   (A) Adequate - e.g. central randomization, sequentially numbered sealed opaque envelopes;
   (B) Unclear – unclear or not reported;
   (C) Inadequate - e.g. open allocation schedule, unsealed or non-opaque envelopes.

3. Blind outcome assessment, recorded as:
   (A) Yes;
   (B) Unclear;
   (C) No;
   (D) Not possible.
Statistical Analysis

A fixed effects model in RevMan Version 4.2 statistical software by The Nordic Cochrane Centre, The Cochrane Collaboration (Copenhagen; 2003), was used. Differences in treatment groups were computed on the basis of Relative Risk (RR) with 95% confidence intervals (CI).

Table 1. Quality assessment of randomized/quasi-randomized control trials

<table>
<thead>
<tr>
<th>Article</th>
<th>Selection bias</th>
<th>Detection bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Random allocation</td>
<td>Allocation concealment</td>
</tr>
<tr>
<td>Frencken JE et al. (2007) [23]</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Frencken JE et al. (2006) [22]</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Gao W et al. (2003) [24]</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Yip H-K et al. (2002) [32]</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Yu C et al. (2004) [34]</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

From the accepted articles datasets were extracted and assessed for their clinical and methodological heterogeneity, following Cochrane guidelines [18]. Datasets were considered to be heterogeneous if they did differ in type of dentition (primary or permanent), assessment criteria (ART [19] or USPHS [20]), cavity type and follow-up period. Chi², degree of freedom (df) and the percentage of total variations across datasets (I²) were used in assessing statistical heterogeneity [21]. Only identified datasets without clinical and methodological heterogeneity were pooled for meta-analysis. Pooled datasets for meta-analysis were assigned a Mantel-Haenszel weight directly proportionate to their sample size.

Results

An initial search of PubMed resulted in 164 articles of which 14 articles [4, 22-34] complied with the inclusion criteria and were selected for review. A subsequent search of the other four databases generated no additional results. From the selected articles, 7 were excluded: 1 article lacked random allocation of subjects [28]; 1 did not reported on loss-to-follow up of subjects per treatment group and thus did not enable computing of data [29]; 2 reported on trials using caries removal by hand excavation combined with chemo-mechanical caries.
removal, followed by cavity restoration with a low-viscosity GIC [26, 27]; 1 article reported on a trial using Cermet (Chelon Silver) compared to a mix of GIC (Chelon Fil) with amalgam as restorative materials [25]; 1 did not report results as computable (dichotomous or continuous) data [33] and 1 article [31] reported on 12-month data that was also reported in the accepted article by Frencken et al. (2007) [23]. Seven articles reporting on randomized and quasi-randomized control trials were accepted [4, 22-24, 30, 32, 34]. Table 1 provides information about quality aspects assessed for the accepted articles. Random allocation of subjects was rated A (Adequate) in one trial [4] and B (Unclear) in all other trials [22-24, 30, 32, 34]. The concealment of random allocation was rated as B in all trials. All B ratings were based on the lack of information describing how random allocation was made and whether the allocation was concealed. Owing to the visible material characteristics of the compared materials (GIC and amalgam), blinding of outcome assessment was rated D (Not possible) in all trials.

From the accepted 7 articles, 27 separate computable dichotomous datasets with relevance to the review objective were extracted. It has to be noted that both articles by Frencken et al. (2006 and 2007) reported on different datasets from the same trial [22, 23]. The articles by Gao et al. (2003) and Yip et al. (2002) also presented the results of different datasets from the same trial [24, 32]. The main characteristics of the datasets are described in Table 2.
Table 2. Main characteristics of datasets from randomized and quasi-randomized control trials.

<table>
<thead>
<tr>
<th>Article</th>
<th>Dataset number</th>
<th>Study design</th>
<th>Evaluation criteria</th>
<th>Age (years)</th>
<th>Type of dentition</th>
<th>Cavity conditioning before GIC placement during ART</th>
<th>Type of cavity</th>
<th>Follow-up period</th>
<th>Glass ionomer cement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frencken JE et al.* (2007) [23]</td>
<td>01</td>
<td></td>
<td>Permanent</td>
<td>7.5</td>
<td>Yes</td>
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<td></td>
<td></td>
<td>Fuji IXGP / Ketac Molar</td>
</tr>
<tr>
<td></td>
<td>02</td>
<td>Parallel group</td>
<td>ART criteria</td>
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<td>Taifour D et al.</td>
<td>2002</td>
<td>Parallel ART criteria 6-7</td>
<td>Yes</td>
<td>36 months</td>
<td>Fuji IXGP / Ketac Molar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Articles reporting on different datasets from the same trials. GIC = Glass ionomer cement; ART = Atraumatic restorative treatment.
Table 3. Comparison of success rates between ART and amalgam restorations per dataset

<table>
<thead>
<tr>
<th>Article</th>
<th>DS</th>
<th>ART n</th>
<th>ART N</th>
<th>Amalgam n</th>
<th>Amalgam N</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ART</td>
<td></td>
<td>Amalgam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>N</td>
<td>n</td>
<td>N</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent dentition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frencken JE et al. (2007) [23]</td>
<td>01</td>
<td>230</td>
<td>355</td>
<td>173</td>
<td>295</td>
<td>1.10</td>
<td>0.98 – 1.25</td>
</tr>
<tr>
<td>02</td>
<td>106</td>
<td>132</td>
<td>68</td>
<td>108</td>
<td>1.28*</td>
<td>1.08 – 1.51*</td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>154</td>
<td>222</td>
<td>74</td>
<td>116</td>
<td>1.09</td>
<td>0.92 – 1.28</td>
<td></td>
</tr>
<tr>
<td>04</td>
<td>39</td>
<td>70</td>
<td>57</td>
<td>108</td>
<td>1.06</td>
<td>0.80 – 1.39</td>
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<tr>
<td>05</td>
<td>454</td>
<td>487</td>
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<td>403</td>
<td>1.02</td>
<td>0.98 – 1.05</td>
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<tr>
<td>06</td>
<td>375</td>
<td>397</td>
<td>289</td>
<td>323</td>
<td>1.06*</td>
<td>1.01 – 1.10*</td>
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</tr>
<tr>
<td>07</td>
<td>334</td>
<td>348</td>
<td>258</td>
<td>267</td>
<td>0.99</td>
<td>0.96 – 1.02</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>274</td>
<td>288</td>
<td>191</td>
<td>218</td>
<td>1.09*</td>
<td>1.03 – 1.15*</td>
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</tr>
<tr>
<td>09</td>
<td>153</td>
<td>161</td>
<td>108</td>
<td>113</td>
<td>0.99</td>
<td>0.94 – 1.05</td>
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<tr>
<td>Frencken JE et al. (2006) [22]</td>
<td>10</td>
<td>138</td>
<td>153</td>
<td>97</td>
<td>108</td>
<td>1.00</td>
<td>0.92 – 1.09</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>52</td>
<td>26</td>
<td>33</td>
<td>1.00</td>
<td>0.80 – 1.25</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>31</td>
<td>34</td>
<td>13</td>
<td>23</td>
<td>1.61*</td>
<td>1.11 – 2.34*</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>29</td>
<td>9</td>
<td>12</td>
<td>1.15</td>
<td>0.80 – 1.64</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>18</td>
<td>21</td>
<td>7</td>
<td>9</td>
<td>1.10</td>
<td>0.75 – 1.63</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>9</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>0.88</td>
<td>0.48 – 1.60</td>
<td></td>
</tr>
<tr>
<td>Gao W et al. (2003) [24]</td>
<td>17</td>
<td>16</td>
<td>17</td>
<td>6</td>
<td>6</td>
<td>0.99</td>
<td>0.77 – 1.27</td>
</tr>
<tr>
<td>Yip H-K et al. (2002) [32]</td>
<td>18</td>
<td>21</td>
<td>21</td>
<td>22</td>
<td>22</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Primary dentition</td>
<td>19</td>
<td>17</td>
<td>17</td>
<td>22</td>
<td>22</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Yu C et al. (2004) [34]</td>
<td>20</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>17</td>
<td>0.95</td>
<td>0.81 – 1.10</td>
</tr>
<tr>
<td>21</td>
<td>12</td>
<td>13</td>
<td>17</td>
<td>17</td>
<td>0.92</td>
<td>0.75 – 1.12</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>1.17</td>
<td>0.65 – 2.10</td>
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</tr>
<tr>
<td>Honkala E et al. (2003) [4]</td>
<td>23</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>1.33</td>
<td>0.79 – 2.26</td>
</tr>
<tr>
<td>Taifour D et al. (2002) [30]</td>
<td>24</td>
<td>24</td>
<td>26</td>
<td>23</td>
<td>25</td>
<td>1.00</td>
<td>0.85 – 1.18</td>
</tr>
<tr>
<td>25</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>0.89</td>
<td>0.67 – 1.19</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>322</td>
<td>376</td>
<td>316</td>
<td>380</td>
<td>1.03</td>
<td>0.97 – 1.09</td>
<td></td>
</tr>
<tr>
<td>* Significant difference in favour of ART (p&lt;0.05); DS = Dataset number; RR = Relative Risk; CI = Confidence Interval; n = Number of successful restorations; N = Total number of evaluated restorations</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

The relative risk (RR) with 95% confidence interval (CI) of most datasets showed no statistical significant difference (p>0.05) between the success rates of ART and amalgam restorations (Table 3). The results of 4 datasets: #02 [23] and #06, #08, #12 [22] indicate a higher success rate of ART in comparison to conventional amalgam restorations. The relative risk calculated for dataset #02 (RR 1.28; 95% CI 1.08 – 1.51; p = 0.004) indicates that ART restorations in posterior Class V cavities of permanent teeth have a 28% higher chance of being rated successful than amalgam restorations after 6.3 years [23].
Table 4. Meta-analysis results of homogeneous datasets reporting on the success rates of ART and amalgam restorations (Class I) in primary teeth.

<table>
<thead>
<tr>
<th>Evaluation period</th>
<th>Test of statistical heterogeneity</th>
<th>RR</th>
<th>95% CI</th>
<th>Statistical difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi²</td>
<td>df</td>
<td>i²</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dataset</td>
<td>Weight %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>020</td>
<td>54.0</td>
<td>0.06</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>021</td>
<td>46.0</td>
<td>1.42</td>
<td>2</td>
<td>0%</td>
</tr>
<tr>
<td>022</td>
<td>14.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>023</td>
<td>14.4</td>
<td></td>
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<tr>
<td>024</td>
<td>71.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>71.5</td>
<td>1.42</td>
<td>2</td>
<td>0%</td>
</tr>
</tbody>
</table>

RR = Relative Risk; CI = Confidence Interval; df = Degree of freedom; i² = Percentage of total variations across datasets due to heterogeneity; Weight% = Mantel-Haenszel weight directly proportionate to sample size.
The relative risk calculated for dataset #06 (RR 1.06; 95%CI 1.01 – 1.10; p = 0.02) and #08 (RR 1.09; 95%CI 1.03 – 1.15; p = 0.004) indicates that ART restorations in posterior Class I cavities of permanent teeth have a 6% higher chance after 2.3 years and a 9% higher chance after 4.3 years, respectively, of being rated more successful than amalgam restorations. The relative risk calculated for dataset #12 (RR 1.61; 95%CI 1.11 – 2.34; p = 0.01) indicates that ART restorations in posterior Class II cavities of permanent teeth have a 61% higher chance of being rated more successful than amalgam restorations after 2.3 years [22]. Only 2 homogeneous datasets for Class I cavities in primary teeth after 12 months [34] and 3 datasets for the follow-up period of 24 months [4, 34] were identified as suitable for meta-analysis (Table 4). No statistical heterogeneity ($I^2 = 0\%$) was found in both pooled datasets. The relative risks after 12 and 24 months (RR 0.93; 95%CI 0.83-1.06, p = 0.26 and RR 1.07; 95%CI 0.91-1.27; p = 0.39, respectively) indicated no statistically significant difference in the success rates of Class I ART and amalgam restorations in primary teeth.

Discussions
Quantitative systematic reviews with or without meta-analysis have value over narrative synthesis in providing the chance for detecting a statistically significant (p<0.05) treatment effect and for improving estimation of such effect by quantifying its outcome [35]. In quantitatively collating clinical information from separate trials carried out for a particular treatment approach, such as ART, in comparison to others, a more objective assessment of a systematic analysis of the currently available evidence is given. In this case, the longevity of GIC ART restorations and equivalent amalgams were compared. Often, owing to the heterogeneity of such trials, the outcome data are not directly comparable and therefore, restrictive inclusion criteria are used to limit the variation and so strengthen the value of the post meta-analysis results. There is a risk, however, that some useful trial data will be excluded from the review, as they may fall outside the inclusion criteria, thus weakening the overall clinical value of the systematic review. In this study, in order to increase the inclusion envelope, split-mouth quasi-random study designs and their data [4, 24, 32, 34] were included and analyzed independently. The reviewed data included the results of 27 datasets, the main characteristics of which are outlined in Table 2. Other aspects in the methodology of this review might have contributed to limitations in its results: (i) not all relevant publications were listed in the selected databases; (ii) not all relevant publications were published in English. Thus, some relevant studies may not have been identified. Despite these considerations, in PubMed only 8.5% of the initially identified 164 articles were randomized/quasi-randomized control trials reporting on the comparison of ART with amalgam as control. Most other studies constituted non-randomized longitudinal ART trials without control groups. Moreover, no further eligible articles were identified in the other databases. Therefore the inclusion of further data sources might not have resulted in the selection of more articles. From the initial
14 included articles, 3 were excluded because they did not comply with the chosen definition of ART [25-27]. This definition was based on the consideration that ART constitutes a synthesis of the concepts of: (A) the retention of remineralizable affected dentine after caries removal by hand excavation [1] and (B) the promotion of remineralization of such affected dentine through the placement of a biomimetic restorative material [1]. Originally, ART was developed for use in underdeveloped regions [1], to address the need for inexpensive instrumentation. Other excavation techniques relying on specialized hand instruments in connection with a chemical agent [36] do not fulfil this criterion. In regard to the material of choice for ART, only GICs have been shown to have a (hyper-) remineralizing effect on hard tooth tissue [37-39]. GIC can therefore be considered as the only material currently proven to be capable of effectively remineralising the retained affected dentine. A previous meta-analysis reported higher restoration longevity with high-viscosity GIC than with low-viscosity GIC for ART [14]. For these reasons the ART definition chosen was considered to be correct and its use as the criterion for exclusion of articles in this review, justified.

The quality of the clinical control trials related to internal validity was assessed, using a structured checklist. The assessment outcome indicated that the results of the trials might be limited by selection bias (Table 1). Such bias or systematic error may affect studies by causing either an over- or under-estimation of the treatment effect of an investigated clinical procedure. The overestimation of such effect has been observed to be the most common [40]. Schulz et al. (1995) reported a 41% treatment effect overestimation due to selection bias, caused by lack of allocation concealment during the randomization process, alone [41]. As all trials accepted in this review did not report on allocation concealment, their results need to be interpreted with caution.

Quantitative assessment, through calculation of the relative risk (RR) with 95% confidence interval of the 27 dichotomous datasets, indicated that all but four datasets in the permanent dentition [22, 23] showed no statistical differences between the success rates of ART GICs and amalgam restorations (p>0.05). Although this current review differed in aspects of methodology and included articles, its findings are in line with the results of a previous meta-analysis [14]. The four datasets with a significant difference in success in favor of the ART GICs (p<0.05) were spread over the three classes of posterior restorations: I, II and V. The relative risks (improvement in favor of ART) for class I occlusal restorations varied from 6 – 9% over a follow up period of 2.3 – 4.3 years (p<0.05); Class V restorations, 28% after 6.3 years and class II restorations, 61% after 2.3 years (p<0.05). It has been reported that non-exposure to occlusion and smaller cavity size are factors supporting the survival duration of tooth restorations [27]. The maximum length of the follow-up period for Class II (= 2-surface restoration with exposure to occlusion), Class I (= 1-surface restoration with exposure to
occlusion) and Class V (= 1-surface restoration with no exposure to occlusion) restorations at which ART had a higher success rate than similar amalgam fillings (at 2.3; 4.2 and 6.3 years, respectively) confirms this. Why these four datasets showed a higher success rate than amalgam is not clear. Additional clinical procedures that enhance ART longevity, such as cavity conditioning before GIC placement have also been reported for datasets, but these have been found to make no difference to the survival rate between both types of restoration in this review (Table 2). However, not material- or technique factors, but operator factors related particularly to operator diligence, especially in the area of clinical indication, caries removal, moisture control, cavity conditioning, material mix and material insertion have been reported to affect the success of ART restorations most [42, 43]. As it has been suggested that these are the main causes of clinical ART failures, it can be assumed that they may be potential confounders that could increase or decrease the success rates of the analyzed datasets. Thus, further high quality randomized control trials are needed to confirm these results. Reporting of such trials should follow the CONSORT statement and, particularly, include a clear description of how the randomized allocation of study subjects was conducted, report on details of any restrictions, and state who generated the allocation sequence, who enrolled the subjects and who assigned subjects to their groups. Reporting should further include information about whether such allocation was concealed from the clinical operators until interventions were assigned and if it was, about how this was done [44].

Conclusions
The systematic literature search identified 7 randomized/quasi-randomized control trials including 27 separate datasets with relevance to the review question. None of the datasets found tooth restorations placed using conventional drilling and amalgam to be a treatment option superior to ART. Regardless of the type of cavity, dentition or length of follow-up there was no difference in longevity between GIC and amalgam; except for 4 datasets where GIC performed better. These datasets compared restorations in Class I, II and V cavities of permanent teeth. No differences could be found in the primary dentition studies over a 2-year follow up period. The answer to the review question was that in comparison to conventional fillings with amalgam of the same size, type of dentition and follow-up period, ART restorations with high-viscosity GIC appear to be equally successful and their survival rate may even exceed that of amalgam fillings. However, these findings have to be regarded with caution and a conclusive statement about the superiority of either type of procedure above the other cannot yet be made, as all the included studies had limited internal validity due to unclear randomized sequence allocation and/or allocation concealment. Further high quality randomized control trials are therefore needed. It is recommended that reporting of such future trials should follow the CONSORT statement.
Conflict of Interest
The authors declare that they have no conflict of interest.

References


Caries preventive effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP): a meta-analysis

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Abstract
Objective. This systematic review with meta-analyses sought to answer the following question: “Does CPP-ACP [casein phosphopeptide-amorphous calcium phosphate], when introduced into the oral environment, provide any caries-preventive benefit superior to that of any other intervention or placebo?” Material and methods. Seven electronic databases were searched for trials relevant to the review question. Twelve articles were accepted after application of inclusion and exclusion criteria. Results. Of the accepted articles, five in situ randomized control trials (RCT) could be pooled for meta-analyses. During the short-term (7–21 days) in situ trials, participants wore appliances containing enamelled slabs that were analyzed in the laboratory after exposure to CPP-ACP. The pooled in situ results showed a weighted mean difference (WMD) of the percentage remineralization scores in favor of chewing gum with 18.8 mg CPP-ACP as compared to chewing gum without CPP-ACP (WMD = 8.01; 95% CI: −10.54 to −5.48; p = 0.00001), as well as compared to no intervention (WMD = 13.56; 95% CI: −16.49 to −10.62; p = 0.00001). A significant higher remineralization effect was also observed after exposure to 0.0 mg CPP-ACP (−7.75; 95% CI: −9.84 to −5.66; p = 0.00001). One long-term in vivo RCT (24 months) with a large sample size (n = 2720) found that the odds of a tooth surface’s progressing to caries was 18% less in subjects who chewed sugar-free gum containing 54 mg CPP-ACP than in control subjects who chewed gum without CPP-ACP (p = 0.03). Conclusion. Within the limitations of this systematic review with meta-analysis, the results of the clinical in situ trials indicate a short-term remineralization effect of CPP-ACP. Additionally, the promising in vivo RCT results suggest a caries-preventing effect for long-term clinical CPP-ACP use. Further randomized control trials are needed in order to confirm these initial results in vivo.

Key Words: Caries, CPP-ACP, meta-analysis

Introduction
The potential of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) to promote remineralization and inhibit demineralization of hard tooth tissue has been observed in laboratory and animal studies [1,2] and in situ studies covering human subjects [3,4]. Explanation of this potential has been based on the ability of casein phosphopeptide (CPP) to stabilize calcium phosphate by binding amorphous calcium phosphate (ACP) and thus forming CPP-ACP clusters [5]. These CPP-ACP clusters act as a calcium and phosphate reservoir that attaches itself to dental plaque and tooth surfaces. On acid challenge, the attached CPP-ACP releases calcium and phosphate ions, thus maintaining a supersaturated mineral environment, thereby reducing demineralization and enhancing remineralization [6–8]. It has been shown that enamel remineralized by CPP-ACP is relatively more acid-resistant than normal tooth enamel [3,7].

The most commonly tested (and used) mode of CPP-ACP application in the human oral environment is via sugar-free sorbitol or xilitol-based chewing gum [3,4,7]. Other vehicles include milk [9], mouth-rinse [10], lozenges [11,12], and dental cream [13]. A recent systematic review, which covered a number of published trials on this topic, reported on the clinical efficacy of casein derivatives, including CPP-ACP [14]. The investigated outcomes included the efficacy of CPP-ACP for caries prevention (10 studies), treating dry mouth (1 study), and treating dentin hypersensitivity (1 study). The authors found "insufficient clinical trial evidence (in quantity, quality or both) to make a recommendation..."
regarding the long-term effectiveness of casein derivatives, specifically CPP-ACP, in preventing caries in-vivo and in treating dentin hypersensitivity or dry mouth”. This conclusion was based on the authors’ assessment of each included trial, using a PICOS (patient; intervention; controls; outcome; study authors’ conclusions) format and a qualitative synthesis of the included articles. However, the disadvantage of qualitative synthesis in systematic reviews is that bias may be introduced if the outcomes of some studies are inappropriately stressed over others [15]. The advantages of meta-analysis over qualitative synthesis is that it provides the opportunity to identify a treatment effect as statistically significant ($p<0.05$) and to improve estimation of the effect by quantifying its outcome; thus making its estimation more precise [15]. Therefore, whilst methodological weaknesses limit what can be inferred in terms of efficacy, the cumulative weight of evidence (as highlighted where possible, in a meta-analysis) provides a more objective assessment of a systematic analysis of the literature.

The inconclusive findings of the Azarpazhooh and Limeback systematic review [14] regarding the outcome “caries prevention” (7 trials favored CPP-ACP in comparison to control, 2 studies found no additional benefit and 1 study had contradictory findings) might have been very different if a meta-analysis of trials reporting on the same outcome had been attempted. This has been the case in a number of systematic reviews where individual studies have had varied outcomes but the cumulative weight of the evidence (elicited through pooling together trials with similar outcomes) has been found to be conclusive for that particular outcome [16-18]. Thus, this systematic review with meta-analysis sought to answer the following question: “Does CPP-ACP, when introduced into the oral environment, provide any caries-preventive benefit superior to that of any other intervention or placebo?”

**Materials and methods**

**Search strategy**

The literature search covered the electronic databases: Biomed Central; Cochrane oral health reviews; Cochrane library; Directory of open access journals (DOAJ); PubMed; Science Direct; Research findings electronic register – ReFeR. In order to search databases, strings of search terms, consisting of relevant text words and boolean links, were constructed. The string of English search terms: “MI Paste OR Recaldent OR casein phosphopeptide-amorphous calcium phosphate OR CPP-ACP OR tooth mousse” was used. All publications listed between the earliest publication year of each particular database and 31 August 2008 were included in the search.
**Inclusion and exclusion criteria**

Publications were selected from the search results if their titles/abstracts were relevant to the review objective and the articles were published in English. Additionally, since the review question dealt with a therapeutic intervention, each included study had to be either a clinical trial (randomized or quasi-randomized; in-situ or in-vivo), or a systematic review (with or without meta-analysis) of published trials that reported on the efficacy of CPP-ACP in any mode of delivery. The rationale behind using broad-based inclusion criteria was that the reviewers could scan the reference sections of all studies on casein derivatives to try to identify additional trials that could be considered for possible inclusion into this review. Case reports, editorials, case series, in-vitro studies, studies that included animal (bovine) tissue, and review papers that were not considered systematic reviews, were excluded. Where only a relevant title without a listed abstract was available, a full copy of the publication was assessed for inclusion. In accordance with published recommendations [19], included articles were reviewed independently by 2 reviewers (VY and SM). Disagreements were resolved through discussion and consensus. Where multiple reports covered the same trial, that covering the longest period and lacking the exclusion criteria was accepted.

**Quality of studies**

The quality assessment of the included trials was undertaken independently by two reviewers (VY and SM) and piloted using trials not included in this review. Quality assessment rating, scored by both reviewers, was derived by consensus. Four commonly accepted quality criteria [20-22] relating to the internal validity of the trials were examined:

1. Generation of randomization sequence, recorded as:
   - (A) Adequate (e.g. computer-generated random numbers, table of random numbers),
   - (B) Unclear,
   - (C) Inadequate (e.g. case record number, date of birth, date of administration, alternation);

2. Allocation concealment, recorded as:
   - (A) Adequate (e.g. central randomization, sequentially numbered sealed opaque envelopes),
   - (B) Unclear,
   - (C) Inadequate (e.g. open allocation schedule, unsealed or non-opaque envelopes);

3. Blind outcome assessment, recorded as:
   - (A) Yes,
   - (B) Unclear,
   - (C) No,
   - (D) Not used/possible;
(4) Completeness of follow-up (whether a clear explanation existed for withdrawals and drop-outs in each treatment group), assessed as:
(A) Yes (drop-outs less than 30%),
(B) Yes (drop-outs more than 30%),
(C) No explanation.

Data extraction and meta-analysis
The primary outcome measure was caries prevention reported in accordance with the requirements listed below.

(a) An improvement in DMFT/DMFS/DFS scores with standard deviations (SDs) or 95% confidence intervals (CI) or standard errors of the mean (SEM)
The measures sought for pooling of data for meta-analyses were the mean DMFT/DMFS/DFS scores with SDs. If the SD was not reported, this was calculated from the 95% CIs or the SEM scores. Where no SD score was included or could be calculated, the paper was excluded.

(b) A percent remineralization (%R) with SDs (increase or decrease)
Since this is a continuous variable, pooling of data (for meta-analysis) from included trials was undertaken, using the Cochrane RevMan, Version 4.2, software package. The differences in the %R scores were calculated as follows: %R control group - %R treatment group. A negative score would imply benefit (more remineralization would have occurred after exposure to CPP-ACP in the treatment group).

(c) A change in lesion depth (either increase or decrease)
Two reviewers (VY and SM) independently extracted data from the accepted articles, using a pilot-tested data extraction form. Disagreements between reviewers during data extraction were resolved through discussion and consensus. The results of the included studies were treated as continuous data. Trials were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines [23]. Trials were considered homogenous if they had not differed substantially in the following clinical and methodological aspects: type of delivery agent used (e.g., chewing gum), type of control material (e.g. chewing-gum without CPP-ACP; no intervention), frequency of application/use, CPP-ACP concentration (e.g. 18.8 mg; 10.0 mg) and outcome measure (e.g. %R). Clinically and methodologically homogenous trials were combined and analyzed separately in sub-groups, for which the random effects model of the meta-analysis software, RevMan 4.2, was used. Studies were assigned a Mantel-Haenszel weight in direct proportion to their sample size. Differences between groups
for each of the assessed pooled outcomes were reported in the form of weighted mean differences (WMDs) and their respective 95% confidence intervals (CIs). Forest plots were used to graphically illustrate results of sub-group meta-analyses undertaken. For trials where pooling of data was not possible, mean differences (MDs) were calculated to reflect differences in the treatment and control groups.

Results
The initial search in the various electronic databases, using the keywords listed in the search strategy, yielded 3459 articles. Application of the broad-based inclusion criteria significantly reduced these to 5 reviews and 30 clinical studies. Of the 35 articles, 23 were not considered after application of the exclusion criteria (Figure 1). Table 1 provides a summary of reasons for their exclusion. Eleven trials [3,4,6-10,12,13,24,25] and one systematic review [14] were finally accepted for this review (see Table 2).

Figure 1. Flow chart of article review and meta-analysis
**Table 1.** Excluded articles and main reasons for exclusion

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aimutis WR 2004 [42]</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Ardu S et al. 2007 [34]</td>
<td>Case report</td>
</tr>
<tr>
<td>Cochrane NJ et al. 2008 [31]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Hay et al. 2005 [11]</td>
<td>Investigated casein derivatives such as calcium phosphate but not CPP-ACP</td>
</tr>
<tr>
<td>Hicks J et al. 2004 [41]</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Mazzaoui SA et al. 2003 [43]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Milnar FJ et al. 2007 [36]</td>
<td>Case report</td>
</tr>
<tr>
<td>Pai D et al. 2008 [29]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Piekarz C et al. 2008 [30]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Rahiotis C et al. 2007 [34]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Ramalingam L et al. 2005 [40]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Reynolds EC 1997 [5]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Reynolds EC 1998 [44]</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Schirrmeister JF et al. 2007 [45]</td>
<td>Study on animal tissues</td>
</tr>
<tr>
<td>Slayton RL 2006 [47]</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Sudjaliim TR et al. 2006 [38]</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Sudjaliim TR et al. 2007 [37]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Tantbirojn D et al. 2008 [32]</td>
<td>In vitro study</td>
</tr>
<tr>
<td>Vlacic J et al. 2007 [33]</td>
<td>Case report</td>
</tr>
<tr>
<td>Yamaguchi K et al. 2006 [39]</td>
<td>Study on animal tissues</td>
</tr>
<tr>
<td>Yamaguchi K et al. 2007 [1]</td>
<td>Study on animal tissues</td>
</tr>
<tr>
<td>Zero DT 2006 [46]</td>
<td>Narrative review</td>
</tr>
</tbody>
</table>

**Appraisal and Quality assessment of included studies**

Table 2 provides a summary of included trials in a PICOS (Population, Intervention, Comparative intervention or control, Outcomes, Study design) format and Table 3 reports on a quality assessment of included trials. Of the 11 trials, nine [3,6-10,12,24,25] were double-blinded, in-situ, randomized controlled trials (RCT) with a crossover component. Most had small sample sizes \((n < 15)\). However, two [6,24] had sample sizes of 30 and short follow-up periods (on average 14 days, with the exception of one trial [25], which had a follow-up of 21 days). Two trials [4,13] were RCTs with longer follow-up periods of 12, and 24 months respectively. In terms of quality assessment, all included trials, except two [9,13] (Allocation concealment was unclear – “B”), scored “A” (adequate) for Randomization, Allocation concealment and Blinding. All of those included provided information on sample sizes, loss-to-follow-up rate and follow-up periods. For the pooled meta-analysis, all of the included papers were rated “A” for Randomization, Allocation Concealment, Blinding, and Drop-outs. However, all of the studies included for the meta-analysis were in-situ in study design and were of short-term (7-21 days) duration.
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparative intervention/controls</th>
<th>Outcome/s</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iijima et al. 2004 [7]</td>
<td>10 healthy subjects, (mean age 32.3; SD +/- 7.9 years)</td>
<td>2 Gum treatments: 1. Dental chewing gum in slabs containing CPP – ACP (18.8 mg) 2. Sugar free gum in slabs without CPP-ACP</td>
<td>Crossover design with 14-day test period followed by 7-day washouts between interventions. In-vitro acid challenge of enamel slabs done for 8 and 16 hours</td>
<td>% Subsurface remineralization [%R] (CPP-ACP versus Control) 3 measures reported 1. %R with no acid challenge (17.88 ± 0.97 vs 9.02 ± 0.74) 2. %R after 8hr acid challenge (12.43 ± 0.90 vs 3.12 ± 0.88) 3. %R after 16-hr acid challenge (10.40 ± 1.09 vs 1.08 ± 1.02)</td>
<td>Double blinded in-situ and in-vitro RCT with crossover</td>
</tr>
<tr>
<td>Itthagarun et al. 2005 [25]</td>
<td>12 healthy subjects (5 males; 7 females; age range 20-47 years)</td>
<td>3 types of sugar free gum containing 1. 30 mg urea 2. 30 mg urea + 25 mg dicalcium phosphate dehydrate 3. 30 mg urea + 47 mg CPP-ACP</td>
<td>Crossover design with 21 day test period for each type of gum followed by 5 day washouts after each test period</td>
<td>Two outcomes reported 1. Mean % change in lesion depth of the samples 2. Mean % change in the mineral content of the samples</td>
<td>Double blinded in-situ RCT with crossover</td>
</tr>
<tr>
<td>Shen et al. 2001 [24]</td>
<td>30 healthy subjects (30 +/- 7; 33 +/- 7 and 34 +/- 6 years)</td>
<td>3 types of gum 1. Sorbitol based pellet gum containing 4 different doses of CPP-APP 2. Sorbitol based slab gum containing 4 different doses of CPP-APP 3. Xylitol based pellet gum containing 4 different doses of CPP-APP</td>
<td>Crossover design with 14 day test period for each type of gum followed by at least one week washout period between interventions</td>
<td>% Subsurface remineralization (%R)</td>
<td>Double blinded in-situ RCT with crossover</td>
</tr>
</tbody>
</table>
**Table 2. Details of included studies (contd.)**

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparative intervention/controls</th>
<th>Outcome/s</th>
<th>Study design</th>
</tr>
</thead>
</table>
| Reynolds et al. 2003 [6] | 30 healthy adults (age range 22-44 years) | Consisted of 2 parts/; A. Mouth-rinse trial – 4 interventions tested  
1. 2% CPP-ACP  
2. 6% CPP-ACP,  
3. Calcium + phosphate slurry mixed as mouth rinse 4. de-ionized water  
B. Chewing gum trial with 2 parts  
(1) Gum either in pellet or slab form contained a calcium additive  
CaCO$_3$ or CaHPO$_4$/CaCO$_3$ or CPP-ACP  
(2) subjects chewed gum pellets containing 9.5 mg CPP-ACP for 4 days without using any other oral hygiene methods. | Mouth-rinse trial- crossover in design; washout period 4 weeks between treatments.  
Chewing gum trial – crossover in design; no washout period stated; in-situ study | For mouth rinse trial-Calium and phosphate levels in supragingival plaque  
For chewing gum trial- % subsurface remineralization (%R) and level of CPP in plaque | Double blinded RCT; Crossover in design; Chewing gum has in-situ component |
| Cai et al. 2007 [3]   | 10 healthy subjects (7 male; 3 female; age range: 23-46 years old) | Three treatments:  
1. Sugar-free pellet gum containing 20mg citric acid + 18.8 mg CPP-ACP  
2. Gum with 20 mg citric acid  
3. Gum with neither citric acid or CPP-ACP  
Three treatments:  
1. 200 ml milk containing 2.0 g CPP-ACP  
2. 200 ml milk containing 5.0 g CPP-ACP  
3. 200 ml milk containing no CPP-ACP  
Four treatments consisting of 1.75g lozenge with:  
1. 18.8 mg CPP-ACP  
2. 56.4 mg CPP-ACP  
3. No CPP-ACP  
4. No lozenge; nil treatment; control  
3 types of gum:  
1. Sorbitol/ Xylitol based 2.0 g slab gum containing no CPP-APP  
2. Sorbitol/Xylitol based 1.5 g pellet (x2) gum containing no CPP-APP  
3. Two gum pellets containing 10 mg CPP-ACP | Crossover trial with 2 week treatment periods followed by 7 day washout  
Crossover trial with 15 day treatment periods (200 ml milk consumed over 60 s) followed by 7 day washout  
Crossover design with 14 day test period for each type of lozenge (4x daily use) followed by at least one week washout period between interventions | 1. % Subsurface remineralization  
2. % Remineralization after 16 hour acid challenge  
% Subsurface remineralization (%R)  
% Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover |
| Walker et al. 2006 [9] | 10 healthy adults | 10 healthy adults  
Three treatments:  
1. Sugar-free pellet gum containing 20mg citric acid + 18.8 mg CPP-ACP  
2. Gum with 20 mg citric acid  
3. Gum with neither citric acid or CPP-ACP  
Three treatments:  
1. 200 ml milk containing 2.0 g CPP-ACP  
2. 200 ml milk containing 5.0 g CPP-ACP  
3. 200 ml milk containing no CPP-ACP  
Four treatments consisting of 1.75g lozenge with:  
1. 18.8 mg CPP-ACP  
2. 56.4 mg CPP-ACP  
3. No CPP-ACP  
4. No lozenge; nil treatment; control  
3 types of gum:  
1. Sorbitol/ Xylitol based 2.0 g slab gum containing no CPP-APP  
2. Sorbitol/Xylitol based 1.5 g pellet (x2) gum containing no CPP-APP  
3. Two gum pellets containing 10 mg CPP-ACP | Crossover trial with 2 week treatment periods followed by 7 day washout  
Crossover trial with 15 day treatment periods (200 ml milk consumed over 60 s) followed by 7 day washout  
Crossover design with 14 day test period for each type of lozenge (4x daily use) followed by at least one week washout period between interventions | 1. % Subsurface remineralization  
2. % Remineralization after 16 hour acid challenge  
% Subsurface remineralization (%R)  
% Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover |
| Cai et al. 2003 [12]  | 10 healthy subjects (6 males; 4 female; mean age 34 ± 6.6 years) | 10 healthy subjects (6 males; 4 female; mean age 34 ± 6.6 years)  
Three treatments:  
1. Sugar-free pellet gum containing 20mg citric acid + 18.8 mg CPP-ACP  
2. Gum with 20 mg citric acid  
3. Gum with neither citric acid or CPP-ACP  
Three treatments:  
1. 200 ml milk containing 2.0 g CPP-ACP  
2. 200 ml milk containing 5.0 g CPP-ACP  
3. 200 ml milk containing no CPP-ACP  
Four treatments consisting of 1.75g lozenge with:  
1. 18.8 mg CPP-ACP  
2. 56.4 mg CPP-ACP  
3. No CPP-ACP  
4. No lozenge; nil treatment; control  
3 types of gum:  
1. Sorbitol/ Xylitol based 2.0 g slab gum containing no CPP-APP  
2. Sorbitol/Xylitol based 1.5 g pellet (x2) gum containing no CPP-APP  
3. Two gum pellets containing 10 mg CPP-ACP | Crossover trial with 2 week treatment periods followed by 7 day washout  
Crossover trial with 15 day treatment periods (200 ml milk consumed over 60 s) followed by 7 day washout  
Crossover design with 14 day test period for each type of lozenge (4x daily use) followed by at least one week washout period between interventions | 1. % Subsurface remineralization  
2. % Remineralization after 16 hour acid challenge  
% Subsurface remineralization (%R)  
% Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover |
| Manton et al. 2008 [8] | 10 healthy subjects (6 males; 4 female) | 10 healthy subjects (6 males; 4 female)  
Three treatments:  
1. Sugar-free pellet gum containing 20mg citric acid + 18.8 mg CPP-ACP  
2. Gum with 20 mg citric acid  
3. Gum with neither citric acid or CPP-ACP  
Three treatments:  
1. 200 ml milk containing 2.0 g CPP-ACP  
2. 200 ml milk containing 5.0 g CPP-ACP  
3. 200 ml milk containing no CPP-ACP  
Four treatments consisting of 1.75g lozenge with:  
1. 18.8 mg CPP-ACP  
2. 56.4 mg CPP-ACP  
3. No CPP-ACP  
4. No lozenge; nil treatment; control  
3 types of gum:  
1. Sorbitol/ Xylitol based 2.0 g slab gum containing no CPP-APP  
2. Sorbitol/Xylitol based 1.5 g pellet (x2) gum containing no CPP-APP  
3. Two gum pellets containing 10 mg CPP-ACP | Crossover trial with 2 week treatment periods followed by 7 day washout  
Crossover trial with 15 day treatment periods (200 ml milk consumed over 60 s) followed by 7 day washout  
Crossover design with 14 day test period for each type of lozenge (4x daily use) followed by at least one week washout period between interventions | 1. % Subsurface remineralization  
2. % Remineralization after 16 hour acid challenge  
% Subsurface remineralization (%R)  
% Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover  
Double blinded in-situ RCT with crossover |
Table 2. Details of included studies (contd.)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparative intervention/controls</th>
<th>Outcome/s</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan et al. 2008 [4]</td>
<td>2720 healthy children randomized into test (n = 1369) and control (n = 1351)</td>
<td>Gum with 54 mg CPP-ACP chewed 3X daily for 10 minutes per session. 926 children completed trial. 439 dropped out</td>
<td>2 RCTs: A. Three mouth rinses containing either 1. 2% w/v CPP-ACP + 450 ppm F as NaF in deionized water 2. 450 ppm F as NaF in deionized water 3. Placebo control rinse as deionized water B. Toothpaste trial. Each toothpaste slurry contained either 1. Placebo 2. 1100 ppm F as NaF 3. 2800 ppm F as NaF 4. 2% CPP-ACP 5. 2% CPP-ACP + 1100 ppm F as NaF</td>
<td>Caries progression or regression at 24 months. Approximal caries diagnosed via digital bitewing x-rays.</td>
<td>Double blind RCT</td>
</tr>
<tr>
<td>Reynolds et al. 2008 [10]</td>
<td>14 healthy subjects (7 males; 7 females; age range 21 to 45 years)</td>
<td>2 RCTs: A. Three mouth rinses containing either 1. 2% w/v CPP-ACP + 450 ppm F as NaF in deionized water 2. 450 ppm F as NaF in deionized water 3. Placebo control rinse as deionized water B. Toothpaste trial. Each toothpaste slurry contained either 1. Placebo 2. 1100 ppm F as NaF 3. 2800 ppm F as NaF 4. 2% CPP-ACP 5. 2% CPP-ACP + 1100 ppm F as NaF</td>
<td>A. Crossover trial with 15 ml rinses 3x per day for 4 days and 1x on fifth day. No other oral hygiene method used in test period. Washout period was 4 weeks between interventions. B. Crossover trial with 4x rinse per day for 14 days followed by 7-day washouts between interventions. In-vitro acid challenge of enamel slabs done after in-situ study</td>
<td>1. Plaque fluoride levels 2. % Subsurface remineralization (%R) 3. % Remineralization after acid challenge</td>
<td>Double blinded in-situ and in-vitro RCT with crossover</td>
</tr>
<tr>
<td>Andersson et al. 2007 [13]</td>
<td>26 healthy subjects (13 boys; 13 girls; mean age 14.6 years; age range 12-16 years; 60 teeth; 152 white spot lesions on canines and incisors) who were debonded following fixed orthodontic treatment</td>
<td>Test group consisted of 13 subjects; 70 sites. Treatment: Brush x2 daily with dental cream containing CPP-ACP for 3 months followed by use of 1100 ppm F toothpaste for 3 months</td>
<td>Control group consisted of 13 subjects; 62 sites. Treatment: 0.05% NaF mouthwash + 1100 ppm F toothpaste for 6 months</td>
<td>Regression of White spot lesions diagnosed via visual inspection and laser fluorescence over 1, 3, 6 and 12 months</td>
<td>RCT</td>
</tr>
<tr>
<td>Author/year</td>
<td>Randomization</td>
<td>Allocation concealment</td>
<td>Blinding</td>
<td>Sample size (n)</td>
<td>Drop-outs</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>Itthagarun et al. 2005 [25]</td>
<td>A- Adequate Central randomization</td>
<td>A- Adequate Central randomization</td>
<td>A-Yes Double-blind</td>
<td>12</td>
<td>A- 3</td>
</tr>
<tr>
<td>Shen et al. 2001 [24]</td>
<td>A- Adequate Central randomization</td>
<td>A- Adequate Central randomization</td>
<td>A-Yes Double-blind</td>
<td>10</td>
<td>A- None</td>
</tr>
<tr>
<td>Walker et al. 2006 [9]</td>
<td>A- Adequate Central randomization</td>
<td>A- Adequate Central randomization</td>
<td>A-Yes Double-blind</td>
<td>10</td>
<td>A- None</td>
</tr>
<tr>
<td>Cai et al. 2003 [12]</td>
<td>A- Adequate Central randomization</td>
<td>A- Adequate Central randomization</td>
<td>A-Yes Double-blind</td>
<td>10</td>
<td>A- None</td>
</tr>
<tr>
<td>Manton et al. 2008 [8]</td>
<td>A- Adequate Central randomization</td>
<td>A- Adequate Central randomization</td>
<td>A-Yes Double-blind</td>
<td>10</td>
<td>A- None</td>
</tr>
<tr>
<td>Morgan et al. 2008 [4]</td>
<td>A- Block randomization</td>
<td>A- Sealed coded envelopes</td>
<td>A-Yes Double-blind</td>
<td>2720 Test Group (n = 1369) Control group (n = 1351)</td>
<td>B- dropouts &gt;30% (33%)</td>
</tr>
<tr>
<td>Reynolds et al. 2008 [10]</td>
<td>A- Adequate Central randomization</td>
<td>A- Adequate Central randomization</td>
<td>A-Yes Double-blind</td>
<td>14</td>
<td>A- None</td>
</tr>
</tbody>
</table>
During these in-situ trials participants wore appliances containing enamel slabs that were analysed in the laboratory after exposure to CPP-ACP.

**Pooling of data for meta-analyses**

Only trials that were considered clinically and methodologically homogenous and reported on similar outcomes were pooled for meta-analyses. For this review, three sub-groups were analysed (Figures 2-4).

---

**Figure 2.** Percent remineralization (%R) – Subgroup 1: Sugar-free gum with CPP-ACP versus sugar-free gum without CPP-ACP

- Review: NETA analysis (CPP-ACP)
- Comparison: 01 CPP-ACP versus control
- Outcome: 02 Percent remineralization (NR) / Control: Sugar-free chewing gum without CPP-ACP

CI = confidence interval; WMD = weighted mean difference; N= sample size

---

**Figure 3.** Percent remineralization (%R) – Subgroup 2

---

**Figure 4.** Percent remineralization (%R) – Subgroup 3

---

CI = confidence interval; WMD = weighted mean difference; N= sample size
Figure 2 provides information on the cumulative weight of evidence for the caries-preventive effect of 18.8 mg CPP-ACP (delivered via sugar-free gum) when compared to that of sugar-free gum without CPP-ACP. Four data sets, from 3 trials (Figure 2) with individual weighted mean differences (WMDs) for control and intervention groups, contributed to the overall effect. This found in favor of groups that chewed gum containing 18.8 mg CPP-ACP (WMD -8.01; 95% CI: -10.54 to -5.48; \( p < 0.00001 \)). All the trials had a crossover in-situ design with a 14-day test period followed by 7-day washout periods between interventions. The outcome of interest (caries prevention) was reflected as the percent remineralization (%R). Similarly, when results for those receiving a lowered dosage of 10.0 mg CPP-ACP were compared with control groups (Figure 3), the cumulative WMD (WMD -7.75; 95%CI: -9.84 to -5.66; \( p < 0.00001 \)) favored the group exposed to 10.0 mg CPP-ACP. In the 3rd sub-group analysis (Figure 4), groups whose interventions contained 18.8 mg CPP-ACP, delivered via sugar-free gum (slab or pellet) or lozenges, were compared with those receiving no intervention. Data for this meta-analysis were obtained from 2 trials [3,24]. There was a significant improvement in the percentage remineralization (%R) in groups exposed to 18.8 mg CPP-ACP over the study period, when compared to the no-treatment groups (WMD -13.56; 95%CI: -16.49 to -10.62; \( p < 0.00001 \)).

The mean differences (MDs) for studies where the data could not be pooled for meta-analysis were also calculated (where possible) to reflect the size of the treatment effect disparity between the intervention (CPP-ACP) and control groups. In the Itthagarun et al. trial [25], three types of chewing gum containing 30 mg urea, 30 mg urea + 25 mg dicalcium phosphate dehydrate or 30 mg urea + 47 mg CPP-ACP gum were tested in an in-situ crossover trial consisting of 12 subjects. Only 9 subjects completed the trial and the caries remineralizing effect of CPP-ACP versus 30 mg urea (reported as change in lesion depth) favored CPP-ACP (MD -16.6; 95%CI -30.37 to -1.95; \( p < 0.03 \)). However, when CPP-ACP was compared with another casein derivative, 25 mg dicalcium phosphate dehydrate, no significant differences were noted for the MDs; implying an equivalent treatment effect (MD -1.0; 95%CI%: -14.58 to 12.58; \( p = 0.89 \)). The Reynolds et al. [6] trial compared the remineralizing effect of CPP-ACP in sugar-free gum against other forms of calcium in gum, in 30 adults in a crossover in-situ study. The MD for 9.5 mg CPP-ACP gum versus gum containing CaHPO\(_4\)/CaCO\(_3\) favored CPP-ACP (MD -7.00; 95% CI: -5.94 to -8.06; \( p < 0.00001 \)). Similar results were obtained when CPP-ACP gum (either in pellet or slab form) was compared to gum with CaCO\(_3\) only.

In another trial, also by Reynolds et al. [10], 14 subjects were given a toothpaste slurry containing (1) placebo, (2) 1100 ppm fluoride, (3) 2800 ppm fluoride, (4) 2% CPP-ACP, or (5)
2% CPP-ACP + 1100 ppm fluoride, in a 14-day crossover trial, with 7-day washouts between treatments. The MDs of the percent remineralization, reported as an outcome between 2% CPP-ACP + 1100 ppm fluoride and 1100 ppm fluoride toothpaste, favored the CPP-ACP group (MD -12.80; 95%CI -9.54 to -16.06; \( p <0.00001 \)). Similar significant MDs were obtained when 2% CPP-ACP + 1100 ppm fluoride was compared against all the other products used in this study. In one trial CPP-ACP was added to bovine milk and its remineralizing effect was investigated by testing 2.0 and 5.0 g/l CPP-ACP in milk against the placebo (milk with no added CPP-ACP) [9]. The milk with 5.0 g/l CPP-ACP had significantly higher %R mean scores than 2.0 g/l CPP-ACP and no CPP-ACP-containing milk (11.4 versus 7.8 versus 4.6 respectively).

One trial reported that the odds of a tooth surface’s progressing to caries in subjects who chewed sugar-free gum containing 54 mg CPP-ACP was 18% less than in controls who chewed gum lacking CPP-ACP (\( p = 0.03 \)) [4]. The large sample size (\( n = 2720 \) children) and long follow-up (24 months) used in this RCT were unique in terms of CPP-ACP efficacy trials.

Andersson and colleagues [25] compared the remineralizing effect of dental cream containing CPP-ACP in 13 subjects using cream for 3 months, followed by 3 months’ use of 1100 ppm fluoride toothpaste. These completed orthodontic treatment and were debonded with a control group (\( n = 13 \)) that used only 0.05% NaF mouthwash + 1100 ppm fluoride toothpaste over a 6- month period [13]. The outcome of interest was the regression of white spot lesions. Although both groups showed significant improvement at 12-month observation, the number of white spot lesions that had completely disappeared at 12 months was significantly greater in the CPP-ACP group (63% versus 25% respectively; \( p <0.05 \)).

**Discussion**

The primary objective of this systematic review with meta-analysis was to determine, through studying published clinical trials, the caries-preventive effect of CPP-ACP. No attempt was made to search for trials in the gray literature or non-English databases and papers published in a language other than English were excluded. Although this introduced an element of bias, the searched databases covered the majority of the biomedical published literature and also included non-English papers. However, no non-English papers or abstracts were identified in the search strategy used for this review.

For all of the pooled meta-analyses reported (Figures 2-4), lesions exposed to CPP-ACP (18.8 mg or 10.0 mg) were found to have a more significant improvement in remineralization
than control lesions that were not exposed to CPP-ACP. All the studies used in the meta-analyses were in-situ RCTs with a crossover component. The obvious limitation of requiring participants to wear appliances containing enamel slabs that were analyzed in a laboratory after exposure was that the length of exposure was relatively short (less than 15 days for most trials). (Slabs were sectioned and the percent mineral profile of each enamel block's demineralization and remineralization lesion was compared with that of the median sound enamel between the lesions of the same section via microradiography.) The in-situ study design used to determine percent remineralization is not ideal but can be justified, as the method used to measure the amount of remineralization required the sectioning of the enamel. Orthodontic patients with teeth due for extraction would be ideal subjects for trials of this nature. However, the evidence from well-conducted randomized controlled trials [4,13] has added to the weight of evidence showing the effectiveness of CPP-ACP.

The significant results obtained for the meta-analyses, shown in Figures 2-4, suggest that a longer-term exposure to CPP-ACP offers hope of an even greater treatment effect in terms of its caries-preventive efficacy. Indeed the results of one RCT provide in-vivo evidence (Table 3) that long-term use of CPP-ACP also provides a significant caries-preventive effect in groups who receive this intervention [4]. It must be noted, though, that the children in the test group in this trial were exposed to 54 mg CPP-ACP added to sugar-free chewing gum, which is significantly greater than the 10.0 and 18.8 mg concentrations used in the short-term in-situ trials (Figures 2-4). One further trial also adds to the weight of evidence supporting the longer-term use of CPP-ACP in patients [13]. In this trial conducted by authors independent of Reynolds et al., who patented the CPP-ACP technology, significant improvements were noted in both groups but the number of white spot lesions that had completely disappeared after 12 months was significantly greater in the CPP-ACP group (63% versus 25% respectively; \( p < 0.05 \)). This randomized control trial provided independent in-vivo confirmation of the mainly in-situ findings of Reynolds et al. Whilst the size of the treatment effect was significant, it should be noted that the small sample size (\( n = 13 \)) in the test and control groups could have led to an over-estimation of the treatment effect.

The Azarpazhooh and Limeback systematic review [14] reporting on the clinical efficacy of casein derivatives, including CPP-ACP, for the caries prevention, dry mouth and dentin hypersensitivity outcomes, found “insufficient clinical trial evidence” (in quantity, quality or both) on which to base a recommendation regarding the long-term effectiveness of casein derivatives, specifically CPP-ACP, in preventing caries in-vivo and in treating dentin hypersensitivity or dry mouth” [14]. In the context of the included trials and their search
strategy limit (up to October 2007), their conclusions were valid. However, one RCT (published in 2008) significantly contributes to the evidence that shows a longer-term caries-preventive effect of CPP-ACP when delivered in sugar-free chewing gum [4]. The large sample size ($n = 2720$), the long-term follow-up (24 months) and the excellent rating achieved in the quality assessment (Table 3) provide good evidence of long-term caries-preventive efficacy. Although the drop-out rate was 33% in this trial (rated “B” in the quality assessment for “Drop-out”), the authors provided detailed reasons for the drop-out rate and this was mainly due to children in the trial moving schools.

The authors of an observational study where the methodological quality of 250 trials from 33 meta-analyses were analyzed to determine the association between methodological quality and estimated treatment effects commented that variables such as random allocation, allocation concealment and blinding were key measures in determining the quality of results reflected in a trial [20]. Random allocation remains the only way to eliminate selection bias [20] and one report [26] warned of potential biases of up to 30% if this is ignored. For allocation concealment and blinding, unclearly concealed trials or trials that were not double-blinded were found to exaggerate the estimates of the treatment effects by up to 30% [20]. Thus, it is clear that systematic reviews, which do not include a comprehensive quality assessment of included trials actually create bias in terms of answering their review question, as the weight of the evidence for or against an intervention is intricately linked to the quality of the included studies. In the case of one trial [4], its high quality rating scores, together with the results obtained, provides strong evidence of a long-term caries-preventive effect for CPP-ACP. Moreover, the assertion [14], that the majority of included in-situ trials were conducted by the group of investigators who patented the CPP-ACP complex (all these trials found in favor of CPP-ACP), creates an impression that the authors of these trials were biased in terms of how they presented their findings [3,6-10,12,24]. This is misleading, as a quality assessment of these (see Table 3) is similar to that of another in-situ trial [25] by authors who were not part of the group that patented the CPP-ACP molecule.

Meta-analyses in systematic reviews provide a powerful tool for deriving meaningful conclusions from data of included studies and often help to prevent errors of interpretation [15]. There are however pitfalls caused mainly by heterogeneity of which there are two types: clinical and statistical [27]. Clinical heterogeneity is determined using qualitative measures such as ensuring that trials are similar with respect to patient demographics, study design and outcome measures. If trials are deemed to be homogenous, then their data can be combined in a meta-analysis using either a fixed or a random effects model. In this study, data from 5 in-
situ trials [3,7,8,12,24] that were considered clinically and methodologically homogenous and reported on similar outcomes were pooled for meta-analyses. These results (reflected graphically as forest plots (Figures 2-4) also provide information on statistical heterogeneity (usually $p < 0.01$) which, if not explained, could render the results of a meta-analysis meaningless. For Figures 2-4, there was significant statistical heterogeneity, which is related to the inconsistency in the size of the treatment effects when the individual trials that were similar in study design, sample size and outcome measures were compared to each other.

The lack of a meta-analyses component in the Azarpazhooh and Limeback systematic review [14] has impacted on the conclusions derived by the authors about the comparative short-term caries-preventive efficacy of CPP-ACP in relation to other interventions. Moreover, this may have led to the error of comparing the number of “positive studies” with the number of “negative studies”. According to the Cochrane Handbook [15], such “vote counting” is considered unreliable, “since whether a study is counted as ‘positive’ or ‘negative’ may depend on how the results are interpreted by the reviewers and it gives no consideration on the relative weight of reliable evidence contributed by each study”. A further report [28] highlighted the tendency to overlook small but clinically important effects when counting votes, particularly when counting studies with statistically insignificant results as ‘negative’ or ‘inconclusive’.

In summary this review has provided evidence of the short-term and long-term (maximum 24 months) use of CPP-ACP for caries prevention. The dosages found to be effective in short term trials ranged from 10.0 mg CPP-ACP to 18.8 mg CPP-ACP contained in sugar-free gum. For long-term efficacy (maximum 24 months), a dosage of 54 mg CPP-ACP contained in sugar-free gum was used. The limitations of the in-situ study design for short-term efficacy should be addressed in future studies by conducting in-vivo randomized control trials. The outcome measure of such should be clinical caries prevention or caries reduction over a longer (>12 months period). Reporting of such trials should follow the CONSORT [48] statement and, particularly, include a clear description of how the randomized allocation of study subjects was conducted, report on details of any restrictions, and state who generated the allocation sequence, who enrolled the subjects and who assigned subjects to their groups. Reporting should further include information about whether such allocation was concealed from the clinical operators until interventions were assigned and if it was, about how this was done [48].
Within the limitations of this meta-analysis, the results of the in-situ clinical trials support the short-term remineralization effect of CPP-ACP. Additionally, the in vivo randomized clinical trials provide promising results for the long-term use of CPP-ACP for caries prevention. Well-designed in vivo randomized clinical trials on the true outcome of caries prevention are warranted.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[27] Flecher J. What is heterogeneity and is it important? BMJ 2007;334: 94-96


CHAPTER 4

Summary of systematic review results
Overview

Minimum (or minimal) intervention dentistry (MI) has been defined as a philosophy of professional care concerned with the first occurrence, earliest detection, and earliest possible cure of disease on micro (molecular) levels, followed by minimally-invasive and patient-friendly treatment to repair irreversible damage caused by such disease\(^1\). Although the focus of MI in dentistry has so far been on caries-related topics\(^2\), the approach follows the 3-step philosophy of: I. disease risk assessment, II. early disease detection and III. minimally invasive treatment (Figure 1). MI enables the healthcare provider to advise healthy patients about their risks regarding possible future ailments\(^3\). Such risks may be due to aspects related to a patient’s lifestyle or to other factors with the potential to have an impact upon health\(^4\). These aspects are then quantitatively assessed (I-a.) to determine the basis on which addressing the identified risk a factor through targeted prevention (I-b.) is possible\(^5\). Patients with manifest disease are helped by identification, as early as possible, of such manifestation (II.)\(^6-8\). Disease at an early stage is often relatively contained and treatment can consequently be simple, very conservative and minimally-invasive (III.)\(^9\). MI concepts, materials and clinical applications need to be based on low-bias research, because the high internal validity of low-bias research provides the prerequisite for successful MI adoption\(^10\). Studies with low bias are identified through systematic reviews, using explicit, systematic methods designed to limit bias and chance effects\(^11\). Where possible the results of the identified studies are statistically combined through meta-analysis, thus providing more precise estimates of healthcare effects\(^10\). Within in the framework of the MI Compendium-PLUS+ data base (http://www.midentistry.com/plus.asp), the prevention-concept of:

\([I-b/1]\) glass-ionomer (GIC) based fissure sealing\(^12\);

as well as the minimally-invasive concepts of:

\([III/1]\) GIC anticariogenic effect\(^13\);
\([III/2]\) GIC based restorative care\(^14\);
\([III/3]\) CPP-ACP based external remineralization\(^15\)

have been systematically reviewed and the identified evidence, where possible, was combined through use of meta-analysis (Figure 1).
In order to summarize the systematic review results for the included MI concepts SWOT (strengths, weaknesses, opportunities, threats) analysis is used. Until now, SWOT analysis has mainly been applied for strategic planning in business. The analysis is structured into an internal and an external part. It identifies the advantages and disadvantages of each by listing strengths and weaknesses as well as opportunities and threats of a particular concept or idea at a single point in time. Although SWOT analysis has not yet been widely utilized in healthcare, it has been applied to assess the organisation and financing of healthcare systems and health technology assessment programmes. It has also been used in the past for evaluation of vaccination programmes. SWOT is a simple qualitative method of assessing new concepts, such as the MI philosophy in dentistry, revealing insights that would not otherwise have been apparent. Against this background SWOT analysis of the systematic review / meta-analysis results of MI concepts, following the MI structure laid out in Figure 1, is given in Table 1.
The result of the SWOT analysis (Table 1) shows a higher proportion of positive aspects (strength and opportunities). It is noted that the identified weaknesses provide a basis for the identified opportunities. This implies that it is possible to rectify the current limitations in clinical and methodological aspects of studies through further high quality trials, while confirming the observed treatment effects. The lack of identified threads and the high strength of the findings support the application of glass-ionomer cements and CPP-ACP in clinical practice.

**Synergy of strengths**

Synergies between key aspects of the identified strengths related to the ‘GIC anticariogenic effect’\(^\text{11}\), ‘GIC restoration (ART)’\(^\text{12}\), ‘GIC-based fissure sealants’\(^\text{10}\), and ‘External remineralization using CPP-ACP’\(^\text{13}\), can be observed. The lack of difference in the caries-preventive effect, between low-viscosity, low retentive GIC and resin-based fissure sealant materials\(^\text{10}\), can be attributed to a general caries-preventive effect of glass-ionomers. Such caries-preventive effect has been confirmed through observations of significantly less carious lesions around glass-ionomer cement restorations than around amalgam after 6 years\(^\text{11}\). On this same basis the observed higher longevity of ART restorations using high-viscosity GIC in comparison to amalgam restorations placed after caries removal by drilling, after 6.3 years, can be explained\(^\text{12}\).

The currently available evidence supports the efficacy of enamel (‘external’) remineralization through application of CPP-ACP\(^\text{13}\). Regardless of the place of study origin, in-situ studies of high internal validity have shown a higher remineralizing effect of CPP-ACP than those obtained from a range of control substances or no intervention. In addition, an in-situ dosage-response effect has been observed: the higher the dosage, the higher the treatment effect. These in-situ findings have been confirmed through in-vivo randomized control trials.

**Weaknesses and opportunities**

A general lack of high-quality trials and/or lack of high-quality reporting of trials was observed. This lack provides the opportunity to further validate the current reviewed evidence\(^\text{10-13}\) through inclusion of future studies; particularly those with adequate randomized sequence allocation, allocation concealment and reporting that follows the CONSORT statement\(^\text{17}\).
Table 1. SWOT analysis results of systematically reviewed MI concepts

<table>
<thead>
<tr>
<th>STRONGS</th>
<th>WEAKNESSES</th>
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<tr>
<td><strong>Internal aspects</strong></td>
<td><strong>External aspects</strong></td>
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<tr>
<td><strong>STRENGTH</strong></td>
<td><strong>WEAKNESSES</strong></td>
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<tr>
<td>I-a. Disease risk assessment</td>
<td>I-a. Disease risk assessment</td>
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<tr>
<td>GIC-based fissure sealants:</td>
<td>GIC-based fissure sealants:</td>
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<tr>
<td>Results based on systematic review &amp; meta-analysis</td>
<td>Results based on systematic review &amp; meta-analysis</td>
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<tr>
<td>I-b. Disease prevention</td>
<td>I-b. Disease prevention</td>
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<tr>
<td>Review based on English &amp; non-English data sources</td>
<td>Review based on English &amp; non-English data sources</td>
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<td>GIC-based fissure sealants:</td>
<td>GIC-based fissure sealants:</td>
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<tr>
<td>Low-viscosity GIC are as caries-preventive as resin-based fissure sealants</td>
<td>So far only trials with low-viscosity (out-dated) GIC reviewed</td>
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<td>II. Early disease detection</td>
<td>II. Early disease detection</td>
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<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
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<tr>
<td>Results based on systematic review &amp; meta-analysis</td>
<td>Results based on systematic review &amp; meta-analysis</td>
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<tr>
<td>III. Minimally-invasive treatment</td>
<td>III. Minimally-invasive treatment</td>
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<tr>
<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
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<tr>
<td>Significantly less caries lesions on single-surface GIC restoration margins in amalgam after 6 years</td>
<td>No difference between GIC and amalgam observed on multiple-surface restorations margins in primary teeth after 3 years</td>
</tr>
<tr>
<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
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<tr>
<td>Indications of less caries on multiple-surface GIC restoration margins in primary teeth after 8 years</td>
<td>Conflicting data for single-surface restorations in primary teeth &lt;8 years</td>
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<tr>
<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
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<tr>
<td>Less caries on GIC restoration margins after caries removal by hand excavation then on amalgam restoration &amp; drilling</td>
<td>Lack of fluoride exposure as confounder in reviewed trials reported</td>
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<tr>
<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
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<tr>
<td>Systematic review &amp; meta-analysis results confirm in-situ/in-vitro (laboratory) observations</td>
<td>Review based on English data sources, only</td>
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<td>GIC restorations (ART):</td>
<td>GIC restorations (ART):</td>
</tr>
<tr>
<td>Results based on systematic review &amp; meta-analysis</td>
<td>Limited trial quality due to unclear randomized subject allocation &amp; allocation concealment</td>
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<td>GIC restorations (ART):</td>
<td>GIC restorations (ART):</td>
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<tr>
<td>Review focus on ART based on high-viscosity GIC &amp; caries removal by hand excavation, only</td>
<td>Limited trial quality due to unclear randomized subject allocation &amp; allocation concealment</td>
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<tr>
<td>GIC restorations (ART):</td>
<td>GIC restorations (ART):</td>
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<tr>
<td>ART restoration have same or higher longevity than same class of fillings with drilling + amalgam</td>
<td>General lack of high-quality trials</td>
</tr>
<tr>
<td>GIC restorations (ART):</td>
<td>GIC restorations (ART):</td>
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<tr>
<td>Systematic review &amp; meta-analysis results in line with previous meta-analysis results</td>
<td>Lack of fluoride exposure as confounder in reviewed trials reported</td>
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<tr>
<td>External remineralization (CPP-ACP):</td>
<td>External remineralization (CPP-ACP):</td>
</tr>
<tr>
<td>Results based on systematic review &amp; meta-analysis</td>
<td>Limited trial quality due to unclear randomized subject allocation &amp; allocation concealment</td>
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<tr>
<td>External remineralization (CPP-ACP):</td>
<td>External remineralization (CPP-ACP):</td>
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<tr>
<td>Significant higher remineralising effect than controls in-situ and in-vivo</td>
<td>Mainly short-term in-situ results identified</td>
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<td>External remineralization (CPP-ACP):</td>
<td>External remineralization (CPP-ACP):</td>
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<tr>
<td>Faster reduction of white-spot lesions</td>
<td>Limited meta-analysis due to inconsistencies in size of observed treatment-effect (statistical heterogeneity)</td>
</tr>
<tr>
<td>External remineralization (CPP-ACP):</td>
<td>External remineralization (CPP-ACP):</td>
</tr>
<tr>
<td>Evidence from high-quality (randomized-control) trials</td>
<td>Review based on English data sources, only</td>
</tr>
<tr>
<td>External remineralization (CPP-ACP):</td>
<td>External remineralization (CPP-ACP):</td>
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<tr>
<td>Independent in-vivo confirmation of in-situ trial results</td>
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<table>
<thead>
<tr>
<th>OPPORTUNITIES</th>
<th>THREATS</th>
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<tr>
<td><strong>Internal aspects</strong></td>
<td><strong>External aspects</strong></td>
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<td><strong>OPPORTUNITIES</strong></td>
<td><strong>THREATS</strong></td>
</tr>
<tr>
<td>I-a. Disease risk assessment</td>
<td>I-a. Disease risk assessment</td>
</tr>
<tr>
<td>GIC-based fissure sealants:</td>
<td>GIC-based fissure sealants:</td>
</tr>
<tr>
<td>Future high-quality trials with high-viscosity GIC may show a 4x higher caries preventing effect than resin-based fissure sealants</td>
<td>No threats identified</td>
</tr>
<tr>
<td>I-b. Disease prevention</td>
<td>I-b. Disease prevention</td>
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<tr>
<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
</tr>
<tr>
<td>Future high-quality trials may confirm current strengths</td>
<td>No threats identified</td>
</tr>
<tr>
<td>II. Early disease detection</td>
<td>II. Early disease detection</td>
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<tr>
<td>GIC anticariogenic effect:</td>
<td>GIC anticariogenic effect:</td>
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<tr>
<td>Future high-quality trials with focus on confounder correction (i.e. operator diligence as confounder) may confirm current strength</td>
<td>No threats identified</td>
</tr>
<tr>
<td>III. Minimally-invasive treatment</td>
<td>III. Minimally-invasive treatment</td>
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<tr>
<td>GIC restorations (ART):</td>
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</tr>
<tr>
<td>Future high-quality trials with focus on confounder correction (i.e. operator diligence as confounder) may confirm current strength</td>
<td>No threats identified</td>
</tr>
<tr>
<td>External remineralization (CPP-ACP):</td>
<td>External remineralization (CPP-ACP):</td>
</tr>
<tr>
<td>Possible greater treatment effect on long-term basis</td>
<td>No threats identified</td>
</tr>
</tbody>
</table>

+/- Positive/negative aspects; GIC = Glass-ionomer cement; CPP-ACP = Casein phosphopeptide/Amorphous calciumphospatate
References


Updates of systematic reviews online
Information on updates of the systematic reviews listed in Chapter 4 are available online at:
http://www.midentistry.com/plus.asp