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Minimum Intervention (MI) in Dentistry

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International Dentistry South Africa, Johannesburg, South Africa
Journal of Oral Science, Tokyo, Japan
Singapore Dental Journal, Singapore

MI Compendium of systematic reviews – Edition 1.4



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Printed in South Africa

Distributed free of charge.

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# CHAPTER 1

## Introduction to minimum intervention in dentistry

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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, masticatoric, 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[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[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[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[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[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[20]. This was followed by the development of the preventive resin restoration (PRR)[21] in the 1980s and the atraumatic restorative treatment (ART) approach[22] and chemo-mechanical caries removal concepts[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[24–26] and excavation of infected carious tooth tissue through selective caries removal or laser treatment[24,26], as well as cavity restoration by applying ART, PRR, or sandwich restoration treatment protocols[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[28]. Failed restorations are repaired rather than replaced[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[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[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.

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# CHAPTER 2

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

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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;
3. Minimally-invasive treatment.

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[19]. Patients with low levels of dental fear are more cooperative during treatment than those with high fear levels[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[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[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[9].

The social system constitutes the community of potential adopters of innovation, categorized as follows: the innovators themselves, early adaptors, early majority, late majority and laggards[9]. Rogers (2003) estimated the percentage distribution of these groups as being 2.5%, 3.5%, 34%, 34% and 16%, respectively[9]. Except for the innovators themselves, these adopter groups' responses to innovation can vary between adoption, non-adoption or rejection[22]. An innovation is considered self-sustaining once it has been accepted by 10-20% of all potential adopters[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[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"[23].

The most important types of bias in clinical studies are selection-, performance-, detection- and attrition bias (Table 1)[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[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[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 ($n_{total}$)[27].

$$R = n_{ill} : n_{total}$$

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 ($R_{old}$)[28].

$$RR = R_{new} : R_{old}$$

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[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[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[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[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[24,29,30]. In addition, it has been acknowledged that various study designs contain various degrees of bias[31-33]. For that reason an 'evidence hierarchy' of study designs has been established (Table 3)[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[34]. Such guidelines include the CONSORT statement for randomized control trials[35] and the STROBE statement

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

| Bias | Description |
|---|---|
| **Selection bias** | 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[43]. |
| **Performance bias** | 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 [44]. |
| **Detection bias** | 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[44]. |
| **Attrition bias** | 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[24]. |

for observational studies, such as Cohort and case control studies[36]. Studies with low bias are identified through systematic reviews, using explicit, systematic methods designed to limit bias and the chance effects[37]. Where possible the results of the identified studies are statistically combined, using meta-analysis and thus providing more precise estimates of healthcare effects[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[38]. Nevertheless, diffusion of innovation is more likely if the evidence supporting it is regarded as being strong[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"[38]. Locock et al. (1999) described RCTs as providing the only form of evidence that may convince clinicians to adopt change[40]. Therefore strong evidence is an important prerequisite for achieving wider adoption of an innovation.

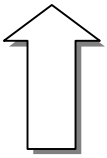
**Table 2.** Bias-reducing interventions

| Bias | Intervention |
|---|---|
| Selection bias | (a) Selection of study subjects using a random allocation sequence<br>(b) Concealment of allocation sequence from investigators[24] |
| Performance bias | Blinding (masking) of study subjects and care providers as to the differences per test- or control group[24] |
| Detection bias | Blinding (masking) of study assessors as to the differences per test or control group[24] |
| Attrition bias | Inclusion of all randomized study subjects into the analysis regardless of their adherence to the study protocol, thus following "intention-to-treat" principle[29,30] |

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[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[42]. The latter may be further reinforced by perceptions of potential adopters as to whether the innovation offers advantages that the current methods do not[22].

**Table 3.** Evidence hierarchy

| | Study Design |
|---|---|
| **Highest** | Quantitative systematic reviews (with meta-analysis) |
|  | Qualitative systematic reviews<br>Randomized control trials (RCT)<br>COHORT studies<br>Case control trials<br>Case series or reports<br>Narrative reviews |
| **Lowest** | |

**MI Evidence**

The need for strong (low-bias) evidence as an important prerequisite for wide adoption of innovation[38-40] applies also to MI. The Cochrane library (online: www.cochrane.org ) and Midentistry's compendium database (online: 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.

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# CHAPTER 3

## Systematic reviews, systematic error and the acquisition of clinical knowledge

Mickenautsch *BMC Medical Research Methodology* 2010, **10**:53
http://www.biomedcentral.com/1471-2288/10/53

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# Systematic reviews, systematic error and the acquisition of clinical knowledge

Steffen Mickenautsch

**Abstract**

**Background:** Since its inception, evidence-based medicine and its application through systematic reviews, has been widely accepted. However, it has also been strongly criticised and resisted by some academic groups and clinicians. One of the main criticisms of evidence-based medicine is that it appears to claim to have unique access to absolute scientific truth and thus devalues and replaces other types of knowledge sources.

**Discussion:** The various types of clinical knowledge sources are categorised on the basis of Kant's categories of knowledge acquisition, as being either 'analytic' or 'synthetic'. It is shown that these categories do not act in opposition but rather, depend upon each other. The unity of analysis and synthesis in knowledge acquisition is demonstrated during the process of systematic reviewing of clinical trials. Systematic reviews constitute comprehensive synthesis of clinical knowledge but depend upon plausible, analytical hypothesis development for the trials reviewed. The dangers of systematic error regarding the internal validity of acquired knowledge are highlighted on the basis of empirical evidence. It has been shown that the systematic review process reduces systematic error, thus ensuring high internal validity. It is argued that this process does not exclude other types of knowledge sources. Instead, amongst these other types it functions as an integrated element during the acquisition of clinical knowledge.

**Conclusions:** The acquisition of clinical knowledge is based on interaction between analysis and synthesis. Systematic reviews provide the highest form of synthetic knowledge acquisition in terms of achieving internal validity of results. In that capacity it informs the analytic knowledge of the clinician but does not replace it.

## Background

Systematic reviews, in healthcare, have been described as providing objective overviews of all the evidence currently available on a particular topic of interest [1]. Such overviews cover clinical trials in order to establish where effects of healthcare are consistent and where they may vary. This is achieved through the use of explicit, systematic methods aimed at limiting systematic error (bias) and reducing the chance of effect [2]. Systematic reviews have been recommended as providing the best source of evidence to guide clinical decisions [3,4] and healthcare policy [5], and they receive twice as many citations as non-systematic reviews in peer-reviewed journals [5-7]. Furthermore, systematic reviews are increasingly utilized in appraising the evidence regarding the cost-effectiveness of interventions [8,9], the costs of guideline dissemination and implementation [10] or evidence from qualitative studies [11].

The use of systematic reviews for the appraisal of clinical studies has been introduced and promoted within the framework of evidence-based medicine (EBM). Sackett et al. recommended EBM as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [12]. These authors defined the practice of evidence-based medicine as "integrating individual clinical expertise with the best available external clinical evidence from systematic research". They described best evidence as "clinically relevant research, often from the basic sciences of medicine, but especially from patient-centred clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens" [12].

Since its inception, EBM has been widely accepted by academia, healthcare funders and healthcare providers. It

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has also been strongly criticised and resisted by some academic groups and clinicians. One of the main criticisms of EBM is that it claims to have unique access to absolute scientific truth, as gained for clinical therapy through randomized control trials (RCT) and subsequent systematic reviews of RCTs. The implication is that EBM claims, on this basis, the ability to exercise judgement (e.g. through appraisal of clinical studies during systematic reviews) and thus devalues and replaces knowledge sources of other types [13].

The types of knowledge sources allegedly threatened by EBM include: (i) the inferences of basic science used for prediction of clinical outcomes [14]; (ii) clinical judgement based on experience - often expressed in the form of single case studies and narrative reviews [15,16]; (iii) qualitative and observational research [16].

Further criticisms of EBM are that it produces population-based research results which are not applicable to individual patients and that research results from which any confounder impact is eliminated (i.e. through randomization and double blinding) can never wholly apply to particular individual situations faced by clinicians in their daily practice [15]. Critics of EBM argue that clinical trials ignore knowledge gained from basic science, in areas such as human physiology and diseases and pharmacology, from which valuable information about the effect of a particular drug or treatment can be inferred [14]. They hold that clinical judgement based on experience is more exact, because of its emphasis on individual cases rather than evidence derived from RCT [15]. As RCTs provide average estimates with confidence intervals from study groups instead of from single individual patients, their results remain allegedly non-applicable to daily clinical practice [15]. Therefore, it is argued, RCTs lack the necessary illustration of nuances of treatment that single-case reports provide [16]. Qualitative, as opposed to quantitative research, is seen to provide in-depth examination of small numbers of patients and is able, unlike hypothesis-driven quantitative EBM research, to provide information regarding the complexity (including psychological and social aspects) of a disease [16]. Qualitative research, it is further argued, has the capacity to explore the meanings that symptoms, consultations and treatments have for a patient – aspects that EBM is accused of degrading or ignoring [16].

In response to such criticism, EBM promoters reply that sole reliance on basic science without clinical testing raises high uncertainties regarding treatment safety and efficiency [14]. Such uncertainties are based on the limits and incompleteness of basic scientific knowledge about the human body and its interaction with the environment [14]. In addition, it is reported that medical history confirms that therapeutic predictions based on sound basic science have, in many cases, been proven wrong after clinical testing [17]. One example is the well-cited case of Flecainide, which was used for treating supraventricular tachycardia. Only after clinical trials had been conducted was it found that it actually increased mortality in patients [18].

Reliance on clinical judgement based on experience can be misleading, owing to the unrecognised play of chance and the easy confusion of the natural history of the disease with the treatment effect [19]. For that reason, patients often get better or worse on their own, notwithstanding intervention [14]. A wide variation in clinicians' judgment has been observed in a group of 819 doctors from Australia and UK [20]. Only 55% correctly recognized the risks for ischaemic heart disease and just 6.7%, the risk of deep-vein-thrombosis. Traditional experience can also be a poor judge of the efficacy of treatments such as the widespread prophylactic removal of pathology-free impacted third molars to prevent cysts and tumours, resorption of second molars, caries and periodontal problems. In contrast, a systematic review found no evidence that this procedure offered clinical benefits [21]. Qualitative and observational study results are often tainted by systematic error and thus, lack the necessary internal validity that could allow any generalisation beyond the studied cases [14]. In terms of the criticism that EBM produces population-based research results that are not applicable to individual patients, EBM promoters respond that risks of disease, identified through population-based research, remain applicable to individual subjects. Once a causality has been detected, such causality will be as valid for individual patients in clinical practice as it is for subjects in the studied groups/populations [15]. Moreover, elimination of confounders through, for example, the randomization process in RCTs, does not render data irrelevant to individuals. Such data remains applicable to an individual patient, to the extent to which the patient shares the characteristics of the subjects studied in the RCT [22].

Against the background of such ongoing debate, this article aims to present a philosophical proposition regarding the acquisition of knowledge, which may help to clarify the relationship between the epistemological concepts that appear to underlie the different standpoints of EBM critics and promoters. It also aims to show how systematic reviews rely on the unity of analysis and synthesis in the process.

**Acquisition of knowledge**

The German philosopher Immanuel Kant regarded experience as the direct encounter of a subject and an object, and knowledge as the judgment of such encounter [23,24]. Reflective judgment of experience could be either 'analytic' or 'synthetic'. While an analytic reflective judgment only asserts logical relations between concepts, a synthetic reflective judgment involves the assertion of real relationships between concepts and objects. Therefore, an analytical judgment of an experience recognises truth by virtue of conceptual meanings only, without depending further on external facts. An example of an analytical judgment is the statement: "Yellow is a colour". We know that this statement is correct. No additional evidence is needed because we know the meanings of the words "yellow" and "colour" [23,24].

In contrast, a synthetic judgment of experience recognises truth by virtue of conceptual meanings **and** external facts. Here, an example is the statement: “This table is yellow.” Although we understand the meanings of the words “table” and “yellow”, we still need to check whether the table is indeed yellow, thus requiring further evidence in order to accept that this statement is true [23,24]. The scientific method of analysis employs analytical reflective judgment. Analysis, according to the classical definition by Leipnitz, is a “process in which we begin with a given conclusion and seek principles by which we may demonstrate this conclusion” [25,26]. This means that causes are inferred from effects through assertion of logical relations between the two concepts and their relationship is used to develop plausible hypotheses [25,26]. During this process, care is taken to ensure that the resulting hypothesis does not contradict already existing knowledge. In clinical praxis this would mean that a doctor examines a patient, discovers symptoms and, on the basis of these and knowledge acquired from basic science and personal clinical experience, infers (diagnoses) a specific disease as the possible cause of such symptoms (effect). Similarly, in scientific research a possible/plausible hypothesis that could explain observations in line with current knowledge may be developed. However, a plausible hypothesis does not necessarily provide actual proof. Such proof may be found through the scientific method of synthesis. The classical definition of synthesis is “a process in which we begin from principles (= Cause) and proceed to build up conclusions” (= Effect) [25,26]. However, this is really only an inverted definition of analysis. It does not consider the need for outside facts and is thus limited to the inference of effects from known causes, (i.e. by inductive reasoning through Analogy or Teleology [25,27] in line with existing knowledge). The solution for this type of problem can be found in the work of Johann Gottlieb Fichte (often wrongly ascribed to Hegel). He defined synthesis as a result of the dialectic interaction/conflict between ‘thesis’ and ‘antithesis’ [28]. ‘Thesis’ represents a formulated idea or concept that can be, for example, an hypothesis developed through analysis. This hypothesis is then engaged by an opposing concept or fact, or external conditions that are not part of the initial hypothesis, created through experiment, scientific trial or other observations: the antithesis. Through this interaction/conflict, truths contained in the thesis and antithesis are reconciled at a higher level, thus forming synthesis. In turn, this synthesis constitutes a new thesis that is opposed by a new antithesis in a continuous process. Reflective judgement of the thesis in relation to the antithesis asserts real relationships between concepts and objects. Therefore, synthetic reflective judgment [23,24] is employed during the process of synthesis by thesis/antithesis [28]. One example is the ‘extension for prevention’ concept mentioned by GV Black (= Thesis) in relation to operative dentistry. It deals with the need to remove carious tooth tissue before restoring a tooth with amalgam, in order to prevent further caries progression [29]. An antithesis to this concept is the observation by Mertz-Fairhurst et al. that caries, after the sealing of retained carious tooth tissue, only progresses very slowly [30]. Frencken et al. reached a synthesis of both views,

by introducing the atraumatic restorative treatment (ART) approach, on the basis of selective caries removal [31]. Selective caries removal according to the ART approach relies upon the removal of infected, soft tooth tissue, using only hand instruments. Affected, remineralisable carious tooth tissue is left behind and sealed with a biomimetic material. A recent systematic review with meta-analysis showed ART restorations to be clinically as successful as amalgam restorations placed according to GV Black's 'extension for prevention' concept [32]. Following Fichte's dialectic view of synthesis, scientists try to test the veracity of existing hypotheses through, for example, conducting clinical trials [27]. In this case, a null-hypothesis would form the thesis and the trial conditions, its antithesis. The result would be the synthesis in the form of rejection or acceptance of the null-hypothesis. In this context the inference, extrapolation (projection from basic science) and application of clinical judgement based on experience are analytic; while synthesis is represented in the conduct of clinical case studies, qualitative-, observational- and randomized control trials, and in systematic reviews with meta-analysis.

**Systematic error**

Systematic error constitutes any factor in the knowledge acquisition process that systematically diverts its outcomes away from true values [33]. Systematic error, therefore, limits the internal validity of acquired knowledge. Internal validity depends upon the linking together, apart from random error, of an inferred or investigated cause and effect; thus ensuring causality [34]. With regard to analytic knowledge acquisition, the problems of (i) inferring from basic science and (ii) applying clinical judgement based on experience alone have been highlighted above [14,17]. With regard to synthetic knowledge acquisition, a range of systematic errors has been identified: selection-, performance-/detection-, and attrition bias [34]. In order to limit the influence of systematic error on clinical trials, the methodological interventions: randomization (random sequence allocation and allocation concealment), blinding and intention-to-treat analysis have been proposed for each type of bias, respectively [34].

Empirical evidence from meta-epidemiological studies indicates that without the application of methodological bias-controlling measures in clinical trials, a systematic error effect may manifest itself in the form of a substantial over-estimation of results. Trials that investigate subjective outcome measures are especially at risk. The level of over-estimation associated with attrition bias (lack of intention-to-treat analysis) can reach up to 25% [35]. The lack of adequate randomization (through sequence allocation and allocation concealment) and blinding (thus minimizing Selection- and Performance-/Detection bias, respectively) may reach above 50% [36]. This means that if a study claims a 20% lower relative risk (RR 0.80) for a new treatment, as compared to a control under a condition of a 50% overestimation, the actual result of the observed treatment effect would be a 20%

increased risk (RR 1.20) for the patient. Thus, it would be the complete opposite of the initial claim. Such high percentages of over-estimation due to bias may therefore lead to situations where ineffective treatment procedures are presented as effective.

The empirical evidence regarding the danger of systematic error suggests that inclusion of bias-controlling measures; such as randomization, blinding and attrition control, into the study design of clinical trials is justified. It also provides the justification for judging the internal validity of clinical trials according to how well bias-controlling measures are implemented in their study designs; i.e. in line with an evidence-hierarchy [37]. Assessment of clinical trials according to their internal validity is part of the systematic review process.

**Systematic review**

Systematic reviews are defined, according to the Cochrane collaboration, as scientific literature reviews aimed at answering clearly formulated questions by use of systematic and explicit methods for identifying, selecting, and critically appraising relevant research, and for collecting and analysing data from the literature included in the review [38]. During a systematic review, meta-analysis may be used as a statistical tool for analysing and summarising the results of the included studies [39]. In order to fulfil this function, a systematic review should: (i) present a synthesis of the acquired knowledge regarding one particular clinical question derived from all relevant studies that are identifiable at one point in time, (ii) identify the level of internal validity and the subsequent potential systematic error risk associated with the acquired knowledge and (iii) provide recommendations for improving any identified shortcoming related to internal validity, for further research. Owing to continued further research, systematic reviews should also provide continued updates of their synthesis.

In order to achieve its objectives, a systematic review includes (i) a systematic search for studies from all known and relevant information sources; (ii) the selection of studies with highest internal validity – or if not many studies can be found, the sub-grouping of available trials in line with their various internal validity strengths; (iii) quality assessment of studies in line with internal validity criteria and, if possible, (iv) meta-analysis of the combined study data.

Through this process, systematic reviews provide the most comprehensive answers to clinical questions, with least possible systematic error. Such high internal validity provides a basis for the external validity of results. External validity describes how well results can be generalised and are applicable to other circumstances [34]. Evidence that is free of systematic error appears to be more likely to remain correct, even under changing circumstances, than results that carry a high risk of over-estimation. However, although external validity can only be possible on the basis of good internal validity [34], good internal validity of evidence from systematic reviews on its own has been shown to provide no

absolute guarantee of good external validity. A case study [40], during which the conduct and management of a systematic review of studies concerning interventions for reducing substance misuse in young children was observed, noted the exclusion of review articles that did not follow a systematic methodology but contained explicit considerations of wider environmental factors impacting upon substance misuse. This study reported that the subsequent guideline development process resolved to ad-hoc inferences regarding the application of the systematic review results, due to its lack of external validity focus [40]. Apart from future systematic reviews with more emphasis on categories of external validity, qualitative research may add important information regarding the external validity of evidence, by investigating the complexity of, for example, the psychological and social aspects of disease [16]. Single case reports may indeed provide the necessary illustration of nuances during the judicious use of current best evidence [16]. For example, a case report [41] that informed on aspects of implementation and patients' response to atraumatic restorative treatment (ART) in an oral healthcare service provided important insights concerning the external validity of ART results that were established through a relevant systematic review [33]. Through systematic reviews focussing on high internal validity, analytical clinical judgment becomes more informed [12]. This implies that synthesis informs analysis and is not in opposition to it as the debate between EBM promoters and critics seems to suggest. Instead, both analysis and synthesis exist in unity.

**Analysis and synthesis unity**

The unity of analysis and synthesis is demonstrated in the suggested model (Figure 1). Analytical knowledge derived through projection from basic science, as well as from experiences, forms the basis for a plausible hypothesis (H). It has been suggested that any empirical test results are meaningless if the tested hypothesis violates principles of basic science [14]. For example, evidence from RCTs supporting the claim of homeopathic remedies to be effective beyond the placebo effect would be seriously doubted, as knowledge derived from basic science does not provide an explanation of how highly diluted homeopathic solutions can contain any active ingredient capable of causing any observed significant ($p < 0.05$) treatment effect [42]. This implies that analysis justifies synthesis. Therefore, as shown above on hand of a plausible hypothesis development [25], sources of "other knowledge" on an analytical basis are extremely important in hypothesis development ($H^D$).

The development of a plausible hypothesis needs to be followed by hypothesis testing ($H^T$). Such testing has to take into consideration the empirical evidence [35,36] for the negative impact of systematic error. This requires a focus on inclusion into the study design of clinical trials, of bias-controlling measures: randomization, blinding and attrition control. Results of clinical trials that utilize such measures, like RCTs can therefore be considered to

have higher internal validity in terms of hypothesis testing. Synthesis by trial is obtained through engagement of the hypothesis (= Thesis) with the rigor of the clinical trial methodology (= Antithesis). However, the knowledge acquired through synthesis by one single trial stands isolated from the results of other trials with similar focus. A systematic review with meta-analysis achieves unification of isolated trial results and thus, can provide a more comprehensive answer to clinical questions than one single trial can. For example, the pooled results of one meta-analysis that included 31 randomized control trials indicated a reduction of risk of recurrence of breast cancer after chemotherapy, in contrast to no chemotherapy, while the individual result of each trial was inconclusive [43]. The synthesis from systematic reviews that include meta-analysis is based (in direct proportion to the sample size of each trial) on the weighted comparison between combined data of conventional treatments as control (= Thesis), with the combined data of newly developed (test-) interventions (= Antithesis). During this process bias-controlling measures, such as the selection of trials with high internal validity (e.g. RCT for therapy related topics), and quality assessment of trials, are utilized.

Through synthesis by systematic review, a comprehensive answer to clinical questions is achieved, with least possible systematic error and with high internal validity. On this basis, the analytic knowledge of the clinician is informed. According to a model by Glaszion and Irwig [44], systematic review results of RCTs would provide a doctor with, for example, information about the net benefit of Warfarin treatment for a patient with fibrillation and the risk of thromboembolic stroke. A systematic review of cohort studies would provide information regarding the potential harm of such treatment (e.g. induction of intracranial bleeding by Warfarin). This evidence would also reveal that the benefit of Warfarin increases along with the increase in risk for thromboembolic stroke and that the danger of for example, bleeding, remains constant. Armed with such information, the doctor would examine his patient for signs of major risk factors such as high blood pressure or previous thromboembolism. The doctor could then, on the basis of the evidence, be able to judge that in absence of any major risk factors, the benefit of Warfarin treatment would be outweighed by its potential harm and might thus decide against treating the patient with Warfarin. From this process new analytical knowledge is formed and clinical judgment altered and updated and, in time, clinical experience on a higher level of acquired knowledge is developed. Such clinical experience in turn provides the analytical basis for future hypothesis development in line with basic science, thus forming a repeated interaction between analysis and synthesis. The repeated interaction results in the continued acquisition of clinical knowledge on higher levels over time.

The acquisition of clinical knowledge is based on the interaction between analysis and synthesis. It is erroneous to judge one as being superior to the other. Systematic reviews provide the highest form of synthetic knowledge acquisition in terms of achieving internal

validity of results. However, this should not imply that systematic reviews are generally superior to other forms of knowledge or can replace, for example, the function of qualitative research results, particularly in relation to aspects of external validity and clinical judgment regarding the care of individual patients. On the other hand, analytical clinical judgment that is not informed by high internal validity synthesis becomes in time obsolete for patient treatment and faces the danger of being affected by systematic error.

**Competing interests**

The author contributes to the conduct and publication of systematic reviews concerned with topics related to Minimum Intervention (MI) in dentistry.

**Author's contribution**

SM developed the concept and outline and wrote this paper.

**Acknowledgement**

The author wishes to thank the staff of the Department of Philosophy, School of Social Science of the University of the Witwatersrand, Johannesburg for their valuable suggestions and advice during the writing of this paper.

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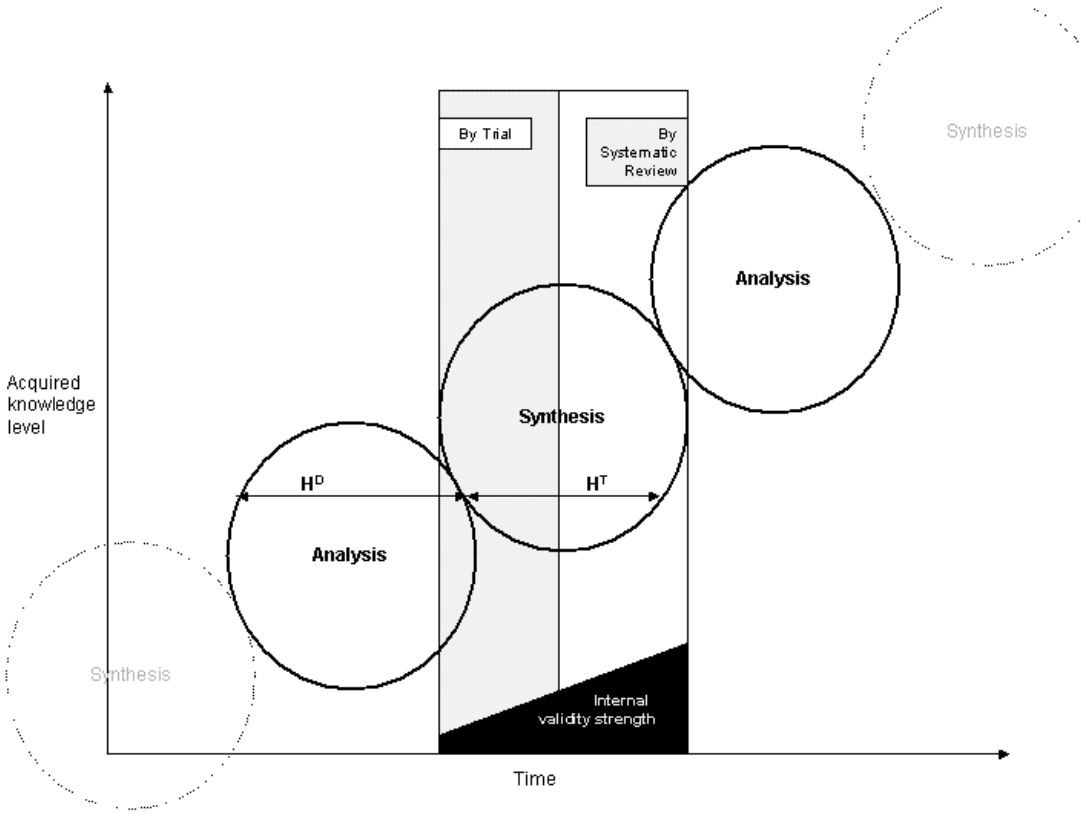
**Figure 1 - Analysis, Synthesis unity**




$H^D$ = Hypothesis development

$H^T$ = Hypothesis testing

# CHAPTER 4

## Systematic Reviews

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# Absence of carious lesions at margins of glass-ionomer and amalgam restorations: a meta-analysis

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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 control 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 restorations with amalgam (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

Carious 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, anatomic 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,

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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

| |
|---|
| 1. Insufficient random allocation of study subjects. |
| 2. Operator and subject not blinded, where appropriate. |
| 3. Not all entered subjects accounted for at the end of the trial. |
| 4. Subjects of both, study and control group, not followed up the same way. |

*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.

| Trial | Country | Study design | Age of subjects (in years) | No. Restorations | | Dentition | Cavity type | Follow-up period |
|---|---|---|---|---|---|---|---|---|
| | | | | GIC | Amalgam | | | |
| Frencken et al. [2007] | Syria | Parallel group | 13.8 | 487 | 403 | Permanent | Single-surface | 6.3 years |
| Mandari et al. [2003] | Tanzania | Split-mouth | 11 | 164 | 177 | Permanent | Single-surface | 6 years |
| Taifour et al. [2002 (Study 1)] | Syria | Parallel group | 6-7 | 441 | 326 | Primary | Single-surface | 3 years |
| Taifour et al. [2002 (Study 2)] | | | | 610 | 425 | | Multiple-surface | |
| Östlund et al. [1992] | Sweden | Parallel group | 4-6 | 25 | 25 | Primary | Multiple-surface | 3 years |
| Welbury et al. [1991] | United Kingdom | Split-mouth | No information | 99 | 99 | Primary | Single/ Multiple - surface | 22.7 – 26.3 months |
| Qvist et al. [2004 (Study 1)] | Denmark | Parallel group | 2.8. - 13.5 | 131 | 87 | Primary | Single-surface | 8 years |
| Qvist et al. [2004 (Study 2)] | | | | 384 | 456 | | Multiple-surface | |

**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

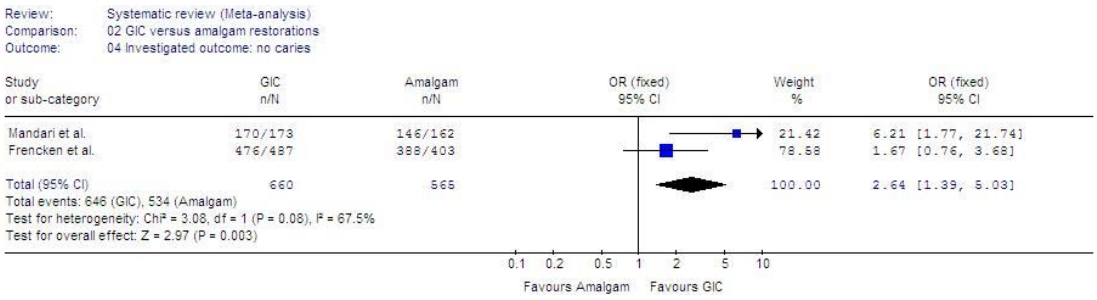
| Study | Randomization | Allocation | Allocation Concealment | Blinding | Drop-outs |
|---|---|---|---|---|---|
| Frencken et al. [2007] | Randomized | B - Unclear (By use of gender-stratified class list) | B - Unclear | D - Not possible | A 84/681 (12.3%) patients |
| Mandari et al. [2003] | Quasi-randomized | C- Inadequate (By toss of a coin) | B - Unclear | D- Not Possible | A 38/152 (25%) - patients |
| Taifour et al. [2002] - Study 1 & 2 | Randomized | B - Unclear (By use of a class list) | B - Unclear | D- Not Possible | A 185/835 (22.1%) - restorations |
| Östlund et al. [1992] | Randomized | B - Unclear | B - Unclear | D- Not Possible | C No explanation |
| Welbury et al. [1991] | Quasi-randomized | A - By use of random permuted block design | B - Unclear | D- Not Possible | A 12/88 (13.6%) - patients |
| Qvist et al. [2004] – Study 1 & 2 | Randomized | C - Alteration | B - Unclear | D- Not Possible | A (7%) - restorations |

*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

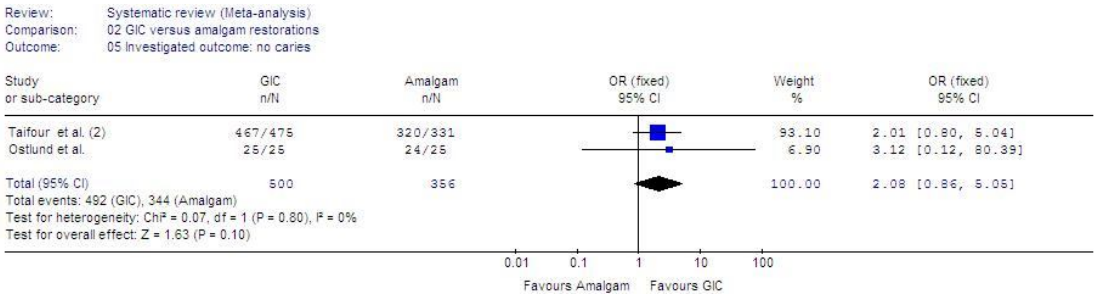
teeth had significantly less carious lesions (p = 0.003) after 6 years than did similar teeth restored with amalgam (OR = 2.64; CI 95% 1.39 – 5.03). No trials covering multiple-surface restorations in permanent teeth were identified.

**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.




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.




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- excavation 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.

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Journal of Oral Science, Vol. 51, No. 3, 373-382, 2009

Original

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

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(Received 30 October 2008 and accepted 16 April 2009)

**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.

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## 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 data- bases until 15 January 2008 were included in the search.

**Table 1.** Exclusion criteria for trials and literature reviews

| Trials | Literature reviews |
|---|---|
| Drop-out rate >33% | Focus on population or intervention not clearly stated in title and abstract |
| Patients and clinicians not 'blinded' where possible and appropriate | Article methodology describes no clear inclusion and exclusion criteria for reviewed publications |
| Baseline differences among groups not statistically adjusted | 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 |
| Clinically important outcomes for patients not assessed.<br>No in-vivo or in-situ study design<br>No randomization/ quasi-rendomization method reported | |

*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

| Authors | Study design | Test material | Control material | Participants / teeth | Age (years) | Tooth | Application | Follow - up Period (years) | Drop-out (%) | Caries preventive Effect | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Test material | Test material |
| Lovadino JR, et al. (32) | RCT (SM) | Chelon Fil | Delton | 22 children | 6-11 | 1st permanent molars | Single | 1 | 31.8% children (7/22) lost<br>GIC – 80% total retention<br>Resin - 33.33% total retention | 100% caries free | 100% caries free |
| Tostes M (33) | RCT (SM) | 1.Ketac Cem<br>2.Fluoroshield<br>3.Fluor varnish | No treatment | 25 children | 6-8 | 1st permanent molars | Single | 2 | 12% children (3/25) lost<br>GIC – 100% partially or total lost Resin – 63.7% partially or total lost | 1.13% of teeth in Resin Group decayed at 24 months 2.27% in GIC group 2.27% in F varnish group. No statistical significance among all 4 groups | 2.27% of teeth in control group decayed p> 0.05 |
| Karlzen-Reuterving G & van Dijken JWV (34) | RCT (SM) | Fuji III | Delton | 47 (26 girls; 21 boys) 148 1st molars | 7 | 1st molar | Single | 3 | 4.3% children (2/47) lost<br>GIC-72.2% partially lost; 98% total loss<br>Resin- 20.8% partially lost; 0% total loss | Carious teeth: 1.4% of GIC F/S teeth | Carious teeth: 4.2% of resin sealed teeth |
| Arrow P, et al. (35) | RCT (SM) | Ketac Fil | Delton | 465 pairs of molars in 465 children | 7 | 1st molar | Single | 3.64 | 10.8%(50/465) children drop-out >60% of both sealants lost 62% GIC lost at 44 months 100% resin lost at 44 months | Carious teeth: 1.5% (6/415) RR=0.19 (CI 0.09-0.4) | Carious teeth: 7.5% (31/415) |
| Williams B, et al. (36) (Only 2 year results reviewed) | RCT (SM) | Fuji III | Delton | 860 sealants placed in 228 children | 6-8 | 1st molar | Single | 2 | 31% (71/157) children lost at 2 years; GIC-93% (274/295) lost Resin-18% (55/295) lost | Carious teeth: 6.4% (19/295) | Carious teeth: 1.4% (4/295) |
| Songpaisan Y, et al. (31) (Part 1) | RCT (PG) | 1. Fuji III | 1. No treatment | 512 children with ≥3 1st molars assigned to 4 groups (Control; 3 | 7-8 | 1st molar | Single and repeated for GIC if missing at 6 months; Topical | 2 | 14% (73/512) lost at 2 years. At 24 months, 96% GIC F/S lost | 1. DFS –for 1st molars reduced by 52%; mean DMFS for whole mouth reduced by 51.3% compared to control | DMFS score increased from 0.43 at baseline to 1.63 at 2 years |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2. Fuji III | 2. No treatment | (Control; 3 Test) | | | Topical fluoride applied at baseline, 6, 12 months | | 2. DFS –for 1st molars reduced by 74%; mean DMFS for whole mouth reduced by 64.7% compared to control | |
| Songpaisan Y, et al. (31) (Part 2) | RCT (PG) | 1. Fuji III | 1. No treatment | 752 children with ≥3 1st molars assigned to 4 groups (Control; 3 Test) | 12-13 | Molar teeth | 1. Single and repeated for GIC if missing at 6 months; Topical fluoride applied at baseline, 6,12 months | 2 | 11% (81/752) lost at 2 years. At 2 years, 99% of GIC F/S lost; 15% of Resin F/S lost. | 1. DFS –for molars reduced by 31%; mean DMFS for whole mouth not significant when compared to control | Resin based sealants performed significantly better than GIC sealants when mean DFS scores were compared at 2 years |
| | | 2. Fuji III | 2. No treatment | | | | 2. Single | | | 2. DFS –for 1st molars reduced by 20%; mean DMFS for whole mouth not significant when compared to control | |
| | | 3. Delton (LC) | 3. No Treatment | | | | 3. Single | | | 3. DFS –for 1st molars reduced by 93%; mean DMFS for whole mouth significantly lower than control | |
| Kerrvanto-Seppälä S et al. (38) | RCT (SM) | Fuji III Chemical cure | Delton (LC) | 599 children who received sealants on 2nd molars | 12-16 yrs | 2nd molars | GIC = single / Resin = defective sealants resealed | 3 | 20% | 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) | |
| Rock WP, et al. (37) | RCT (SM) | GIC (Baseline) | Resin (Fluoro-shield – contains F –Light Cure) | 86 children received GIC F/S on one side of mouth and Resin F/S on contra-lateral side | 7-8 | 1st molar | single | 3 | At 3 years, 24% (21/86) lost to follow-up. At 3 years, 0% GIC F/S intact; 70% Resin FS intact. | At 3 years, caries present in 13.8% of GIC F/S teeth; | At 3 years, caries present in 3.2% of Resin Filled teeth. Statistically significant. |

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 Mejáre 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.

**Table 3.** Excluded articles and main reasons for exclusion

| Authors | Reason for Exclusion |
|---|---|
| Forss H & Halme E (20) | Drop-out rate = 42% |
| Mejare I & Mjor IA (21) | No randomization method described; Adult drop-out rate = 38% (no information on drop-out rate for children) |
| Boksman L et al. (22) | Drop-out rate = 98.3% of sealants; Trial abandoned at 6 months |
| Herle GP et al. (23) | No randomized controlled, in-vivo or in-situ study |
| Poulsen S et al. (24) | Drop-out rate = 35.2% |
| Yip H-K & Smales RJ (19) | 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 |
| Simonsen RJ (8) | 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 |
| Basting RT et al. (25) | No randomized controlled, in-vivo or in-situ study |
| Navarro MFL et al. (26) | 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) |
| Ganesh & Shobha (27) | No randomized controlled, in-vivo or in-situ study |
| Kantovitz KR et al. (28) | No randomized controlled, in-vivo or in-situ study |
| Delfino CS et al. (29) | No randomized controlled, in-vivo or in-situ study |
| Beiruti N et al. (30) | Drop out rate greater than 50% after 5 years |
| Poulsen S et al. (31) | 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. |

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

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 Mejáre 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 Mejáre 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 and 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).

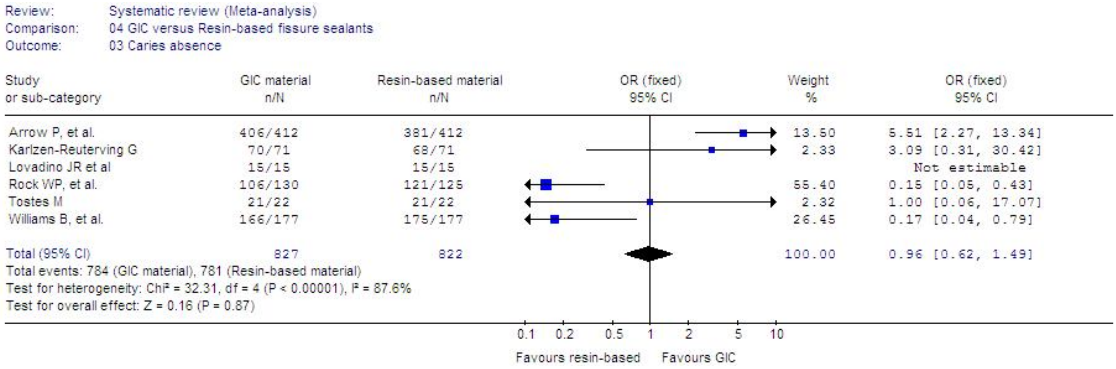
The Kervanto-Seppälä et al. (38) trial studied 2nd permanent molars only, and the GIC sealant was applied only once in a 3-year follow-up period, while the resin sealants were resealed during annual evaluations, in the event of being defective or lost.

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

| Study | Randomization | Allocation | Allocation Concealment | Blinding | Drop-outs |
|---|---|---|---|---|---|
| Lovadino JR et al. (33) | Quasi-randomized | B- Unclear | B- Unclear | D - Not possible | B 7/22 (31.8%) |
| Tostes M (34) | Quasi-randomized | B-Unclear | B-Unclear | D- Not Possible | A 3/25 (12%) |
| Karlzen-Reuterving G & van Dijken JWV (35) | Quasi-randomized | B-Unclear | B-Unclear | D- Not Possible | A 2/47 (4.3%) |
| Arrow P et al. (36) | Quasi-randomized | C- By use of month of birth | B- Unclear | D- Not Possible | A 50/465 (10.8%) |
| Williams B et al. (37) (2 year results) | Quasi-randomized | A- By use of computer generated random numbers | B-Unclear | D- Not Possible | B 71/157 (31%) |
| Songpaisan Y, et al. (32) (Part 1) | Randomized | B-Unclear | B-Unclear | D- Not Possible | A 73/512 (14%) |
| Songpaisan Y, et al. (32) (Part 2) | Randomized | B-Unclear | B- Unclear | D- Not Possible | A 81/752 (11%) |
| Kerrvanto- Seppälä S et al. (39) | Quasi-randomized | C- By use of birthday | B-Unclear | D- Not Possible | A 20% |
| Rock WP et al. (38) | Quasi-randomized | A- By use of random number tables | B-Unclear | D- Not Possible | A 21/86 (24%) |

**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

*Meta-analysis*

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 to11 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

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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*Eur. J. Prosthodont. Rest. Dent.*, Vol. 18, No. 3, pp 139-145
Printed in Great Britain


doi:10.1922/EJPRD_905Mickenautsch07

# Absence of Carious Lesions at Margins of Glass-Ionomer Cement (GIC) and Resin-Modified GIC Restorations: A Systematic Review

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**Abstract** - *This systematic review sought to quantitatively answer the question as to whether, in tooth cavities of the same size, type of dentition and follow-up period, resin-modified glass-ionomer (GIC) restorations, when compared to conventional GIC restorations, offer a significant caries preventive effect, as measured by the absence of caries lesions at the margin of restorations. Six databases were searched for articles in English, Portuguese or Spanish until 07 May 2009. Four articles were accepted and 22 separate datasets extracted. The difference between both types of material were computed as Relative Risk (RR) with 95% Confidence Interval (CI). No meta-analysis was undertaken due to aspects of clinical/methodological heterogeneity. The results of the extracted datasets ranged between RR 0.90 (95%CI 0.81 – 1.01) and 1.08 (95%CI 0.71 – 1.63; p>0.05) indicating no difference in the caries preventive effect between both types of materials. Further high-quality randomized control trials are needed in order to confirm these results.*

KEY WORDS: Glass-ionomer cement, caries, systematic review

## INTRODUCTION

Secondary caries is the most common reason for replacing restorations[1] and an ideal restorative material would have, as one of its properties, the ability to prevent demineralization and/or promote remineralization at the cavity margin. Since ionic fluoride has been shown to reduce the incidence of caries at the population level, both in the water supply[2] and in other vehicles such as toothpaste[3], considerable attention has been focused on fluoride-containing restorative materials.

The earliest fluoride-releasing restorative material was silicate cement (now superseded). Anecdotal evidence of its caries-preventive effect was related to the paucity of reports of secondary caries seen in association with silicate cement despite its high intra-oral solubility[4]. This observation led to the inclusion of fluoride into restorative materials such as amalgam and resin-based materials, although published evidence of an anti-caries effect was not observed[5].

The glass-ionomer cements (GIC) that were introduced clinically in the early 1970s contained fluoride as a necessary part of the manufacturing process. This originated in part from silicate cement that also contained fluoride[6]. Thus, there was considerable interest in the effect of GIC on the adjacent tooth structure in terms of its purported anti-caries effect; as to whether it could influence the demineralisation-remineralisation cycle. The original glass-ionomer cements, now generally referred to as 'conventional' glass-ionomers (C-GIC), hardened in the tooth cavity because of an acid-base reaction between the fluoroaluminosilicate glass powder and the polyalkenoic acid liquid. However, they were sensitive to water uptake and loss in the first hours or days after setting, and this led to the development of 'resin-modified' GICs (RM-GIC): approximately 10% of the set material is resin, usually hydroxyethylmethacrylate (HEMA)[7].

Published studies that have examined the association of secondary caries with C-GIC restorations have reported variable findings. A retrospective study of 1283 C-GIC restorations, reported a failure rate of 7%, none being due to secondary caries[8]. Conversely, a further study investigated the reasons for replacing 412 C-GIC restorations and reported that almost half were replaced because of secondary caries[9]. A qualitative systematic review without meta-analysis found no evidence for or against the inhibition of secondary caries by C-GICs[10] and a subsequent literature review[5] confirmed this report. However, in a recent systematic review with meta-analysis, significantly less caries lesions were observed on single-surface C-GIC restorations in permanent teeth after 6 years compared to restorations with amalgam (Odds ratio 2.64 – 95%CI 1.39 – 5.03, p = 0.003)[11]. The advantages of meta-analysis over qualitative or narrative synthesis are that it provides the chance to detect whether a treatment effect is statistically significant ($p<0.05$) and improves estimation of the effect by quantifying its outcome, resulting in a more precise estimation[12]. No systematic review with meta-analysis regarding the caries-preventive effect of RM-GIC has been published. A combining of the recently confirmed anticariogenic properties of C-GIC[11] with the more water-resistant

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characteristics achieved by inclusion of HEMA[8] would greatly benefit restorative treatment. Thus, this systematic review sought to quantitatively answer the question as to whether, in tooth cavities of the same size, type of dentition and follow-up period, RM-GIC restorations, when compared to C-GIC restorations, offer a significant caries preventive effect, as measured by the absence of caries lesions at the margin of restorations.

## Materials and methods

*Data collection*

Five Anglophone databases (Biomed Central; Cochrane Library; Directory of Open Access Journals; PubMed; Science-Direct) 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 07 May 2009. The string of MeSH and text search terms with Boolean operators: *"Glass Ionomer Cements AND Dental Caries OR Root Caries AND resin modified glass ionomer cement"* was used to search the Anglophone databases and the strings of text terms: *"agentes cariostáticos [Descritor de assunto] and cimentos de ionômeros de vidro [Descritor de assunto] and cárie dentária",* as well as *"cariostatic agents [Descritor de assunto] and glass ionomer cements [Descritor de assunto] and dental caries [Descritor de assunto]"* were used to search LILACS. 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, Portuguese or Spanish;
3. Two-arm longitudinal clinical 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 that complied with the inclusion criteria were reviewed further. Two reviewers (VY and SM) independently reviewed full copies of articles in accordance with the exclusion criteria[13]:

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;

4. No computable data reported for both control (comparison) and test groups.

Where several articles had reported on the same trial over similar time periods, the article covering the trial most comprehensively in accordance with the exclusion criteria was accepted. Disagreements between reviewers were resolved by discussion and consensus.

*Data extraction from accepted trials*

The outcome measure was the absence of caries lesion at the margin of restorations. Individual dichotomous datasets including the number of caries-free restorations (n) and total number of evaluated restorations (N) for both the control (comparison) and the test groups were extracted from each article. 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-child basis. However, as in other similar reviews[14], 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[15]. Trials not included in this review were used to pilot the process. Subsequently, a 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.

(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/masked outcome assessment, recorded as:
(A) yes;
(B) unclear;
(C) no;
(D) not possible

*Statistical Analysis*

A random effects model in RevMan Version 4.2 statistical software (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). Datasets were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines[16]. Datasets were considered to be heterogeneous if they differed in type of dentition (primary or secondary), cavity type, caries status at baseline, fluoride exposure from other sources and follow-up period. $Chi^2$, degree of freedom (df) and the percentage of total variations across datasets ($I^2$) were used in assessing statistical heterogeneity[17]. Only identified homogeneous datasets (clinical and methodological homogeneity) were combined for meta-analysis. Studies were assigned a Mantel-Haenszel weight directly proportional to their sample size.

**Results**

An initial search of PubMed resulted in 220 articles, of which four[18-21] complied with the inclusion and exclusion criteria and were selected for review. A subsequent search of the other four Anglophone databases and the one Lusophone database generated no further results. All four reviewed articles reporting on randomized[18] and quasi-randomized control trials were accepted[19-21]. Table 1 provides information about quality aspects assessed for the accepted trials. Random allocation of subjects was rated A (Adequate) in one trial[21], B (Unclear) in one[20], and two trials[18,19] were rated as C (Inadequate). The random allocation in the latter two was rated inadequate because one trial alternated allocation of the two materials[18] and the other used a preconceived allocation table in order to ensure that each material was placed in the more anterior, middle or posterior tooth position an equal number of times[19]. As the used allocation mode in both trials made allocation concealment impossible, the quality of allocation concealment in these trials was also rated as C (Inadequate). The allocation concealment of the remaining two trials[20,21] was rated as B (Unclear). All B ratings were based on the lack of information in the text.

From the four accepted articles, 22 separate computable dichotomous datasets relevant to the review question were extracted. The main characteristics of the datasets are described in Table 2. Clinical and methodological heterogeneity between all datasets was observed. The datasets differed in type of dentition; type of restored cavity; fluoride exposure and follow-up period. Furthermore, two articles presenting eight separate datasets, did not report on the caries status of subjects in the different groups at baseline[18,20] and three articles, including 12 separate datasets, did not report on fluoride exposure from other sources[18,20,21]. For that reason, no meta-analysis was conducted and statistical heterogeneity was not further assessed. The Relative Risk (RR) with 95% Confidence interval (CI) of the separate datasets, ranging from 0.90 (95%CI 0.81 – 1.01) to 1.08 (95%CI 0.71 – 1.63), showed no difference ($p>0.05$) between the two materials with regard to absence of caries on restoration margins (Figure 1).

**Discussion**

The aim of this quantitative systematic review was to explore whether in tooth cavities of the same size, type of dentition and follow-up period, RM-GIC restorations remained as free of secondary caries as did C-GIC restorations. Despite the identification of 220 articles dealing with dental caries and glass-ionomer cements, only four fulfilled the selection criteria. Often in systematic reviews, restrictive exclusion criteria concerning methodological aspects are used to limit the inclusion of bias and so strengthen the external validity of the results. One of the methodological considerations in systematic reviews concerning topics of therapy is selection of randomized control trials (RCT) that follow only a parallel group design[13]. Besides randomized parallel-group studies, 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, it has been suggested that split-mouth studies should be regarded as “quasi-randomized”, as the common practice of including patients with at least one pair of treatable teeth results in exclusion of other potential study subjects and thus introduces a selection bias[22]. For this reason systematic reviews should, strictly speaking, not include split-mouth trials. There is a risk, however, that some useful trial data would be excluded from the review, thus weakening the overall clinical value. Therefore, in order to increase the inclusion envelope in this review, split-mouth quasi-random study designs and their data[19-21] were included and analyzed independently. Further 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, Portuguese or Spanish. Thus, some relevant studies may not have

been identified. Despite these considerations, in PubMed only 1.8% of the initially identified 220 articles were randomized/quasi-randomized control trials reporting the comparison of RM-GIC with C-GIC. Moreover, no further eligible articles were identified in the other databases. It can therefore be assumed that there is a general lack of published studies on this topic and the inclusion of further data sources might not have resulted in the selection of more articles.

Although trials with statistically significant results have been shown to be more likely to be published in English[23], non-English language trials may contribute in average 17.5% to the weight in individual meta-analyses and a decrease in average precision (Inverse of standard error) of meta-analysis results from 8.34 down to 7.68 after exclusion of non-English language trials was observed[24]. For this reason it was decided to search, besides English databases, also the well-known Lusophone database LILACS and to include, besides English language articles, also publications in Portuguese and Spanish.

The quality of the four accepted trials related to internal validity was assessed, using a structured checklist[15]. The assessment outcome indicated that the results of the trials might be limited by selection and detection 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[25]. A 41% treatment effect overestimation due to selection bias, caused by lack of allocation concealment during the randomization process alone has been reported[26]. Since none of the trials accepted in this review included or reported 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 22 dichotomous datasets showed no statistical differences in caries absence between RM-GIC and C-GIC (Figure 1). Qvist et al. (Datasets # 01-04) used a C-GIC (Ketac Fil) and an RM-GIC (Photac Fil) for 451 and 543 restorations respectively, in various cavities in deciduous teeth[18]. No information was provided on randomization. Restorations were followed for a maximum of 8 years. However, by then 60% of restorations could not be evaluated because of tooth loss. Three percent of both types of GIC restoration had secondary caries diagnosed during the study period. McComb et al. (Datasets # 05-14) restored cervical caries lesions in 45 high-caries-risk patients[19]. Each patient received three restorative materials in the same quadrant: Ketac Fil C-GIC; Vitremer RM-GIC (3M ESPE); and a non-fluoride containing resin composite (Z100, 3M ESPE). In total, 50 sets of restorations were placed and, after 24 months, only one of the GIC restorations, which was an RM-GIC, had developed secondary caries. Brackett et al. (Datasets # 15-18) restored non-carious cervical lesions (NCCL) with either a C-GIC (Ketac Fil; 3M ESPE, Seefeld,

Germany) or an RM-GIC (Photac-Fil; 3M ESPE)[20]. Thirty-four pairs of restorations were placed and the allocation of the two materials to the patients was random. After 2 years, 15% of restorations were not available for examination and there was one caries lesion associated with each of the GICs, both being in the same patient, among the 85% of restorations examined. Hübel and Mejàre (Datasets # 19-22) also compared C-GIC (Fuji II; GC Corp, Japan) and RM-GIC (Vitremer)[21]. However, the restorations were in approximal cavities in deciduous teeth. A mainly split mouth design with random allocation was used, with 62 C-GIC and 53 RM-GIC restorations. After 3 years, four Fuji II restorations and zero Vitremer restorations had developed secondary caries. However, no statistical tests for this evaluation criterion were reported. There is therefore no evidence from the two trials in permanent teeth[19,20] that any difference exists in the incidence of secondary caries adjacent to C-GIC and RM-GIC restorations. In deciduous teeth, the findings are equivocal: one study[18] found no difference between C-GIC and RM-GIC with respect to secondary caries, while the other study[21] found significantly more failures of the C-GIC, but mostly due only to loss of retention.

The lack of difference between RM-GIC and C-GIC with respect to secondary caries may be due to their similar fluoride release characteristics[5]. Wiegand et al. have extensively reviewed the dynamics of fluoride release and recharge characteristics of several fluoride-containing materials, including the glass-ionomers, polyacid-modified resin composites ('compomers'), giomers, amalgam and silicate cement[5]. Although there are differences between brands, the release of fluoride from C-GIC and RM-GIC is broadly similar in amount and pattern. Moreover, in laboratory studies, the amount released is dependent on the eluant, e.g., whether it is distilled water, artificial saliva or saline[5]. It is also evident that the amount of fluoride released is inversely associated with the acidity of the eluant, and this may be of clinical importance. However, from a clinical perspective, the amount of fluoride release required for inhibition of secondary caries, or for remineralisation of demineralised enamel adjacent to a restoration, is not known. Thus, estimating the anti-caries activity of glass-ionomers from laboratory data remains problematic. That these considerations are equally valid for both C-GIC and RM-GIC explains the lack of clinical differences between both types of materials with regard to caries.

This review identified a lack of high-quality trials on the review topic (Table 1). Therefore, further high quality randomized control trials are needed to confirm the observed results. Reporting of such trials should follow the CONSORT statement[27] 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, as well as whether or not participants, clinical operators and evaluators of the study results were aware of group assignment and if not, how the success of such masking was assessed.

**Conclusions**

The systematic literature search identified four randomized/quasi-randomized control trials including 22 separate datasets with relevance to the review question. None of the datasets found one material to be superior to the other in terms of caries absence. The answer to the review question was that in comparison to conventional GIC of the same size, type of dentition and follow-up period, the margins on restorations with resin-modified GIC appear to remain as free of secondary caries as conventional GIC restorations. However, these findings have to be regarded with caution, as all the included studies had limited internal validity due to unclear randomized sequence allocation and/or allocation concealment, as well as patient, operator and evaluator masking. Further high quality randomized control trials are therefore needed. It is recommended that reporting of such future trials should follow the CONSORT statement.

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

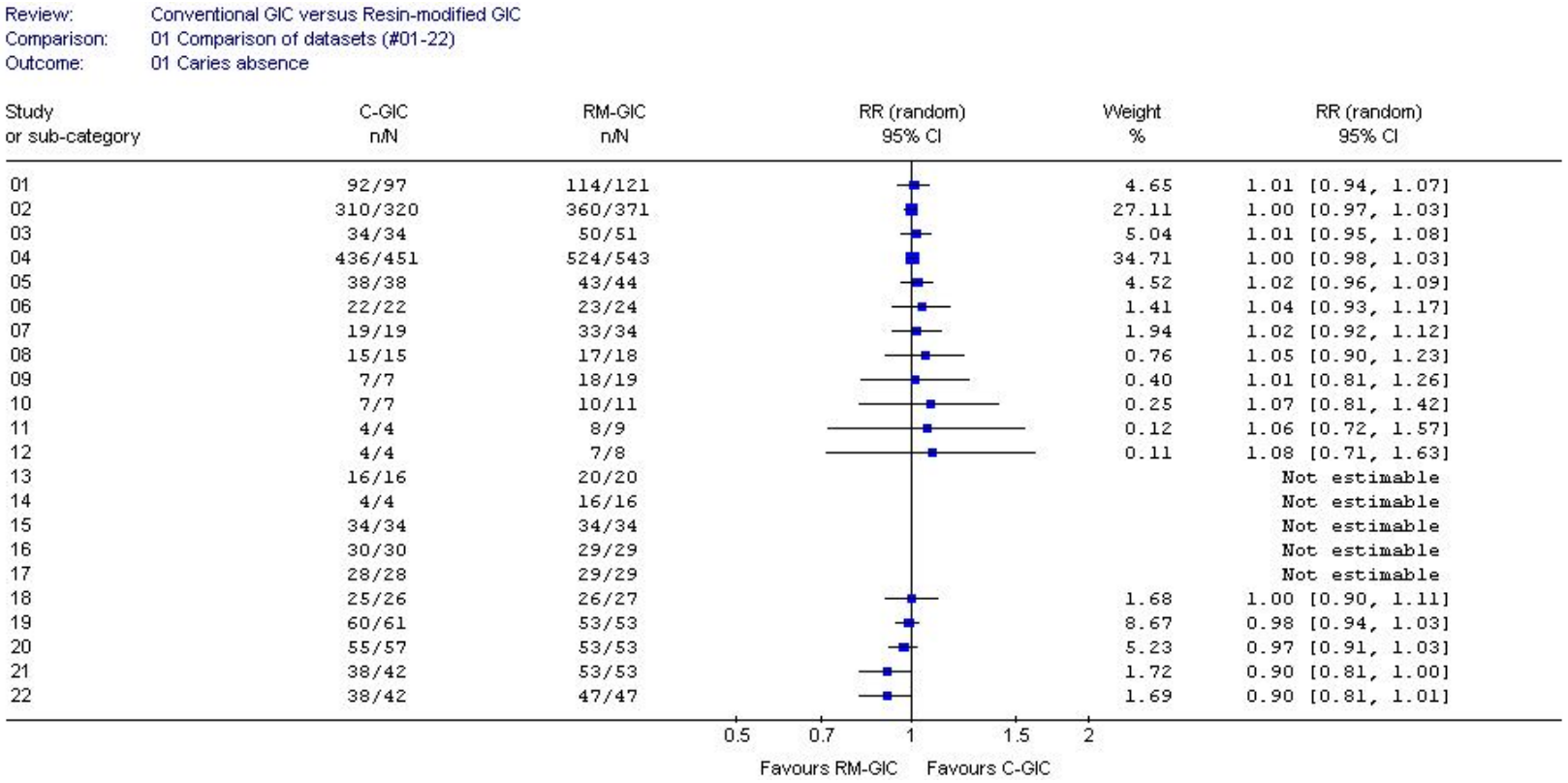
| Article | Selection bias | | Detection bias |
|---|---|---|---|
| | Random allocation | Allocation concealment | Evaluator blinding |
| Qvist V et al. (2004)[18] | C | C | B |
| McComb D et al. (2002)[19] | C | C | D |
| Brackett WW et al. (1999)[20] | B | B | A |
| Hübel S and Mejáre I (2003)[21] | A | B | C |

**Table 2**. Main characteristics of datasets from randomized and quasi-randomized control trials.

| Article | DS | Study type | Outcome measure | RM-GIC | C-GIC | Study subjects Age | Dentition | Type of restored cavity | Caries status at baseline | Fluoride exposure from other sources | Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Qvist V et al. (2004)[18] | 01<br>02<br>03<br>04 | RCT | Caries absence | Photac Fil | Ketac Fil | >3 years | Primary | Class I<br>Class II<br>Class III+V<br>All types | No info | No info | 8 years |
| McComb D et al. (2002)[19] | 05 | Split-mouth | Caries absence | Vitremer | Ketac Fil | >18 years | Permanent | Class V | Patients with at least 3 cervical carious lesions / All patients had received prior radiation therapy involving head and neck | Independent from Fluoride exposure | 6 months |
| | 06 | | | | | | | | | No Fluoride exposure | |
| | 07 | | | | | | | | | Independent from Fluoride exposure | 12 months |
| | 08 | | | | | | | | | No Fluoride exposure | |
| | 09 | | | | | | | | | Independent from Fluoride exposure | 18 months |
| | 10 | | | | | | | | | No Fluoride exposure | |
| | 11 | | | | | | | | | Independent from Fluoride exposure | 24 months |
| | 12 | | | | | | | | | No Fluoride exposure | |
| Brackett WW et al. (1999)[20] | 13 | Split-mouth | Caries absence | Photac Fil | Ketac Fil | Median 45 years | Permanent | Cervical abrasion/ abfraction lesions | No info | Fluoride exposure | 6 months |
| | 14 | | | | | | | | | | 12 months |
| | 15 | | | | | | | | | No info | 6 months |
| | 16 | | | | | | | | | | 12 months |
| | 17 | | | | | | | | | | 18 months |
| | 18 | | | | | | | | | | 24 months |
| Hübel S and Mejáre I (2003)[21] | 19 | Split-mouth | Caries absence | Vitremer | Fuji II | 4-7 years | Primary | Class II | Mean defs 4.7 (SD = 2.9) | No info | <12 months |
| | 20 | | | | | | | | | | 12-23 months |
| | 21 | | | | | | | | | | 24-35 months |
| | 22 | | | | | | | | | | >35 months |

DS = Number of dataset; RCT = Randomized control trial; RM-GIC = Resin-modified glass-ionomer cement; C-GIC = Conventional glass-ionomer cement; SD = Standard deviation.

**Figure 1.** Comparison results in caries absence on restoration margins between both materials




N = Total number of evaluated restorations; n = Number of restorations without caries;

RR = Relative risk; CI = Confidence interval; C-GIC = Conventional glass-ionomer cement; RM-GIC = Resin-modified glass-ionomer cement

“Not estimable” = Results of both groups the same (= RR 1.00); “Study or sub-category” = Number of dataset

# Resin-modified glass-ionomer cements versus resin-based materials as fissure sealants: a meta-analysis of clinical trials

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## Abstract

**AIM:** To appraise quantitatively current evidence regarding the caries-preventing effect of resin-modified glass-ionomer cements (RM-GIC) fissure sealants in comparison to that of resin-based fissure sealants. **STUDY DESIGN:** Systematic review with meta-analysis. **METHODS:** 8 Anglophone databases and 2 Lusophone databases were searched until 15 April 2009, using a pre-determined search strategy. Clinical trials were considered for inclusion if their titles/abstracts were relevant to the topic, published in English, Portuguese or Spanish and had a two-arm longitudinal study design. The outcome measure of the caries-preventive effect was caries absence on sealed teeth. Two reviewers independently extracted data from the accepted articles in order to complete a 2x2 table for meta-analysis. The unit of interest was the tooth, and the number of caries-free teeth (n) at the end of each time interval (6, 12 and 24 months) was compared against the total number of evaluated teeth (N) **STATISTICS:** Datasets were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines, and only homogeneous datasets were combined for meta-analysis, using a random effects model (RevMan 4.2). Differences in the caries-preventive effect were computed on basis of the combined Relative Risk (RR) with 95% confidence interval (CI). RESULTS: Of the 212 articles identified, only 6 trials were included. From these, 19 separate datasets were extracted. For the pooled data, equivalent caries-preventive effects were observed at 6 months (RR= 0.98, 95% CI 0.95-1.00; p = 0.08); 12 months (RR=1.00, 95% CI 0.96-1.04, p = 0.99) and 24 months (RR=1.01, 95% CI 0.84-1.21, p = 0.91). The 36-month data (not pooled) favoured resin-based sealants (RR 0.93, 95% CI 0.88-0.97, p = 0.002) **CONCLUSIONS:** This meta-analysis found no conclusive evidence that either material was superior to the other in preventing dental caries.

## Introduction

Use of pit and fissure sealants (FS) has become accepted as an effective intervention for the prevention of occlusal caries in the molar teeth of young children [Kitchens, 2005; Ahovuo-Saloranta et al., 2008]. The evidence for the clinical efficacy and cost-effectiveness of FS in reducing occlusal caries in molars has been highlighted in recent papers [Kitchens, 2005; Ahovuo-Saloranta et al., 2008]. Resin-based FS materials are most commonly used and are regarded as the 'gold standard' for sealing pits and fissures [Feigal, 2002; Simonsen, 2002; Adair, 2003]. Their caries- preventive effect relies on the sealing of pits and fissures through micro-retention, created through tags after acid etching of enamel. However, these are easily destroyed by saliva contamination, reducing micro-retention and consequently, the caries-preventive effect [Bishara et al., 2002]. Moreover, the preventive benefits and resin-based FS retention are gained and maintained only as long as the sealants remain completely intact and bonded in place [Oliveira et al., 2008].

Under clinical conditions, it is difficult to maintain an absolutely dry environment in the oral cavity, in which to place resin-based FS; especially in uncooperative children and in settings where isolation is rarely possible and equipment such as rubber dam and dental suction is not readily available. Under the generally wet conditions in the oral cavity, glass-ionomer cement (GIC) FS offer an effective alternative to resin sealants, mainly because they have hydrophilic properties [Smith, 1998].

The original glass-ionomer cements, set through an acid-base reaction, between the fluoroaluminosilicate glass powder and the polyalkenoic acid liquid, are generally regarded as 'conventional' glass-ionomers (C-GIC). However, C-GICs are sensitive to water uptake and loss in the first hours or days after setting, and this led to the development of 'resin-modified' GICs (RM-GIC) which, in the set material, contain approximately 10% of resin, usually hydroxyethylmethacrylate (HEMA) [Ikeda et al., 1999].

It has been suggested that the 'gold standard' in caries prevention through FS administration should be based on biological outcomes rather than physical (material retention on the tooth surface) ones [Smith, 1998]. Such biological outcomes are measured in relation to the absence of caries in pits and fissures after FS application. A recent meta-analysis [Yengopal et al., 2009] that assessed biological outcomes found evidence that neither (low-viscosity) C-GIC nor resin-based FS was superior to the other in the prevention of dental caries. To date, no systematic review of the topic of caries-preventive effects of RM-GIC versus resin-based FS has been attempted. Thus, the aim of this systematic review with meta-analysis was to appraise quantitatively the current evidence regarding the caries-preventing effect of RM-GIC fissure sealants in comparison to that of resin-based fissure sealants.

**Key words:** Resin-modified glass ionomers; resin; fissure sealant; meta-analysis

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**Materials and Methods**

*Search strategy*

The literature search covered 8 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, and 2 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 and MeSH words. The string of English search terms: *"Pit and Fissure Sealants"[Mesh] AND "Glass Ionomer Cements"[Mesh] and "resin modified glass ionomer" AND "fissure sealant*"* 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 April 2009 were included in the search.

*Inclusion and exclusion criteria*

Articles reporting on clinical trials were selected for review from the search results on the basis of their compliance with the inclusion criteria:

4. Titles/abstracts relevant to topic;
5. Published in English, Portuguese or Spanish;
6. Two-arm longitudinal study design.

Where only a relevant title without a listed abstract was available, a full copy of the article was assessed for inclusion. A reference check of the included articles was conducted in order to identify further trials suitable for inclusion.

Only articles that complied with the inclusion criteria were reviewed further. Full copies of articles were reviewed independently by two reviewers (VY and SM), using the exclusion criteria [Sutherland, 2001]:

5. No random or quasi-random allocation of study subjects;
6. Not all entered subjects accounted for at the end of the trial;
7. Subjects of both groups not followed up the same way;
8. No computable data reported for both control (comparison) and test groups;
9. No in-vivo study design.

Where several articles had reported on the same trial over similar time periods, the article covering the trial most comprehensively in accordance with the exclusion criteria was accepted. Disagreements between reviewers were resolved by discussion and consensus.

*Quality Assessment*

The quality assessment of the included trials was undertaken independently by two reviewers (VY and SM) and followed established guidelines [Jüni et al., 2001; The Grade working group, 2004]. Trials not included in this review were used in piloting the quality assessment process. Disagreements between the reviewers regarding quality assessment ratings scored were resolved through discussion and consensus. 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.

*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. Data were extracted in the form of datasets with common characteristics (Table 2). Each dataset included the number of caries-free teeth (n) and total number of evaluated teeth (N) for both the control (comparison) and the test group. Where possible, missing data were calculated from information given in the tables and texts of the articles, in order to complete a 2x2 table for meta analysis. 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. The split-mouth study design is commonly used in dentistry to test interventions and has the advantage of having an individual serve as both 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 analyzed as "paired data" on a patient basis. However, as in other systematic reviews where split-mouth trials are included [Ahovuo-Saloranta et al., 2008], the decision was to analyze the pairs independently in order to avoid the exclusion of trials that was directly related to the research question.

*Meta-analysis*

Datasets were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines [The Cochrane Collaboration, 2006]. Datasets 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; measured outcome. The percentage of total variations across datasets ($I^2$) and the associated p-value (<0.10) were used in assessing statistical heterogeneity [Thompson, 1994]. Only identified homogeneous datasets from included trials (clinical and methodological homogeneity) were combined for meta-analysis, for which the random effects model of the meta-analysis software, RevMan 4.2 was used. The differences in the caries-preventive effect were computed on basis of the combined Relative Risk (RR) with 95% confidence interval (CI). Datasets were assigned a Mantel-Haenszel weight in direct proportion to sample size.

For datasets that were not suitable for meta-analysis, due to aspects related to clinical and methodological heterogeneity, RR scores with 95% CI were calculated for each dataset and reported separately.

**Results**

An initial search in PubMed resulted in 212 articles, of which eight trials [Raadal et al., 1996; Kilpatrick et al., 1996; Winkler et al., 1996; Tantbirojn et al., 1997; Smales and Wong, 1999; Pardi et al. 2005; Kantovitz et al., 2006; Oliveira et al., 2008] complied with the inclusion criteria. A reference check and a subsequent search of the other seven Anglophone databases and the two Lusophone databases generated no further results. Of the eight articles, two [Tantbirojn et al., 1997; Kantovitz et al., 2006] were excluded because they reported on in-vitro trials. Hence only six articles [Raadal et al., 1996; Kilpatrick et al., 1996; Winkler et al., 1996; Smales and Wong, 1999; Pardi et al. 2005; Oliveira et al., 2008] were accepted for quality assessment and further data extraction.

*Quality assessment and Data extraction of accepted articles*

Table 1 presents data on the quality assessment of the included trials. All trials scored “B” (unclear) for Randomized sequence allocation, and Allocation concealment, owing to lack of clear information in the text, “D” (not possible for Blinding), and “A” (adequate) for completeness of follow-up.

From the six accepted articles, 19 separate computable dichotomous datasets with relevance to the review question were extracted. The main clinical and methodological characteristics of the extracted datasets are described in Table 2. The reason for separating the data in this format was the need for avoidance of clinical and/or methodological heterogeneity. Additionally, this allowed for the identification of homogenous datasets, which then could be pooled together for meta-analysis. Considerable variation existed among the datasets in terms of most of the items reported in Table 2. This had an impact upon determining whether the compiled datasets could be pooled for the meta-analyses reported in Figures 1-3. The dataset # 17, extracted from the trial by Kilpatrick et al. [1996], could not be pooled with any of the other datasets because fissure sealants were placed on permanent premolar teeth, as opposed to permanent molar teeth in all of the other datasets. In addition, the reporting times, patient characteristics, methods of application and other variables also differed and these factors were considered during compilation of the 19 datasets extracted from the six accepted trials (Table 2).

*Pooling of data for meta-analyses*

Only datasets that were considered clinically and methodologically homogenous were pooled for meta-analysis. The unit of interest was the tooth and the number of caries- free teeth (n) at the end of each time interval (6, 12 and 24 months) was compared against the total number of evaluated teeth (N). Datasets from three trials [Raadal et al., 1996; Winkler et al., 1996; Oliveira et al., 2008] were pooled for the 6-month evaluation (Figure 1). The pooled data covered 491 teeth (227 resin-modified glass-ionomer sealants and 264 resin sealants). The pooled relative risk (0.98, 95% CI 0.95-1.00; p = 0.08) suggests that both materials had an equivalent caries-preventive effect at 6 months post placement. Datasets from four trials [Raadal et al., 1996; Winkler et al., 1996; Pardi et al., 2005; Oliveira et al., 2008] were pooled for the 12-month evaluation (Figure 2). The pooled data covered 719 teeth (341 resin-modified glass-ionomer sealants and 378 resin sealants) and the pooled relative risk (1.00, 95% CI 0.96-1.04, p = 0.99) also implied equivalent caries-preventive effects at 12 months post placement. Similar results were obtained for the 24-month evaluation (Figure 3, RR 1.01, 95% CI 0.84-1.21, p = 0.91). Only one dataset (#16) was available for comparison at 36 months [Raadal et al., 1996]: thus no meta-analysis was attempted. The results (RR 0.93, 95% CI 0.88-0.97, p = 0.002) indicate that teeth sealed with resin-based fissure sealants have a 7% higher chance than those sealed with RM-GIC sealants, of remaining caries-free after 36 months.

A further seven datasets could also not be included in the meta-analyses, due to aspects related to clinical and methodological heterogeneity (Table 3). Of these, none showed any difference in caries absence between teeth sealed with RM-GIC or resin-based materials after 1-, 6-, 12-, 24- or 27 months.

*Discussion and Conclusion*

This systematic review with meta-analyses sought to quantitatively appraise the current evidence regarding the caries-preventing effect of RM-GIC fissure sealants in comparison to that of resin-based fissure sealants over varying time intervals. Of the more than 200 articles identified through the search strategy for this review, only six were included. The quality assessment of these trials (Table 1) warrants that the data be treated with caution, owing to the increased risk of bias. All of the included papers scored “B” (unclear) for an important quality item dealing with two key aspects of selection bias: randomized sequence allocation and allocation concealment. Such bias or systematic error may affect studies by causing either an over- or an under-estimation of the treatment effect of an investigated clinical procedure. Overestimation of such effect has been observed to be the most common

[Chalmers et al., 1977]. 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. Since all trials accepted in this review did not include or report on allocation concealment, their results need to be interpreted with caution. Thus, for systematic reviews, readers should note that while in terms of the hierarchy of evidence [Sprague et al., 2008] this form of study design is rated the highest, the level of evidence contained in such a review is only as high as that of the studies, which it covers.

Meta-analysis of homogeneous datasets at three time intervals (Figures 1-3) showed no statistical differences between RM-GIC and resin-based fissure sealants, in caries absence. The results of seven further heterogeneous datasets (#01, 03, 05, 07, 11, 12, and 17) are in line with the meta-analysis findings (Table 3). At 36 months, the resin-based sealant performed, by a margin of 7%, significantly better (RR 0.93, 95% CI 0.88-0.97, p = 0.002) than RM-GIC. However, caution is warranted as the data were drawn from a study with a high risk of bias [Raadal et al., 1996].

Previous publications [Forss and Halme, 1998; Mejáre et al., 2003; Ahovuo-Saloranta et al., 2008] have highlighted a number of factors that could potentially affect the caries-preventive effect of fissure sealants. Only some of the trials reported on these factors. They include: (a) baseline caries prevalence in the study population (none of the included trials reported on this); (b) number of applications of sealant material – single or repeated (all trials reported single application); (c) type of sealant material (all included trials); (d) follow-up period (all included trials); (e) type of tooth and location in jaw (reported only by Raadal et al., 1996); (f) fluoride content of drinking water (none); (g) operator factors (one trial [Oliveira et al., 2008]); (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 RM-GIC trials, should be noted, as these sealants are effective long after being regarded as “lost” or “partially lost” [Songpaisan et al., 1995, Williams et al., 1996]. It has been hypothesized that although the GIC sealants appear clinically as “partially” or “totally” lost, the opening of the fissures remains sealed [Oong et al., 2008]. In addition, the effectiveness of GIC has been attributed to the isolation of bacteria from nutrients in sealed lesions; the release of fluoride into the dentin or a combination of both factors [Oong et al. 2008].

In contrast, resin-based sealants have been shown to lose almost all of their protective effect once their retention is lost [Beiruti et al., 2006]. Hence, the measured outcome of interest when comparing RM-GIC and resin-based sealants should be caries incidence/increment or caries presence/absence rather than retention of the sealant material.

The meta-analyses presented in Figures 1-3 used a random effects model. This model is recommended over a fixed-effect model when heterogeneity is suspected; even after qualitative assessment for clinical and methodological heterogeneity suggests that the data from different trials could be pooled together [Higgins et al., 2003]. This usually is the case in trials having large variations in the size and direction of the treatment effect. After the pooled result is obtained and reflected in the form of a forest plot (Figures 1-3), statistical heterogeneity needs to be assessed [Higgins et al., 2003]. If this occurs (usually reflected as a high $I^2$ value above 75%) and a significant p-value below 0.10), then a suitable explanation is required as to whether genuine clinical or methodological differences exist between the pooled datasets. In the case of Figure 3, the statistical heterogeneity ($I^2$ = 85.1%, p = 0.009) can be explained by the inconsistency in the observed treatment effect across the two datasets. The Raadal et al. [1996] trial found slightly in favor of the resin-based sealant, whilst the trial by Pardi et al. [2005] favored RM-GIC sealants for the same outcome (Figure 3). For Figure 1, the test for heterogeneity did not apply, as the pooled result comprised results from only one estimable dataset. The result of a dataset is regarded as 'not estimable' when data (n/N) from the test- and the control group are identical, with a subsequent Relative Risk (RR) of 1.00. Figure 2 reflects a moderate $I^2$ value (48.3%), with a p-value of 0.12 that suggests little variation in the size and direction of the treatment effect across pooled datasets.

In conclusion, this systematic review with meta-analysis found no evidence that either material was superior to the other in preventing dental caries. Therefore, both materials appear to be equally suitable for clinical application as fissure sealants after a period of up to 2 years. However, the poor quality of the included trials warrants that further high-quality randomized control trials are needed to obtain conclusive evidence of equivalence or difference in caries prevention. Further trials should also investigate the long-term caries preventive effect of both materials beyond the period of 2 years. Trial reporting should follow the CONSORT statement [Moher et al., 2001] and, particularly, include a clear description of how the randomized allocation of study subjects to test- and control groups was conducted; 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 such concealment was done. Reports should indicate, where possible, whether assessment of the treatment outcome was conducted by evaluators who were blinded to allocation of the study subjects into groups and also discuss details of any possible confounding factors with potential influence on the observed treatment effect.

**Acknowledgement**

The authors like to thank Dr Luciana Oliveira from the São Leopoldo Mandic Research Center, Campinas, São Paulo, Brazil for conducting the literature search in the Lusophone databases.

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**Table 1.** Quality assessment of included trials.

| Article | Selection bias | | Detection bias | Attrition bias |
|---|---|---|---|---|
| | Random allocation | Allocation concealment | Evaluator Blinding | Completeness to follow up |
| Oliveira et al., 2008 | B | B | D | A (start n=108; 6 months n=98; 12 months n=88) |
| Pardi et al., 2005 | B | B | D | A( at start 356 teeth; end n=329 |
| Smalles and Wong, 1999 | B | B | D | A (start n=14; end n=14) |
| Raadal et al., 1996 | B | B | D | A (start n=53; end n=53) |
| Kilpatrick et al., 1996 | B | B | D | A (start n=76; end n=58) |
| Winkler et al., 1996 | B | B | D | A (start n=50; 6 months n=43; 12 months n=40 |

.n = Number of patients.

**Table 2.** Characteristics of data sets (DS) with potential influence on study outcome – Part I.

| Article | DS | 2-arm study design | Test material (RM-GIC) | Control material (Resin-based) | Outcome measure | | Patient / Age, gender | Dentition | Type of tooth | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Aspect | Definition | | | | |
| Oliveira et al., 2008 | 01<br>02<br>03<br>04<br>05<br>06<br>07<br>08 | PG - I | Vitremer | Delton | Caries absence | No softness, no opacity, no etch on enamel | Age: mean 7.5 (SD 1.25) years, Range 5 – 10 years<br>Gender: no info | Permanent | 1st Molar teeth | 6 months<br>12 months |
| Pardi et al., 2005 | 09<br>10 | PG -I | Vitremer | Revolution | Caries absence | "No visible caries" | Age: 7-8 years<br>Gender: no info | Permanent | 1st Molar teeth | 12 months<br>24 months |
| Smales and Wong, 1999 | 11 | Not reported | K-512 (Fuji III LC) | Delton | Caries absence | No softness, no opacity, no etch on enamel | Age: mean 22 years, Range 15-27 years<br>Gender: 12 female/7 male | Permanent | No info | 24 months |
| Raadal et al., 1996 | 12<br>13<br>14<br>15<br>16 | SG | Vitrebond | C( | Caries absence | Caries diagnostic criteria by Möller, Grades "0" and "1" | Age: Range 5-7 and 11-13 years<br>Gender: 29 female/24 male | Permanent | 1st / 2nd Molars | 1 month<br>6 months<br>12 months<br>24 months<br>36 months |
| Kilpatrick et al., 1996 | 17 | PG-II | Vitrebond | Concise | Caries absence | "Caries absent" | Pediatric patients and older patients with learning difficulties or development delays | Permanent | Premolar teeth | 27 months |
| Winkler et al., 1996 | 18<br>19 | SG | Fuji II LC | Concise | Caries absence | No softness, no opacity, no etch on enamel | Age: Range 7-10 and years<br>Gender: no info | Permanent | 1st Molar teeth | 6 months<br>12 months |

PG-I = Parallel group design with patients as unit of investigation; PG-II = Parallel group design with sealed teeth as unit of investigation; SG = Splitmouth design; SD = Standard deviation.

**Table 2.** Characteristics of data sets (DS) with potential influence on study outcome – Part II.

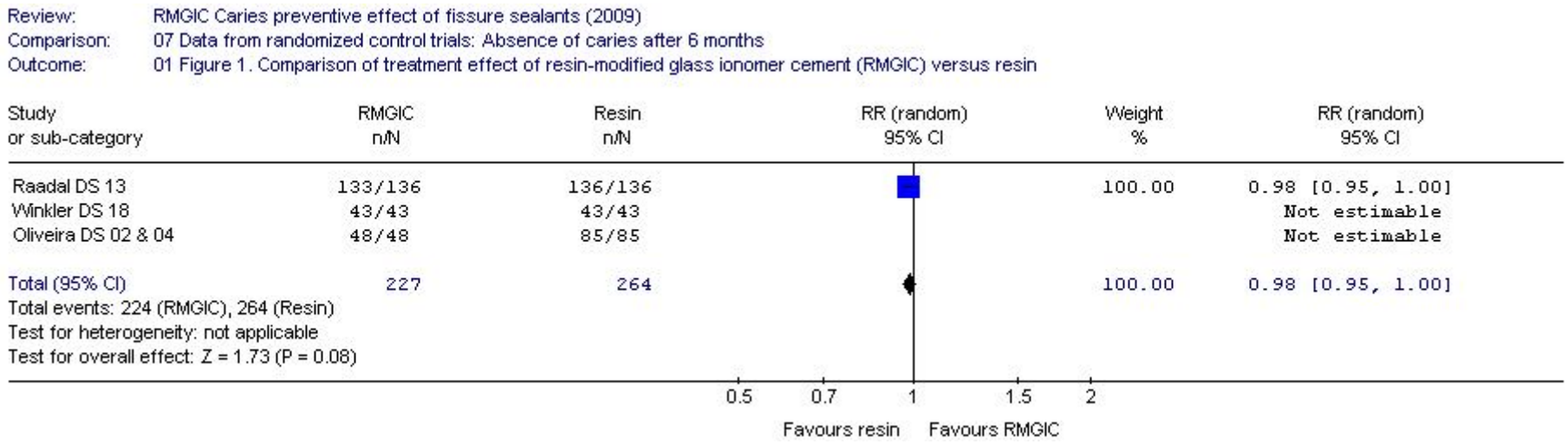
| Article | DS | Caries activity, risk or prevalence | | RM-GIC Powder/ liquid mixture (Ratio) | Moisture control | Material re-application | Process of outcome measurement | Presentation of results |
|---|---|---|---|---|---|---|---|---|
| Oliveira et al., 2008 | 01 | Groups matched per dmft/DMFT | No info | 0.25 : 1 | Delton applied under moisture control with rubber dam | No | Clinical examination | In percentages, number of teeth calculated by hand |
| | 02 | | | 1 : 1 | Delton applied under moisture control with rubber dam | | | |
| | 03 | | | 0.25 : 1 | Delton applied under moisture control with cotton wool rolls | | | |
| | 04 | | | 1 : 1 | Delton applied under moisture control with cotton wool rolls | | | |
| | 05 | | | 0.25 : 1 | Delton applied under moisture control with rubber dam | | | |
| | 06 | | | 1 : 1 | Delton applied under moisture control with rubber dam | | | |
| | 07 | | | 0.25 : 1 | Delton applied under moisture control with cotton wool rolls | | | |
| | 08 | | | 1 : 1 | Delton applied under moisture control with cotton wool rolls | | | |
| Pardi et al., 2005 | 09<br>10 | Caries free teeth | No info | 1 : 2 | Moisture control with cotton wool rolls | No | Clinical examination | Number of teeth reported |
| Smales and Wong, 1999 | 11 | No info | No info | No info | No info | No | Bitewing radiographs | Number of teeth reported |
| Raadal et al., 1996 | 12<br>13<br>14<br>15 | Caries free teeth | No info | No info | Moisture control with cotton wool rolls | No | Clinical examination, bitewing radiographs | Number of teeth reported |
| Kilpatrick et al., 1996 | 16<br>17 | Teeth with early carious lesions | No info | No info | Moisture control with cotton wool rolls or rubber dam | Yes | Clinical examination | Number of teeth reported |
| Winkler et al., 1996 | 18<br>19 | Caries free teeth | No info | No info | Moisture control with cotton wool rolls or rubber dam | No | Clinical examination | Number of teeth reported |

**Table 3.** Results of datasets not included in the meta-analyses.

| Article | DS | RM-GIC | | Resin | | RR | 95%CI | p-value |
|---|---|---|---|---|---|---|---|---|
| | | n | N | n | N | | | |
| Oliveira et al., 2008 | 01 | 51 | 51 | 34 | 34 | 1.00 | - | - |
| | 03 | 51 | 51 | 51 | 51 | 1.00 | - | - |
| | 05 | 51 | 51 | 34 | 34 | 1.00 | - | - |
| | 07 | 51 | 51 | 48 | 51 | 1.06 | 0.98, 1.15 | 0.13 |
| Smales and Wong, 1999 | 11 | 46 | 47 | 38 | 41 | 1.06 | 0.96, 1.16 | 0.26 |
| Raadal et al., 1996 | 12 | 136 | 136 | 136 | 136 | 1.00 | - | - |
| | 16 | 126 | 136 | 136 | 136 | 0.93 | 0.88, 0.97* | 0.002* |
| Kilpatrick et al., 1996 | 17 | 66 | 66 | 66 | 66 | 1.00 | - | - |

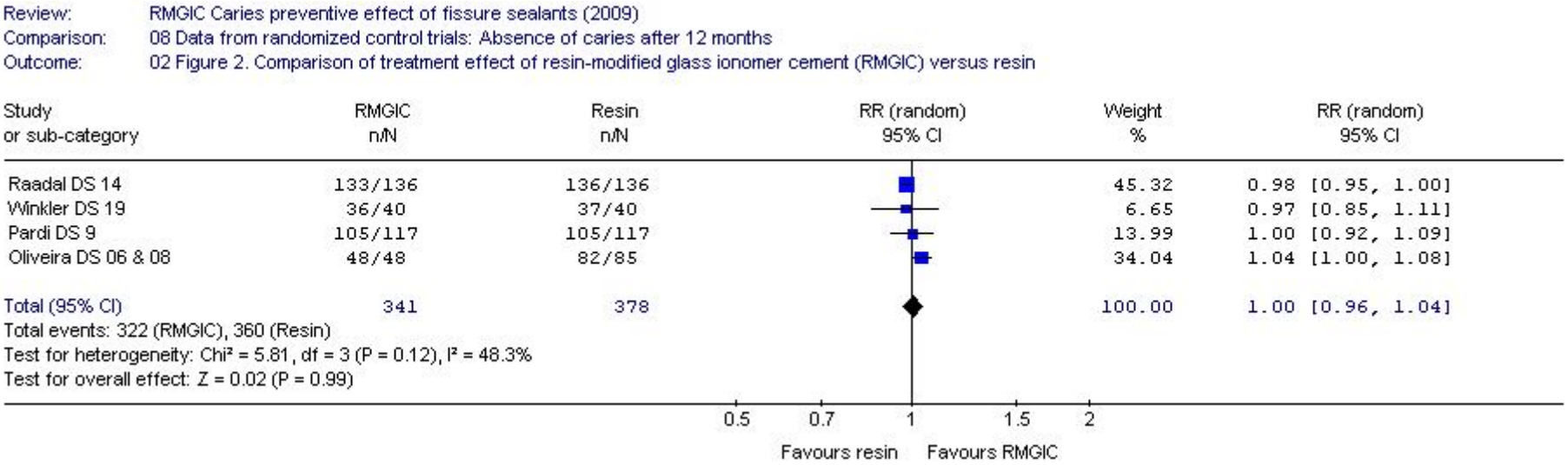
DS = Dataset number; RM-GIC = Resin-modified glass-ionomer cement; Resin = Resin-based material;
n = number of caries free sealed teeth; N = Total number of sealed teeth evaluated;RR = Relative risk; CI = Confidence interval;
* Statistically significant difference in favour of resin.

**Figure 1.** Meta-analysis results of treatment effect after 6 months



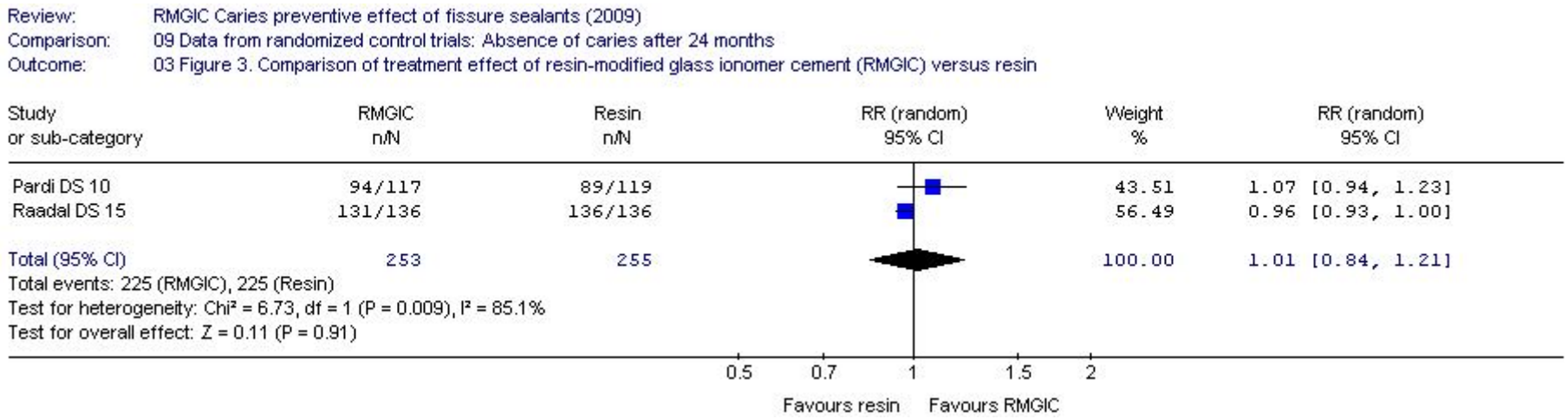

DS = Dataset; RMGIC = Resin-modified glass-ionomer cement; Resin = Resin-based material; n = number of caries free sealed teeth; N = Total number of sealed teeth evaluated; RR = Relative risk; CI = Confidence interval; Not estimable = Data of both groups identical (RR = 1.00).

**Figure 2.** Meta-analysis results of treatment effect after 12 months




DS = Dataset; RMGIC = Resin-modified glass-ionomer cement; Resin = Resin-based material; n = number of caries free sealed teeth; N = Total number of sealed teeth evaluated; RR = Relative risk; CI = Confidence interval.

**Figure 3.** Meta-analysis results of treatment effect after 24 months




DS = Dataset; RMGIC = Resin-modified glass-ionomer cement; Resin = Resin-based material; n = number of caries free sealed teeth; N = Total number of sealed teeth evaluated; RR = Relative risk; CI = Confidence interval.

DENTAL MATERIALS XXX (2010) XXX–XXX

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# Pulp response to resin-modified glass ionomer and calcium hydroxide cements in deep cavities: A quantitative systematic review

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ARTICLE INFO

*Article history:*
Received 2 October 2009
Received in revised form
1 December 2009
Accepted 16 March 2010
Available online xxx

*Keywords:*
Resin-modified glass ionomer cement
Calcium hydroxide
Pulp histology
Cavity lining
Meta-analysis
Systematic review
Indirect pulp capping

ABSTRACT

*Objective.* To quantitatively determine whether the pulp response to resin-modified glass ionomer cements placed in deep cavities differs from that generated by calcium hydroxide cement.

*Sources.* Five databases were searched for articles up to 31 May 2009.

*Study selection.* Inclusion criteria: titles/abstracts relevant to topic; published in English; two-arm longitudinal in vivo trial; containing computable dichotomous datasets for test and control group. Exclusion criteria: not all entered subjects accounted for at the end of the trial; subjects of both groups not followed up in the same way; trial on animal tissue.

*Data.* One randomized and five non-randomized control trials, reporting on 1 and 17 datasets, respectively, were accepted. From non-randomized trials, the Relative Risk with 95% Confidence Interval of 13 datasets showed no statistically significant differences ($p > 0.05$) and 4 showed a statistically significant difference between both materials. Meta-analysis of datasets from these trials found no difference between the inflammatory cell response after 30 days (0.87; 95%CI 0.59–1.26; $p = 0.46$); 38% less inflammatory cell response with calcium hydroxide after 60 days (0.62; 95%CI 0.50–0.76; $p < 0.00001$); higher number of intact odontoblasts beneath restored cavities after 381 days (0.56; 95%CI 0.38–0.82; $p = 0.0008$). The results from the randomized control trial (1.40; 95%CI 0.92–2.14; $p = 0.11$) indicated no difference in clinically identifiable pulp symptoms after two years. All trials showed limited internal validity due to selection bias.

*Conclusion.* No conclusive statement about the superiority of either type of material can yet be made. Further high-quality randomized control trials are needed.



## 1. Introduction

Management of deep carious lesions and the associated histopathological pulpal changes is important for caries management in operative dentistry. The pulp requires protection from further bacterial invasion from the carious process, thermal/electrical conduction (depending on the conductivity of the restorative material placed upon it) and chemical protection from the overlying restorative materials. An important function of a therapeutic lining material is to stimulate the pulp odontoblasts to lay down reparative dentin and pro-

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doi:10.1016/j.dental.2010.03.021

mote remineralization of existing dentine; thus encouraging the dentine-pulp complex and eventually, the carious lesion, to heal [1]. For many years, the material of choice beneath an amalgam restoration has been calcium hydroxide cement, placed as a thin layer on the cavity surface closest to the pulp. Much research has been carried out investigating its value in the above roles [2,3], indicating its relative merits along with its simplicity of use. However, concerns exist regarding the long-term solubility of calcium hydroxide cements, their lack of chemical or mechanical adhesiveness, and their potential accelerated degradation after being acid-etched during the adhesive bonding process, thus leading to a reduced area on the cavity surface for material adhesion [4]. With the development of the principles of minimally-invasive dentistry, the rationale of potentially leaving caries-affected dentine within the depths of a cavity and then sealing the lesion with an adhesive restorative material has been suggested [5]. As the intrinsic qualities of restorative materials have improved over the last decade, there is now a serious need to establish whether a separate "lining" stage is needed in the restorative process, as adhesive materials such as conventional glass ionomer cements (GIC) have been suggested to have biomimetic properties [6]. In contrast, resin-modified glass ionomer cements (RM-GIC) have been reported to be more harmful to the pulp [7]. This has been explained on basis of the HEMA (Hydroxyethylmethacrylate) content in RM-GIC, which may diffuse through dentine and cause inflammation of the pulp [8]. So far, the volume of scientific articles on the topic of RM-GIC-related biocompatibility and pulp response has been discussed, via a number of narrative reviews with conflicting findings [7-11]. However, no systematic review has been attempted.

Therefore, this systematic review sought to quantitatively answer the question as to whether resin-modified glass ionomer cements (RM-GIC) placed in deep cavities generate a pulp response different from that of calcium hydroxide cement as comparison.

## 2. Materials and Methods

### *2.1. 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 31 May 2009. The string of MeSH/text search terms, with boolean operators: "*Dental Pulp" OR "Dental Pulp Necrosis" OR "Dental Pulp Devitalizatio" AND "Glass Ionomer Cements AND "Calcium Hydroxide"*, was used to search all databases. From the search results, articles were selected for review on the basis of their compliance with the following inclusion criteria:

1. Titles/abstracts relevant to topic;

2. Published in English;
3. Two-arm (progressive) longitudinal clinical trial (randomized control trial, non-randomized clinical control trial);
4. Containing computable dichotomous data for both test- and control group.

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

*2.2. Article review*

Only articles that complied with the inclusion criteria were reviewed further. Full copies of articles were reviewed independently by two reviewers (VY and SM), to determine whether the exclusion criteria applied [12]:

10. Not all entered subjects accounted for at the end of the trial;
11. Subjects of both groups not followed up the same way;
12. Trial conducted on animal tissue.

Where several articles had reported on the same trial over similar time periods, the article covering the trial most comprehensively in accordance with the exclusion criteria was accepted. Disagreements between reviewers were resolved by discussion and consensus.

*2.3. Data extraction from accepted trials*

Outcome measures related to pulp tissue response to cavity restorations with either material were assessed. 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. 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.

*2.4. Quality of studies*

The quality assessment of the accepted trials followed Cochrane guidelines [13] and 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. The following criteria were used in the scoring of randomized control trials (RCT) and non-randomized clinical control trials:

Randomized control trials (RCT):
(1) Generation of randomization sequence (allocation), recorded as:
(A) Adequate - e.g. computer-generated random numbers, table of random numbers;
(B) Unclear – not reported;
(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 – not reported;
(C) Inadequate - e.g. open allocation schedule, unsealed or non-opaque envelopes.

(3) Blind outcome assessment, recorded as:
(A) Adequate - Yes;
(B) Unclear – No information given whether assessment was blinded;
(C) Inadequate - Reported in text that assessment was not blinded;
(D) Not possible.

Non-randomized clinical control trials:
(1) Test- and control groups matching
(A) Adequate – Clear statement in text that both groups were matched;
(B) Unclear – No statement in text that both groups were matched;
(C) Inadequate – Baseline data differ significantly between groups ($p < 0.05$).

(2) Accounting of confounders and/or statistical adjustment
(A) Adequate – Confounders are accounted for and have either no significant impact or are statistically adjusted, e.g. using analysis of co-variances (ANCOVA);
(B) Unclear – No information about confounders reported;
(C) Inadequate - Confounders with significant impact are accounted for but have not been statistically adjusted.

(3) Blind outcome assessment, recorded as:
(A) Adequate - Yes;
(B) Unclear – No information given as to whether assessment was blinded;

(C) Inadequate - Reported in text that assessment was not blinded;
(D) Not possible.

Clinical control trials lacking randomization were considered to have lower internal validity and evidence strength than RCTs [14].

*2.5. Statistical Analysis*

A random effects model in RevMan Version 4.2 statistical software, developed 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). Datasets extracted from the accepted articles were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines [15]. Datasets were considered to be heterogeneous if they differed regarding: study type, outcome measure aspect and definition, the pulp proximity, cavity floor size, exposure duration, dentition type, cavity type and location, caries presence or absence and type of pulp assessment method. The percentage of total variations across datasets ($I^2$) was used in assessing statistical heterogeneity [16,17]. Only identified homogeneous datasets were pooled for meta-analysis. Pooled datasets were assigned a Mantel-Haenszel weight directly proportionate to their sample sizes.

## 3. Results

An initial search of PubMed resulted in 31 articles, 11 of which [18-28] complied with the inclusion criteria and were selected for review. During the subsequent search of the four other databases, no further articles were identified as suitable for selection. From the 11 selected articles, five were excluded, as these covered animal trials [20,21,23,27,28]. One randomized control trial [19] and five non-randomized clinical control trials were accepted for data extraction [18,22,24-26]. Assessment of histomorphometric outcome measures in the non-randomized clinical control trials was possible, as this included extraction of the studied teeth for orthodontic reasons. Table 1 provides information about the quality aspects assessed for the accepted RCT and for the clinical control trials. Owing to the visible material characteristics of the compared materials, (resin-modified glass ionomer and calcium hydroxide), blinding of outcome assessment was rated “D” (Not possible) in all trials. For the RCT [19], random allocation of subjects and concealment of random allocation were rated “B” (unclear), since no information about both was given in the text. Group matching and

confounder assessment were rated as “B” (unclear) in all clinical control trials [18,22,24-26], owing to lack of information in the text.

From the six accepted trials [18,19,22,24-26], 18 separate computable dichotomous datasets were extracted. The outcome measures of these datasets related to pulp response were: (a) histomorphometric outcomes measures: inflammatory cell response, hard tissue formation, soft tissue organization, bacteria leakage, odontoblast changes, intact odontoblast numbers; as well as (b) lack of clinically identifiable pulp symptoms. The main characteristics of the datasets are described in Table 2. The results of two trials [24,26], for both test- and control groups, were calculated by the reviewers (SM and VY), using the percentages of totals reported in the text. The Relative Risk (RR) with 95% Confidence Interval (CI) of most datasets showed no statistically significant differences ($p > 0.05$) between the two materials (Table 3). Four of the 18 datasets showed a significant difference between these materials: a 39% lower inflammatory cell response with calcium hydroxide (Dataset #05: RR 0.61; 95%CI 0.50 – 0.76; $p < 0.00001$) [25]; a larger area of reactionary hard tissue repair with calcium hydroxide (Dataset #17: RR 0.34; 95%CI 0.22 – 0.52; $p = 0.003$) [24]; a higher number of intact odontoblasts beneath restored cavities with a remaining dentin thickness (RDT) below 0.05 mm with calcium hydroxide after 381 days (Dataset #15: RR 0.45; 95%CI 0.32 – 0.64; $p = 0.008$ and #16: RR 0.66; 95%CI 0.53 – 0.84; $p = 0.04$) [24,26]. All four datasets were extracted from non-randomized clinical control trials.

Clinical and methodological heterogeneity between most datasets was observed (Table 2). For this reason meta-analysis was conducted for only three groups of two datasets each. The results of the 3 groups were:

(i) No difference between the inflammatory cell response after 30 days (Pooled datasets #01 and #10: RR 0.87; 95%CI 0.59 – 1.26; $p = 0.46$);

(ii) A 38% lower inflammatory cell response with calcium hydroxide after 60 days (Pooled datasets #05 and #13: RR 0.62; 95%CI 0.50 – 0.76; $p < 0.00001$);

(iii) A higher number of intact odontoblasts beneath restored cavities with a remaining dentin thickness (RDT) below 0.05 mm with calcium hydroxide after 381 days (Pooled datasets #15 and #16: RR 0.56; 95%CI 0.38 – 0.82; $p = 0.0008$).

Despite clinical and methodological similarities between datasets #15 and #16, a high statistical heterogeneity ($I^2 = 72.3\%$) was observed. This was due to a variation in the size and direction of the treatment effect. No statistical heterogeneity ($I^2 = 0\%$) was found in the other pooled datasets. All datasets pooled for meta-analysis originated from non-randomized

clinical control trials. The results from one dataset (#18: RR 1.40; 95%CI 0.92 – 2.14; $p$ = 0.11), originating from the only randomized control trial, indicated no difference between calcium hydroxide and RM-GIC, in clinical and radiologically identifiable pulp symptoms after two years [19].

## 4. Discussion

Quantitative systematic reviews are more valuable than qualitative synthesis in that they provide opportunities for detecting statistically significant ($p < 0.05$) treatment effects and for improving estimation of such effects by quantifying their outcomes [29]. Quantitative collation of clinical information from separate trials covering a particular treatment approach and comparison of materials used provides a more objective assessment of a systematic analysis of the currently available evidence.

In this case, the pulpal response to calcium hydroxide was compared with the response to RM-GIC linings. Often, owing to aspects of internal validity, restrictive inclusion criteria, such as the acceptance of randomized control trials (RCT) only, are used in order to strengthen the internal validity of the systematic review results. There is a risk, however, that available data will be excluded from the review, as they may fall outside the inclusion criteria; thus weakening the overall informative value of the systematic review. In this systematic review the reviewed data included the results of 18 datasets, only one of which originated from an RCT [19]. In order to provide more data for assessment, five non-randomized control trials, from which 17 datasets could be extracted, were also included. However, owing to the lack of randomization, the results of these datasets may have been influenced by selection bias.

Other aspects in the methodology of this review might further 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 35.5% of the initially identified 31 articles complied with the broad-based inclusion criteria. Moreover, no further eligible articles were identified in the other databases.

From the initial 11 included articles, five were not accepted because they reported on animal trials [20,21,23,27,28]. A structured checklist was used in assessing the quality of the accepted trials in relation to their internal validity. The assessment outcome indicated that the results of the trials were limited by bias (Table 1). Such bias or systematic error may affect studies by causing either an over- or an under-estimation of the treatment effect of an investigated clinical procedure. Overestimation has been observed to be the most common [30]. Egger et al. (2003) reported a treatment effect overestimation of between 21% and 54%

due to selection bias, solely caused by lack of allocation concealment during the randomization process [31]. As no trials accepted in this review reported on allocation concealment, their results need to be interpreted with caution.

The characteristics of the studies included in the systematic review are presented in Table 2. It is evident, that neither the type of RM-GIC nor the age range (9-32 years) of patients affected the outcome data. The remaining dentine thickness (ranging from 0.83-2.5mm) did appear to have an effect on the histological response. Aspects regarding the clinical handling of the cavity preparation and the material used could also not be easily standardized and, therefore, contributed to the heterogeneity observed in the outcomes reported.

Quantitative assessment, through calculation of the relative risk (RR) with 95% confidence interval of the 18 dichotomous datasets, indicated that most datasets [24-26] showed no statistical differences between the histological pulp responses beneath either tested material ($p > 0.05$). Four datasets indicated a significant difference in favor of calcium hydroxide with respect to reduced inflammatory cells, increased hard tissue repair and increased numbers of odontoblasts over a period of 381 days. As these datasets are based on a larger sample size, they may have provided a more objective estimation of the true treatment effect. It has been suggested that trials with small sample size, inadequate random sequence allocation, and inadequate allocation concealment generate higher overestimation of the observed treatment effect in the test group than do trials having larger sample size but the same internal validity [32]**.** For this reason, the treatment effect of RM-GIC in the datasets showing no difference between the materials may have been overestimated; not only because of the lack of adequate random sequence allocation and allocation concealment, but also because of their very small sample size (Table 3).

In line with the histomorphometric results of the datasets (#01-04; #06-14) with small sample size, the clinical and radiological result of the single randomized control trial [19] appears to confirm no difference between calcium hydroxide cement and RM-GIC (Table 3). However, owing to unclear random allocation and allocation concealment in this trial, these results may also be questioned on the basis of potential influence of selection bias (Table 1).

The weight of evidence of a systematic review is only as good as the quality of the included trials. In this review, the risk of bias in the included trials was found to be high, which implies that the results of the pooled and individual data should be interpreted with caution. At best, the pooled data for this review provide evidence of the direction (does not favor/ favors test material) and size of the treatment effects which, for most of the outcomes, were shown to be equivalent (not-significant). In addition, this systematic review provides an overview of

the current evidence regarding the pulp response towards RM-GIC versus calcium hydroxide in deep cavities.

Against this background, recommendations concerning the methodology of future trials can be made: future trials should be based on a randomized controlled study design and their reporting should follow the recommendations of the CONSORT statement. Every trial should, 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 [33].

## 5. Conclusion

This systematic review identified six randomized- and non-randomized-control clinical human trials from which 18 separate datasets with relevance to the review question could be extracted. When assessing pulpal inflammatory cell response, hard/soft tissue repair, bacterial leakage and changes in odontoblast numbers beneath the two tested materials, most datasets showed no statistically significant difference between calcium hydroxide and RM-GIC. However, an overall conclusive statement cannot yet be made, as all the included studies exhibited limited internal validity and thus had a high risk of bias. Further high-quality randomized control trials are therefore needed. It is recommended that reporting of such trials follow the CONSORT statement.

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**Table 1.** Quality assessment of accepted trials

| **Randomized control trials** | | | |
|---|---|---|---|
| Article | Selection bias<br>Random allocation | Allocation concealment | Detection bias<br>Evaluator blinding |
| Marchi JJ et al. (2006) [19] | B | B | D |
| **Non-randomized control trials** | | | |
| Article | Selection bias<br>Groups are matched | Performance bias<br>Confounders accounted for | Detection bias<br>Evaluator blinding |
| Costa CAS et al. (2003) [22] | B | B | D |
| Murray PE et al. (2001) [25] | B | B | D |
| Mousavinasab M et al. (2008) [18] | B | B | D |
| About I et al. (2001) [26] | B | B | D |
| Murray PE et al. (2002) [24] | B | B | D |

**Table 2**. Characteristics of data sets (DS) with potential influence on study outcome – Part I

(next page)

| Article | DS | Type of study | Test material RM-GIC | Control material $Ca(OH)_2$ | Outcome measure | | Patient / Age | Proximity to the pulp | Size of cavity floor | Duration of exposure |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Aspect | Definition | | | | |
| Costa CAS et al. (2003) [22] | 01 | Non-randomized clinical control trial | Vitrebond | Dycal | Inflammatory cell response | None of few scattered inflammatory cells present in the pulp area, characteristic to normal pulp tissue | Human subjects – age 12-19 years (mean = 15 years) | 2.5 mm cavity depth | 1.5 mm width of cavity floor | 30 days |
| | 02 | | | | Hard tissue formation | Absence | | | | |
| | 03 | | | | Soft tissue organisation | Characteristic to normal soft tissue | | | | |
| | 04 | | | | Bacteria leakage | Absence | | | | |
| Murray PE et al. (2001) [25] | 05 | Non-randomized clinical control trial | Vitrebond | Dycal | Inflammatory cell response | Absence of inflammatory cells as defined by FDI and ISO | Human subjects – age 9-25 years (mean = 12.54 years) | Remaining dentin thickness (RDT) 0.04-2.993 mm (mean 0.9 mm) | Width 0.99 – 3.17 mm (mean 1.86 mm) | Mean 68.45 days |
| | 06 | | | | Odontoblast changes | Remarkable changes of odontoblast cells absent | | | | |
| | 07 | | | | Inflammatory cell response | None of few scattered inflammatory cells present in the pulp area, characteristic to normal pulp tissue | | | | 7 days |
| | 08 | | | | Hard tissue formation | No abnormal or reparative dentin observed | | | | |
| | 09 | | | | Odontoblast changes | Remarkable changes of odontoblast cells absent | | | | |
| Mousavinasab M et al. (2008) [18] | 10 | Non-randomized clinical control Trial | Vivaglass | Dycal | Inflammatory cell response | None of few scattered inflammatory cells present in the pulp area, characteristic to normal pulp tissue | Human subjects – age 13-32 years (mean 18 years) | Excavation until red feature of pulp was observed | No info | 30 days |
| | 11 | | | | Hard tissue formation | No abnormal or reparative dentin observed | | | | |
| | 12 | | | | Odontoblast changes | Remarkable changes of odontoblast cells absent | | | | |
| | 13 | | | | Inflammatory cell response | None of few scattered inflammatory cells present in the pulp area, characteristic to normal pulp tissue | | | | 60 days |
| | 14 | | | | Hard tissue formation | No abnormal or reparative dentin observed | | | | |
| About I et al. (2001) [26] | 15 | Non-randomized clinical control trial | Vitrabond + Vitremer | Dycal | Intact odontoblast numbers per 2112 $\mu m^2$ of pulpal unit area | - | Human subjects – age 9-25 years | RDT 0.008-2.578 mm (mean = 0.833 mm) | Axial floor with 1.012-3.392 mm (mean = 1.943) | 381 days |
| Murray PE et al. (2002) [24] | 16 | Non-randomized clinical control Trial | Vitrabond + Vitremer | Dycal | Intact odontoblast numbers per 2112 $\mu m^2$ of pulpal unit area | - | Human subjects – age 9-17 years | RDT 0.058-2.933 (mean = 0.890) | Axial floor width 0.460 – 3.335 mm (mean= 1.895 mm) | 381 days |
| | 17 | | | | Hard tissue formation | No abnormal or reparative dentin observed | | | | |
| Marchi JJ et al. (2006) [19] | 18 | Randomized control trial | Vitremer | Dycal | Clinically successful outcome | Absence of spontaneous pain and/or sensitivity to pressure; absence of fistula and/or edema; absence of pathological mobility; absence of radiolucencies at the interradicular and/or periapical regions as determined by periapical radiographs; absence of increase of the periapical space; absence of dentin resorption due to exfoliation process. | Human subjects – age 4-9 years | Close proximity to pulp with great risk of exposure as determined by X-Ray | No info | 48 months |

**Table 2.** Characteristics of data sets (DS) with potential influence on study outcome – Part II

(next page)

| Article | DS | Dentition | Type /location of cavity | Caries | Cavity preparation | Material application | Assessment method |
|---|---|---|---|---|---|---|---|
| Costa CAS et al. (2003) [22] | 01<br>02<br>03<br>04 | Permanent | Class V – buccal surface, pre-molars | Caries free | - Rubber dam application<br>- Polishing with rubber cup+prophylaxis paste<br>- Teeth cleaned with 70% ethanol<br>- #1091 diamond bur with active tip limited to 2.5 mm with a resin stop + high speed copious water irrigation<br>- bur replacement after each 4 cavities<br>- axial well smoothed using bur at low speed and water cooling<br>- cavity rinsed and cleaned | Following manufactures recommendations + acid etch of enamel and lateral cavity walls | Histomorphometric analysis under light microscope |
| Murray PE et al. (2001) [25] | 05 | Permanent | Class V – buccal surface (1 mm above cemento-enamel junction) 2nd Maxillary molars Mandib. premolars | Caries free | - Drilling with 400 000 speed rpm | - Etching with 37% phosphoric acid | Histomorphometric analysis under light microscope |
| Mousavinasab M et al. (2008) [18] | 06<br>07<br>08<br>09<br>10<br>11<br>12<br>13<br>14 | Permanent | Class I – buccal surface, 1st premolars | Caries free | - 440 diameter point bur + high speed + copious water spray coolant<br>- New burs used after every 4 teeth<br>- Axial cavity wall excavated using carbide round bur+ low speed | - Light cured for 20 sec<br>- 2 layers of copalite added | Histomorphometric analysis under light microscope |
| About I et al. (2001) [26] | 15 | Permanent | Class V – buccal surface (1 mm above cemento-enamel junction) 1st / 2nd premolar | Caries free | - Drilling with 400 000 rpm + water spray cooling | 37% acid etch | Histomorphometric analysis under light microscope |
| Murray PE et al. (2002) [24] | 16<br>17 | Permanent | Class V – buccal surface (1 mm above cemento-enamel junction) 2nd premolars | Caries free | - With least possible pressure<br>- Preparation with 400 000 rpm + water spray coolant | - 37% phosphoric acid (60 sec)<br>- Rinsed for 30 sec with water<br>- Air dried for 20 sec | Histomorphometric analysis under light microscope |
| Marchi JJ et al. (2006) [19] | 18 | Primary | Class I, Molars | Deep caries, no signs of irreversible pulpitis (= spontaneous pain or sensibility o pressure) | - Removal of undermined enamel with carbide bur #245 at high speed + copious water/air spray<br>- Complete caries removal from lateral cavity walls with low speed burs #2-8<br>- Caries removal at risk of pulp exposure with #6 or 8 carbide bur with low speed<br>- Cavity rinsed with phosphate buffered saline (pH 7.4) | - 10% phosphoric acid gel for 15-18 sec<br>- Acid removal with water fro 15 sec<br>- Cavity dried with air+cotton pellet<br>- Application of primer + light cured for 20 sec | Clinical and X-Ray examination |

**Table 3.** Results of comparison between both material groups per dataset

| Pulp response / Outcome measure | DS | RM-GIC | | Calcium hydroxide | | RR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|---|
| | | n | N | n | N | | | |
| | | | | | | | | **Clinical control trials** |
| | 01 | 10 | 11 | 4 | 4 | 0.97 | 0.68 - 1.40 | 0.88 |
| | 05 | 51 | 100 | 83 | 100 | 0.61 | 0.50 - 0.76* | <0.00001* |
| Inflammatory cell response | 07 | 0 | 8 | 2 | 5 | 0.13 | 0.01 - 2.32 | 0.14 |
| | 10 | 3 | 5 | 5 | 6 | 0.72 | 0.32 - 1.60 | 0.40 |
| | 13 | 2 | 6 | 3 | 6 | 0.67 | 0.17 - 2.67 | 0.56 |
| | 02 | 11 | 11 | 4 | 4 | 1.00 | | - |
| | 08 | 8 | 8 | 5 | 5 | 1.00 | | - |
| Hard tissue formation | 11 | 2 | 5 | 3 | 6 | 0.80 | 0.21 - 3.05 | 0.74 |
| | 14 | 2 | 6 | 1 | 6 | 2.00 | 0.24 - 16.61 | 0.51 |
| | 17 | 14 | 43 | 19 | 19 | 0.34 | 0.22 - 0.52* | 0.003* |
| Soft tissue organisation | 03 | 10 | 11 | 4 | 4 | 0.97 | 0.68 - 1.40 | 0.88 |
| Bacteria leakage | 04 | 9 | 11 | 4 | 4 | 0.88 | 0.58 - 1.33 | 0.60 |
| | 06 | 3 | 8 | 2 | 5 | 0.94 | 0.23 - 3.79 | 0.93 |
| Odontoblast changes | 09 | 2 | 5 | 4 | 6 | 0.60 | 0.18 - 2.02 | 0.38 |
| | 12 | 2 | 6 | 1 | 6 | 2.00 | 0.24 - 16.61 | 0.51 |
| Intact odontoblast numbers | 15 | 19 | 43 | 19 | 19 | 0.45 | 0.32 - 0.64* | 0.008* |
| | 16 | 28 | 43 | 19 | 19 | 0.66 | 0.53 - 0.84* | 0.04* |
| | | | | | | | | **Randomized control trials** |
| Clinical/radiological success | 18 | 14 | 15 | 8 | 12 | 1.40 | 0.92 - 2.14 | 0.11 |

* Significant difference in favour of calcium hydroxide ($p<0.05$); DS = Dataset number; RM-GIC = Resin-modified glass ionomer cement; n = Number of teeth without pulp response; N = Total number of assessed teeth; RR = Relative Risk; CI = Confidence Interval.

Journal of Oral Science, Vol. 52, No. 3, 347-357, 2010

Original

# Demineralization of hard tooth tissue adjacent to resin-modified glass-ionomers and composite resins: a quantitative systematic review

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(Received 27 January and accepted 12 April 2010)

**Abstract: The purpose of this systematic review was to quantitatively find out whether resin-modified glass-ionomers (RM-GIC), in comparison to fluoride-containing composite resin and composite resin without fluoride, are associated with a more effective reduction of demineralization in hard tooth tissues under caries challenge. Five databases were systematically searched on clinical trials up to 6 April 2009. Article inclusion criteria: titles/abstracts relevant in answering the review question, published in English, two-arm (prospective) longitudinal trial; Exclusion criteria: not all included subjects accounted for at the end of the trial; subjects of both groups not followed up the same way; no randomized, quasi-randomized controlled study design for *in situ* and clinical trials; contains no computable continuous data. Quality assessment of the accepted *in situ* and clinical trials was performed. Data were extracted in the form of datasets, containing numbers of evaluated samples and mean result with standard deviation for both groups. Fifteen articles were selected for review. Two lacked computable data and were excluded; nine laboratory trials, three randomized *in situ* trials and one randomized control trial were accepted. From these, 97 continuous datasets were extracted. The evidence suggests that RM-GIC is associated with a higher reduction of demineralization in adjacent hard tooth tissue than composite resin without fluoride. No difference was found when RM-GIC was compared with fluoride-containing composite resin. RM-GIC showed efficacy in reducing demineralization. However, the internal validity of the current evidence is limited and further high-quality trials are needed. (J Oral Sci 52, 347-357, 2010)**

Keywords: demineralization; resin-modified glass-ionomer; composite resin; systematic review.

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## Introduction

An important part of caries management is encouraging hard tooth tissue remineralization (1). Ten Cate and van Duinen have shown, *in situ*, a hyper-remineralization effect in demineralized tooth tissues bordering glass-ionomer cement (GIC) type restorations (2). The significant remineralizing potential of GIC has been ascribed to the release of fluoride ions, facilitated by a hydrophilic environment (3). The remineralizing effect has been explained clinically (4) on the basis of its fluoride release into saliva, leading to an increase in the salivary fluoride content from 0.04 to 0.30 ppm after one year (5). However, the actual amount of fluoride in saliva required to have any effect on the mineral content of teeth is still unclear (6). Two recent systematic reviews with meta-analyses of RCTs have confirmed the caries-preventive effect of GIC on restoration margins (7) and on pits and fissures sealed with GIC (8). These findings have been established for conventional glass-ionomers (C-GIC) which set through an acid-base reaction between fluoroaluminosilicate glass powder and polyalkenoic acid liquid. However, C-GICs remain sensitive to water uptake and are lost in the first hours after setting, which led to the development of 'resin-modified' GICs (RM-GIC). In the set material, approximately 10% of RM-GIC is resin, usually hydroxyethyl-

methacrylate (HEMA) (9). Compared to other dental materials, such as non-fluoride-containing composite resins, laboratory research has shown a higher caries-resistance in bovine enamel located considerably distant from the margins of RM-GIC restorations (10). The *in situ* trial by Cenci et al. showed lower demineralization in both enamel and dentine around RM-GIC restorations (11) and the RCT by Pascotto et al. reported RM-GIC to be statistically more efficient than composite resin without fluoride, in reducing enamel demineralization around orthodontic brackets in clinic (12).

One systematic review without quantitative synthesis has been published regarding a secondary caries treatment effect of GIC restorations (13). This review included C-GIC and RM-GIC but did not distinguish differences between these types of material. A more recent review by Wiegand et al. included an overview covering the influence of RM-GIC on the demineralization of enamel and dentin (14). The results of this review indicate a reduction of carious lesions adjacent to RM-GIC in laboratory trials. However, no conclusive evidence was obtained from *in situ* and clinical trials. Although the review by Wiegand et al. included a systematic search strategy, it did not report on quality aspects related to the internal validity of the included trials and employed only a qualitative synthesis during the assessment of the trial results (14).

To date, no systematic review using quantitative synthesis, with or without meta-analysis, has been attempted on this topic. Thus, the aim of this systematic review was to quantitatively appraise the current evidence and to answer the review question about whether RM-GIC, in comparison to fluoride-containing composite resin and composite resin without fluoride, is associated with a higher reduction of demineralization in hard tooth tissues under caries challenge.

## 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 6 April 2009. The strings of MeSH/text search terms with boolean operators: (i) "*Tooth Remineralization OR Tooth Demineralization* AND *Glass Ionomer Cements AND Composite Resins" and* (ii) *"Dental Caries OR Dental Caries Susceptibility OR Root Caries AND Glass Ionomer Cements AND Composite Resins"* were used to search the databases. Articles were selected for review from the search results on the basis of their compliance with the inclusion criteria:

- Titles/abstracts relevant in answering the review question;

- Published in English;
- Two-arm (progressive) longitudinal trial;
- Focus on materials used for orthodontic and restorative application.

It was expected that only a few RCTs, would be found relating to this topic. The investigation of the mineral content of hard tooth tissue often requires evaluation of extracted teeth under laboratory conditions. For this reason, clinical trials in this field are challenged by ethical considerations and randomized, double-blind short-term *in situ* trials involving a small number of subjects appear to be the study design of choice. Moreover, laboratory trials may also provide additional valuable data on this topic. However, laboratory trials present weak evidence only, owing to the uncertainty of extrapolating their results to physiological effects in humans (15). Thus, it was decided to include laboratory, *in situ* and clinical trials in this review but to assess their outcomes separately in accordance with the evidence hierarchy (16). Where only a relevant title without a listed abstract was available, a full copy of the article was assessed for inclusion. References of the included articles were checked, in order to identify further trials suitable for inclusion.

*Article review*

Only articles that complied with the inclusion criteria were reviewed further. Full copies of articles were reviewed independently by two reviewers (VY and SM) in accordance with the exclusion criteria (15):

1. Not all entered subjects accounted for at the end of the trial;
2. Subjects of both groups not followed up the same way;
3. No randomized, quasi-randomized controlled study design for *in situ* and clinical trials;
4. Contains no computable continuous data for extraction (including the number of evaluated samples (n) and the mean result of the measured outcome with standard deviation (SD) for both material groups).

Where several articles had reported on the same trial over similar time periods, the article covering the trial most comprehensively in accordance with the exclusion criteria was accepted. Disagreements between reviewers were resolved by discussion and consensus.

*Quality of studies*

The quality assessment of the accepted *in situ* and clinical trials followed guidelines concerning the internal validity of clinical studies (17) and 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 through consensus. The following criteria were used:

(1) Generation of randomization sequence (allocation), recorded as:
(A) Adequate - e.g. computer-generated random numbers, table of random numbers,
(B) Unclear – not reported,
(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 – not reported;
(C) Inadequate - e.g. open allocation schedule, unsealed or non-opaque envelopes;

(3) Blind outcome assessment, recorded as:
(A) Adequate - Yes;
(B) Unclear – No information given as to whether assessment was blinded;
(C) Inadequate - Reported in text that assessment was not blinded;
(D) Not possible.

No quality assessment was done for accepted laboratory trials.

*Data extraction from accepted trials*

Outcome measures related to the mineral content of hard tooth tissue under caries challenge in contact with or adjacent to either material were assessed. Two reviewers (VY and SM) independently extracted data from the accepted articles. Individual continuous datasets for the control- and test group were extracted from each article. Where possible, missing data were calculated from information presented in the text or tables. Authors of articles were also contacted, in order to obtain missing information. Data were extracted in the form of datasets, each containing the number of evaluated samples (n) and the mean result of the measured outcome with standard deviation (SD) for both material groups. Disagreements between reviewers during data extraction were resolved through discussion and consensus.

*Statistical Analysis*

A random 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 mean difference (MD) with 95% confidence intervals (CI). From the accepted articles, extracted datasets were assessed for their clinical and methodological heterogeneity, following Cochrane guidelines (18). Datasets were considered heterogeneous if they differed in type of study (laboratory, *in situ* or clinical study type); whether the control material (composite resin) contained fluoride or not; aspect and definition of outcome measure; and type of hard tooth tissue. In addition, datasets within each study type were considered heterogeneous if they differed in the following aspects: (i) Laboratory study: initial exposure period; tissue distance from material (ii) *In situ*: saliva function; fluoride exposure from other sources; tissue distance from material; follow-up period (iii) Clinical study: saliva function; fluoride exposure from other sources; type of dentition; type of cavity; follow-up period. The percentage of total variations across datasets ($I^2$), together with its associated *p*-value (<0.10), was used in assessing statistical heterogeneity (19). Only identified homogeneous datasets were considered suitable for meta-analysis. All datasets were assigned a Mantel-Haenszel weight directly proportionate to their sample size.

**Results**

*Systematic literature search and review*

An initial search of PubMed, using both strings of MeSH/Text words (i. and ii.), resulted in 403 and 490 articles, respectively. Of these, 15 articles (10-12, 20-31) complied with the inclusion criteria and were selected for review. No further articles were identified for selection during the subsequent search of the other four databases, and during the reference check. From the 15 selected articles, two were excluded because they lacked computable data (20,21).

Thirteen articles; nine laboratory trials (10,22,23,26-31), three randomized *in situ* trials (11,24,25) and one RCT were accepted for further quality assessment and data extraction (12).

*Quality assessment and data extraction*

For all *in situ* and clinical trials random allocation of subjects, concealment of random allocation and evaluator blinding were rated “B” (unclear), since no information about these items was given in the text.

From the accepted laboratory, *in situ* and clinical trials, 51, 24 and 22, separate computable continuous datasets with relevance to the review question were extracted,

respectively. The outcome measures of these datasets related to the mineral content of hard tooth tissue were:

(A) Outcome measures that indicate the mineral loss after caries challenge:
    a. Laboratory trials: Volume% mineral loss; Knoop microhardness loss value; Reciprocal microhardness value, as well as the difference in surface microhardness before and after artificial caries challenge; Lesion area and Lesion area + lesion depth
    b. *In situ* trials: Mineral loss; Lesion depth; Increase of indention length

(B) Outcome measures that indicate the remaining mineral content after caries challenge:
    a. Laboratory trials: Mean density; Knoop microhardness
    b. Clinical trial: Knoop microhardness

The main characteristics of the extracted datasets are described in Table 1-3. Large clinical and methodological heterogeneity was observed between all datasets and therefore, no meta-analysis was attempted and statistical heterogeneity was not further investigated. Instead, the mean difference between the outcome effects of both material groups was calculated with 95% confidence intervals (MD; 95% CI) for each dataset. The results are presented per study design in Figures 1-3.

*Comparison of RM-GIC versus fluoride-containing composite resin*

The results of the laboratory trials (Figure 1) found no statistically significant mean difference (MD) between the mean density values of both materials (Dataset #04: MD 25.00; 95% CI –2.99, 52.99; $p = 0.08$) after a 30 min artificial caries challenge (28). The mean difference in the Knoop microhardness ranged between MD –11.30 (Dataset #32: 95% CI –37.45, 14.85; $p < 0.00001$; in favor of RM-GIC) and MD 127.40 (Dataset #24: 95% CI 85.53 – 169.27; $p = 0.40$) after 10 days of artificial caries challenge (29). One dataset (#97), reporting on the area of demineralized enamel in 100 µm distance from the materials, showed a statistically significant smaller demineralized area (in $\mu m^2$) around RM-GIC (MD -11635.99, 95% CI -13739.68, -9532.30, $p < 0.00001$) (31).

The results from one *in situ* trial (30) showed statistically non-significant mean differences (MD) between mineral loss values (datasets #62 and 64) and in lesion depth (datasets #63 and 65) of both types of material after four weeks (Figure 2). No results from clinical trials were identified during this review.

*Comparison of RM-GIC versus composite resin without fluoride*

The results of the laboratory trials (Figure 1) showed statistically significant ($p < 0.05$) lower mineral loss after artificial caries challenge in hard tissues adjacent to RM-GIC, with exception of four datasets (#17-20) that found no difference between the reciprocal microhardness values of the two material types (10,22,23,27). In addition, the mean density of hard tooth tissues adjacent to RM-GIC was statistically significantly higher than for composite resin after 30 minutes (Dataset #05) and after 3 months (Datasets #01-03) of artificial caries challenge (26,28). The laboratory results for the Knoop microhardness values (Datasets #33-41) showed a range of the mean difference between the two materials; from MD 14.90 (Dataset #41: 95% CI -41.55, 71.35; $p = 0.60$) to MD 158.20 (Dataset #33: 95% CI 125.60, 190.80; $p < 0.00001$; in favor of RM-GIC) (29). Datasets (#92-96) that measured the demineralized areas around both materials after artificial caries challenge found statistically significant smaller lesion areas surrounding RM-GIC (Figure 1) (30,31).

The results of *in situ* trials (Figure 2) indicate a statistically significant lower increase of indention length for RM-GIC after 70 days (25) and a mean difference in mineral loss after 14 days, ranging from MD -0.05 (Dataset #61: 95% CI –0.60, 0.50; $p = 0.87$) to a statistically significant MD –2.59 (Dataset #50: 95% CI –4.66, -0.52; $p = 0.01$) in favor of RM-GIC (11).

The results of the single RCT (Figure 3) indicate a mean difference in the Knoop microhardness of hard tooth tissue after 30 days, ranging from MD –3.60 (Datset #73: 95% CI –13.54, 6.34; $p = 0.48$) to a statistically significant MD 70.80 (Datset #88: 95% CI 50.75, 90.85; $p < 0.00001$) in favor of RM-GIC (12). The results of this trial were obtained in the laboratory after extraction of the teeth for orthodontic reasons and with the informed consent of the patients (12).

*Factors with influence on measured outcomes*

The Knoop microhardness results of the laboratory trials (Figure 1) indicate that RM-GIC was found in favor when the point of measurement in the tissue was at shallow depth range, even if the RM-GIC was compared to fluoride- containing composite resin (datasets #24-26). Both materials were found to have an equal effect if the point of tissue measurement was chosen at deeper depth ranges, even when the RM-GIC was compared to composite resin without fluoride (datasets #36-41) and the tissue measurement was made at close proximity range to the material (datasets #27-31,37-40).

In ten of the extracted datasets, fluoride exposure from fluoridated toothpaste used during the trial period was reported: two laboratory and eight *in situ* datasets #94,95 that measured lesion area plus depth of lesion (Table 1) and #54-61, measuring mineral loss

(Table 2), respectively. The laboratory results favored RM-GIC (Figure 1) (30) and the *in situ* results showed no difference between for the compared materials (Figure 2) (11).

The measurements for two clinical datasets (#82,91 – Table 3) were taken at lingual tooth surfaces, where neither of the two materials was applied (Figure 3) (12).

**Discussion**

The aim of this systematic review was to quantitatively appraise the current evidence, in order to answer the review question as to whether RM-GIC is associated with a higher reduction of demineralization in hard tooth tissues under caries challenge than fluoride-containing composite resin and composite resin without fluoride. Quantitative synthesis with, or without, meta-analysis has a greater value than qualitative or narrative synthesis in providing the opportunity for detecting a statistically significant ($p < 0.05$) treatment effect and for improving estimation of such effect by quantifying its outcome (30). In quantitatively collating clinical information from separate trials in comparison to others, a more objective assessment of the currently available evidence is obtained. Often, owing to the heterogeneity of such trials, the outcome data are not directly comparable. Therefore, restrictive exclusion criteria are used to limit the variation and so strengthen the value of review results. There is a risk, however, that some informative data will be excluded from the review, as they may fall outside the inclusion criteria, thus weakening the overall informative value. In this systematic review, in order to increase the inclusion envelope, two-arm *in situ* and laboratory studies were accepted for data extraction. The authors recognized that ethical challenges exist for clinical trials that follow a RCT study design in attempting to elicit an answer to the review question. For that reason it was expected that only a few RCTs would be found and a randomized, double-blind *in situ* study design was accepted as an alternative. Besides one single RCT (12), only three *in situ* trials (11,24,25) were identified for review and the further inclusion of nine two-arm laboratory trials (10,22,23,26-31) was, therefore, accepted. The advantage of *in situ* and laboratory trials, in addressing the review question, is that both provide objectively assessed outcomes. Such outcomes are based on recognized laboratory procedures and include objective, instrument-based, measurements. This is especially the case for laboratory study designs where confounding clinical factors, such as fluoride exposure or oral hygiene measurements, are absent. It has been suggested that bias or systematic error caused by a lack of randomized sequence allocation, allocation concealment or evaluator blinding has less influence on objectively assessed outcomes trials (32). For that reason, no quality assessment concerning the internal validity of included laboratory trials was conducted in this review. However, laboratory trials, particularly those involving non-human tissue, carry the uncertainty of extrapolation of their results to physiological effects in humans. For this reason,

the laboratory results reported in this systematic review are regarded as weak evidence for clinical considerations trials (27).

The obvious limitation of the *in situ* trials, requiring participants to wear appliances containing enamel slabs that were analysed in a laboratory after exposure, was that the length of exposure was relatively short and the number of participants was limited (Table 2). It has been suggested that trials with small sample size, inadequate random sequence allocation and inadequate allocation concealment generate higher overestimation of the observed treatment effect in the test group than do trials with larger sample size trials (33). All three *in situ* trials scored "B" (unclear) for randomized sequence allocation, allocation concealment and evaluator blinding, owing to lack of information in the text (Table 1). Thus, the *in situ* results favoring RM-GIC above composite resin may have been overestimated; not only because of the lack of adequate random sequence allocation and allocation concealment, but also because of the very small sample sizes of the *in situ* trials.

Quality assessment of the single RCT (12) also indicated uncertainty about whether the randomized sequence allocation, allocation concealment and evaluator blinding was conducted effectively in order to control bias (Table 1). Such bias or systematic error may affect studies, causing either an over- or an under-estimation of the treatment effect of an investigated clinical procedure. Overestimation has been observed to be the most common (34). Kjaergard et al. reported a treatment effect overestimation of 48% caused by lack of random sequence allocation (33) and Egger et al. reported a treatment effect overestimation of 54% and 53% due to lack of allocation concealment and lack of evaluator blinding, respectively (35). As the single RCT (12) included in this review did not provide clear information about these items, its results may have been affected by selection and detection bias.

Despite the danger of bias influence on the accepted *in situ* (11,24,25) and clinical (12) results, the extent of such influence might be limited, as all outcomes were derived by objective (laboratory-based) assessment (32).

As in any systematic review, other aspects in the review methodology may also have contributed to limitations in its results, despite its comprehensive approach to systematically searching for relevant literature: (i) not all relevant publications were listed in the selected databases, (ii) not all relevant publications were published in the specified review language (English), (iii) not all relevant publications could be identified through using the constructed strings of search terms. Thus, some relevant studies may not have been identified.

Within the limitations of this quantitative systematic review, the results suggest that RM-GIC is associated with a higher reduction of demineralization during caries challenge of hard tooth tissue than non-fluoride containing composite resin. An equal effect between RM-

GIC and fluoride containing composite resin was identified in laboratory and *in situ* trials. Owing to the large clinical and methodological heterogeneity of the extracted data (Table 2), it was not possible to express quantitatively the differences of measured outcomes between the compared materials, as combined weighted mean difference (WMD), pooled by meta-analysis. Instead, results were reported quantitatively as individual mean differences (MD) with 95% confidence intervals per dataset (Figure 1-3). The presented mean differences (MD) were shown to depend on the proximity of the point of measurement to the material (11,12,23) and the depth of measurement from the tissue surface (29). Furthermore, no preventive effect of RM-GIC superior to that of non-fluoride containing composite resin was observed *in situ* if participants brushed their teeth with a fluoride-containing (1.1 µg F/g) toothpaste (11).

In conclusion: the evidence, established through this quantitative systematic review, suggests that RM-GIC are associated with a higher reduction of demineralization in adjacent hard tooth tissue under caries challenge than composite resin without fluoride. No difference was found when RM-GIC was compared with fluoride-containing composite resin *in situ*. The observation of such effect is dependent upon the point of measurement (proximity and depth) in the tissue, as well as upon the exposure of patients to other fluoride sources. The poor internal validity of the included trials warrants further high-quality (clinical or alternatively, *in situ*) RCTs; in order to answer the review question more conclusively. Reporting of such trials should follow the CONSORT statement (36) and, particularly, include a clear description of how the randomized allocation of study subjects to test- and control groups was done 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 such concealment was done. Reports should, where possible, indicate whether assessment of the treatment outcome was conducted by evaluators who were blind to allocation of the study subjects into groups and should also discuss details of any possible confounding factors with potential influence on the observed treatment effect.

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**Figure legends**

Figure 1 Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (Laboratory trials)
Abbreviations: DS = Dataset number; N = Number of analysed items; SD = Standard deviation; MD = Mean difference; CI = Confidence interval; Weight % = Mantel-Haenszel weight directly proportionate to sample size.

Figure. 2 Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (*In situ* trials)

Abbreviations: DS = Dataset number; N = Number of analysed items; SD = Standard deviation; MD = Mean difference; CI = Confidence interval; Weight % = Mantel-Haenszel weight directly proportionate to sample size.

Figure 3 Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (Clinical trial)

Abbreviations: DS = Dataset number; N = Number of analysed items; SD = Standard deviation; MD = Mean difference; CI = Confidence interval; Weight % = Mantel-Haenszel weight directly proportionate to sample size.

**Table 1**. Characteristics of datasets (DS) with potential influence on study outcome (laboratory trials)

| Article | DS | RM-GIC | Composite resin | | Outcome measure | | Hard tooth tissue | Artificial caries challenge | | | Lesion distance from material |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Type | With fluoride | Aspect | Definition | | Cycle / exposure | Demineralising solution content | Initial exposure period | |
| Lee et al. (26) | 01<br>02<br>03 | Vitremer | Z250 | No | Mean density | The mean of 25 values from 5 randomly selected on each of randomly selected slices of specimen. Density measured using Vworks software | E | Suspended in demineralising solution for 3 days, afterwards placed into artificial saliva at 37°C | 2.2 mM $Ca^{2+}$, 2.2 m$MPO_4^{3-}$, 50 mM acetic acid, pH 4.4 | After 3 months in arti-ficial saliva | Adjacent |
| Samuel and Rubinstein (28) | 04 | Vitremer | Helio -molar | Yes | Knoop micro-hardness (KHN) | Measure of the length of the major diagonal left by penetration of a diamond and calculated with Standard deviation | E | Placed in demineralising solution for 30 min, artificial saliva 3hrs, demineralising solution for 30 min | According to Serra (1992), pH 4.3 | 30 min | Opposite in neighboring tooth at contact point |
| | 05 | | Z100 | No | | | | | | | |
| Tantbirojn et al. (10) | 06<br>07<br>08<br>09<br>10<br>11 | Vitremer | Bis-GMA resin | No | Volume % mineral loss (ΔZ) | Knoop microhardness value converted into Vol% mineral = 4.3 √KHN+11.3 | BE | Placed in demineralising solution | 6% by weight hydroxyethylcellulose in 0.1 mol/l lactic acid, pH 5.1 | 3 weeks | 0.2 mm<br>0.5 mm<br>1.0 mm<br>2.0 mm<br>4.0 mm<br>7.0 mm |
| Hara et al. (22) | 12<br>13 | Fuji II LC | Z250 | No | Knoop micro-hardness-loss value | Difference between KHN before and after artificial caries challenge | RD | 1 hr in demineralising solution, 23 hrs in remineralising solution | 2.0 mM $Ca^{2+}$, 2.0 m$MPO_4^{3-}$, 74 mM acetic acid, pH 4.3 | 3 days | Adjacent |
| Hara et al. (23) | 14<br>15<br>16<br>17<br>18<br>19<br>20<br>21<br>22<br>23 | Fuji II LC Improved | Z250 | No | Reciprocal micro-hardness values | = 1 : KHN | BRD | 30 min in demineralising (DE) solution, 3 hrs in remineralising (RE) solution 30 min in DE solution, 20 hrs in RE solution | 2.0 mM $Ca^{2+}$, 2.0 m$MPO_4^{3-}$, 74 mM acetic acid, pH 4.3 | 2 days | 50 µm<br>100 µm<br>150 µm<br>300 µm<br>600 µm<br>900 µm<br>1200 µm<br>1500 µm<br>1800 µm<br>2100 µm |

**Table 1**. Characteristics of datasets (DS) with potential influence on study outcome (laboratory trials) - contd.

| Article | DS | RM-GIC | Composite resin | | Outcome measure | | Hard tooth tissue | Artificial caries challenge | | | Lesion distance from material | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Type | With fluoride | Aspect | Definition | | Cycle / exposure | Demineralizing solution content | Initial exposure period | | |
| Takeuti et al. (29) | 24 | Vitremer | Tetric Ceram | Yes | Knoop micro-hardness (KHN) | Measure of the length of the major diagonal left by penetration of a diamond and calculated with Standard deviation | E (prim) | 3 hrs in demineralising solution, 21 hrs in remineralising solution | 2.2 mM $Ca^{2+}$, 2.2 mM $PO_4^{3-}$, 50 mM acetic acid, pH 4.8 | 10 days | Depth: 100 µm | 50 µm |
| | 25 | | | | | | | | | | | 150 µm |
| | 26 | | | | | | | | | | | 250 µm |
| | 27 | | | | | | | | | | 200 µm | 50 µm |
| | 28 | | | | | | | | | | | 150 µm |
| | 29 | | | | | | | | | | | 250 µm |
| | 30 | | | | | | | | | | 300 µm | 50 µm |
| | 31 | | | | | | | | | | | 150 µm |
| | 32 | | | | | | | | | | | 250 µm |
| | 33 | | | | | | | | | | | 50 µm |
| | 34 | | | | | | | | | | 100 µm | 150 µm |
| | 35 | | | | | | | | | | | 250 µm |
| | 36 | | Z250 | No | | | | | | | 200 µm | 50 µm |
| | 37 | | | | | | | | | | | 150 µm |
| | 38 | | | | | | | | | | | 250 µm |
| | 39 | | | | | | | | | | 300 µm | 50 µm |
| | 40 | | | | | | | | | | | 150 µm |
| | 41 | | | | | | | | | | | 250 µm |
| Rodrigues et al. (27) | 42 | Vitremer | Z100 | No | Percentage change of surface micro-hardness ($\%SMH_C$) | Difference in surface microhardness before and after artificial caries challenge X 100% | BE | 6 hrs in demineralising solution, 18 hrs in remineralising solution | 2.0 mM $Ca^{2+}$, 2.0 mM $PO_4^{3-}$, 75 mM acetic acid, pH 4.7 | 5 days | | 150 µm |
| | 43 | | | | | | | | | | | 300 µm |
| | 44 | | | | | | | | | | | 450 µm |
| | 45 | | | | | | | | | | | 600 µm |
| Vorhies et al. (30) | 92 | Fuji Ortho LC | Trans-bond XT | No | Area plus depth of demineralized lesion around bracket | Average depth (in µm) and a standardized area of demineralization with 0.5 mm occlusogingival width (in $\mu m^2$) | E | 3x 20 min intervals for a total of 60 min at 7:00 a.m; 12:00 p.m.; 6:00 p.m. 3x 20 min intervals for a total of 60 min at 7:00 a.m; 12:00 p.m.; 6:00 p.m. + 2x daily with 1500 ppm fluoride dentifrice | 2.2 mM $Ca^{2+}$, 2.2 mM $PO_4^{3-}$, 50 mM acetic acid, pH 4.4 | 30 days | In contact with bonded brackets | |
| | 93 | Advance | | | | | | | | | | |
| | 94 | Fuji Ortho LC | | | | | | | | | | |
| | 95 | Advance | | | | | | | | | | |
| Wilson and Donly (31) | 96 | Fuji Ortho LC | Concise | No | Area of demineralized lesion around bracket | As measured 100 µm from residual bonding agent with a computerized imaging system (in $\mu m^2$) | E | Suspension into demineralising solution | 2.2 mM $Ca^{2+}$, 2.2 mM $PO_4^{3-}$, 50 mM acetic acid, pH 4.5 | 5 days | 100 µm from bonded bracket | |
| | 97 | | Light Bond | Yes | | | | | | | | |

RM-GIC = Resin-modified class ionomer cement; E = Enamel (permanent dentition), E (prim) = Enamel (primary dentition); BE = Bovine enamel; RD = Root dentin; BRD = Bovine root dentin

**Table 2**. Characteristics of data sets (DS) with potential influence on study outcome (*in situ* trials)

| Article | DS | RM-GIC | Composite resin | | Outcome measure | | Hard tooth tissue | Patients | | | | Hard tooth tissue distance from material | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Type | With fluoride | Aspect | Definition | | Age | Gender | Saliva function | Fluoride exposure from other sources | | |
| Cenci et al. (11) | 46 | Vitremer | Z250 | No | Mineral loss (vol% min x µm) | Mineral loss was quantified by transversal microradiography | E | 18-31 years | 7 male / 7 female | No info | No | 50 µm | 14 days |
| | 47 | | | | | | | | | | | 100 µm | |
| | 48 | | | | | | | | | | | 150 µm | |
| | 49 | | | | | | | | | | | 200 µm | |
| | 50 | | | | | | D | | | | | 50 µm | |
| | 51 | | | | | | | | | | | 100 µm | |
| | 52 | | | | | | | | | | | 150 µm | |
| | 53 | | | | | | | | | | | 200 µm | |
| | 54 | | | | | | | | | | | 50 µm | |
| | 55 | | | | | | E | | | | Fluoride containing dentifrice (1.1 µg F/g) | 100 µm | |
| | 56 | | | | | | | | | | | 150 µm | |
| | 57 | | | | | | | | | | | 200 µm | |
| | 58 | | | | | | | | | | | 50 µm | |
| | 59 | | | | | | D | | | | | 100 µm | |
| | 60 | | | | | | | | | | | 150 µm | |
| | 61 | | | | | | | | | | | 200 µm | |
| Kielbassa et al. (24) | 62 | Vitremer | Tetric Ceram | Yes | Mineral loss (vol% min x µm) | Calculated by integrating the difference between mineral content in sound (= 88 vol%) and demineralized enamel over the depth of lesion | E | 21-46 years | 4 male / 7 female | No info | Fluoridated water (0.3 ppm) | <100 µm | 4 weeks (storage in 10% sucrose solution during extra-oral periods) |
| | 63 | | | | Lesion depth (µm) | Distance from the original flat surface to the site of the lesion where mineral content was more than 95% of the mineral content in sound enamel. | | | | | | | |
| | 64 | | | | Mineral loss (vol% min x µm) | Calculated by integrating the difference between mineral content in sound (= 88 vol%) and demineralized enamel over the depth of lesion | | | | | | >500 µm | |
| | 65 | | | | Lesion depth (µm) | Distance from the original flat surface to the site of the lesion where mineral content was more than 95% of the mineral content in sound enamel. | | | | | | | |
| Kotsanos (25) | 66 | Vitremer | Pertac II | No | Micro-hardness (µm) | Increase of indentation length | BE | 60 and 75 years | 1 male / 1 female | Normal (UWS >15 ml/min) | No info | 0 | 70 days (No brushing, storage in 3% sucrose solution for 10 min x 4 per day) |
| | 67 | | | | | | | | | | | 0.4 mm | |
| | 68 | | | | | | | | | | | 0.8 mm | |
| | 69 | | | | | | | | | | | 12 mm | |

**Table 3** - Characteristics of data sets (DS) with potential influence on study outcome (clinical trial)

| Article | DS | Type of study | RM-GIC | Composite resin | | Outcome measure | | | Hard tooth tissue | Patients | | | Dentition / Type of tooth | Type of cavity | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Type | With fluoride | Aspect | Definition | | | Age | Saliva function | Fluoride exposure from other sources | | | |
| Pascotto et al. (12) | 70 | RCT | Fuji Ortho LC | Concise | No | Knoop-micro-hardness | Hardness increase due to reduction of demineralisation at different depths from enamel surface: For materials at different proximity, under, occlusal and cervical to the brackets on labial and lingual (control) surface: For materials and positions at depth of 10 µm: | 10 µm | E | 12-17 years | Normal flow rate (>1.0 ml/min); Buffer capacity (final pH 6 – 7) | Fluoridated piped water | Permanent premolars | Ortodo-dontic brackets | 30 days |
| | 71 | | | | | | | 20 µm | | | | | | | |
| | 72 | | | | | | | 30 µm | | | | | | | |
| | 73 | | | | | | | 50 µm | | | | | | | |
| | 74 | | | | | | | 70 µm | | | | | | | |
| | 75 | | | | | | | 90 µm | | | | | | | |
| | 76 | | | | | | | Oclusal / 0 µm | | | | | | | |
| | 77 | | | | | | | Occlusal / 100 µm | | | | | | | |
| | 78 | | | | | | | Occlusal / 200 µm | | | | | | | |
| | 79 | | | | | | | Cervical / 0 µm | | | | | | | |
| | 80 | | | | | | | Cervical / 100 µm | | | | | | | |
| | 81 | | | | | | | Cervical / 200 µm | | | | | | | |
| | 82 | | | | | | | Lingual | | | | | | | |
| | 83 | | | | | | | Underneath | | | | | | | |
| | 84 | | | | | | | Oclusal / 0 µm | | | | | | | |
| | 85 | | | | | | | Occlusal / 100 µm | | | | | | | |
| | 86 | | | | | | | Occlusal / 200 µm | | | | | | | |
| | 87 | | | | | | | Underneath | | | | | | | |
| | 88 | | | | | | | Cervical / 0 µm | | | | | | | |
| | 89 | | | | | | | Cervical / 100 µm | | | | | | | |
| | 90 | | | | | | | Cervical / 200 µm | | | | | | | |
| | 91 | | | | | | | Lingual | | | | | | | |

RM-GIC = Resin-modified glass ionomer cement; RCT = Randomized control trial with parallel group design; E = Enamel (permanent dentition).

**Figure 1.** Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (laboratory trials)

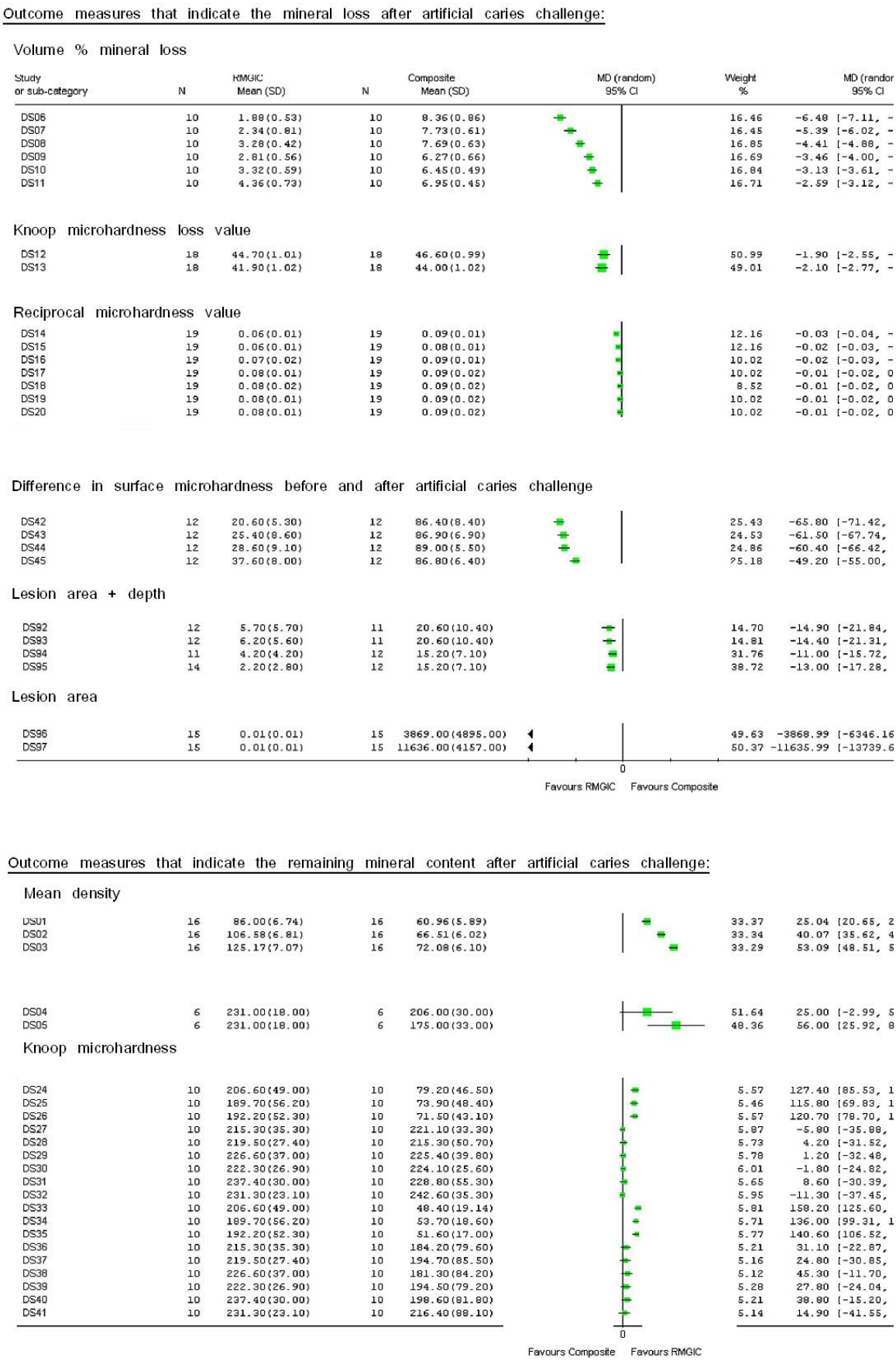


**Figure 2.** Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (*in situ* trials)

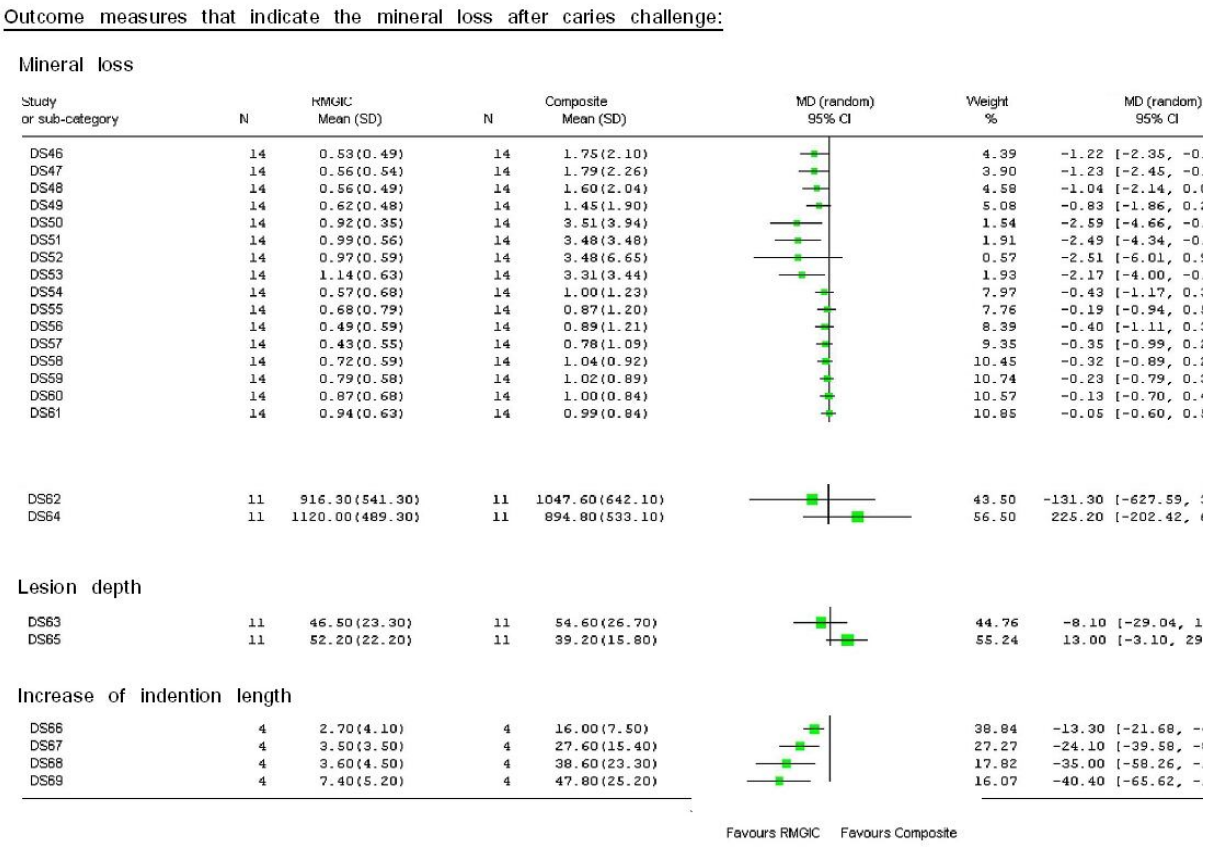
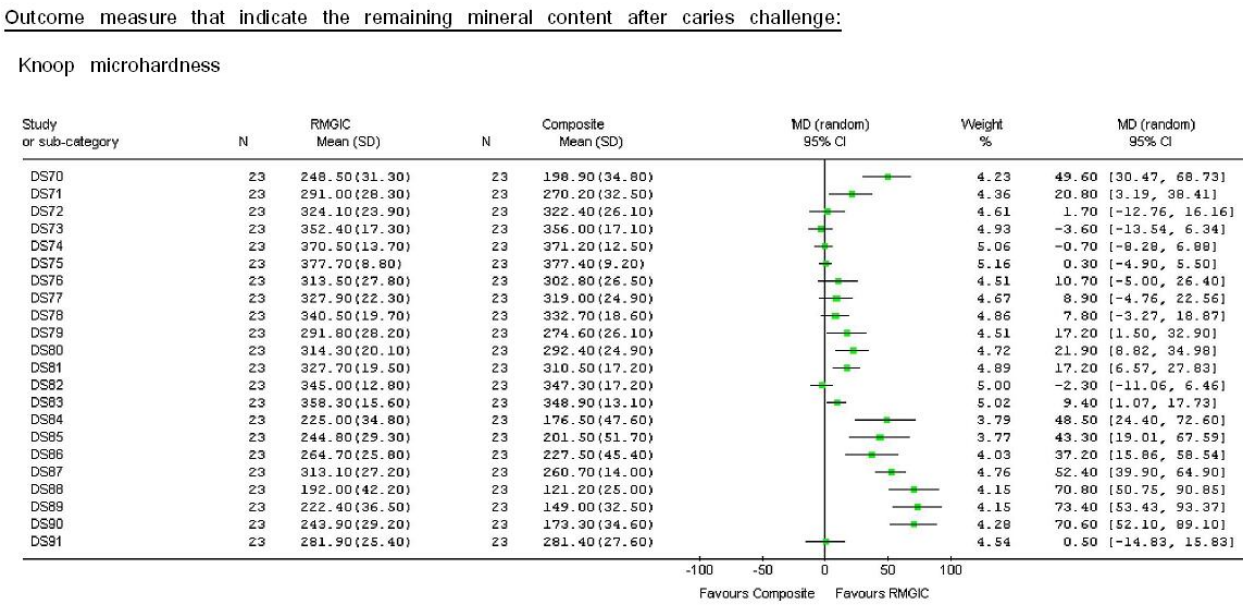


**Figure 3.** Demineralization of hard tooth tissue adjacent to RM-GIC or Composite resin (clinical trial)



Clin Oral Invest
DOI 10.1007/s00784-009-0335-8

REVIEW

# Atraumatic restorative treatment versus amalgam restoration longevity: a systematic review

**Steffen Mickenautsch · Veerasamy Yengopal · Avijit Banerjee**

Received: 25 May 2009 / Accepted: 3 August 2009


**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

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Published online: 18 August 2009

## 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 1$^{st}$ 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:

5. Titles/abstracts relevant to topic;
6. Published in English;

7. 2-arm longitudinal in-vivo trial;
8. 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]:

9. No random or quasi-random allocation of study subjects;
10. Not all entered subjects accounted for at the end of the trial;
11. 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

| Article | Selection bias | | Detection bias |
|---|---|---|---|
| | Random allocation | Allocation concealment | Evaluator blinding |
| Frencken JE et al. (2007) [23] | B | B | D |
| Frencken JE et al. (2006) [22] | B | B | D |
| Gao W et al. (2003) [24] | B | B | D |
| Yip H-K et al. (2002) [32] | B | B | D |
| Yu C et al. (2004) [34] | B | B | D |
| Honkala E et al. (2003) [4] | A | B | D |
| Taifour D et al. (2002) [30] | B | B | D |

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. $Chi^2$, degree of freedom (df) and the percentage of total variations across datasets ($I^2$) 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.

| Article | Dataset number | Study design | Evaluation criteria | Age (years) | Type of dentition | Cavity conditioning before GIC placement during ART | Type of cavity | Follow-up period | Glass ionomer cement |
|---|---|---|---|---|---|---|---|---|---|
| Frencken JE et al.* (2007) [23] | 01 | Parallel group | ART criteria | 7.5 | Permanent | Yes | Posterior Class I | 6.3 years | Fuji IXGP / Ketac Molar |
| | 02 | | | | | | Posterior Class V | | |
| | 03 | | | | | | Small Class I | | |
| | 04 | | | | | | Large Class I | | |
| Frencken JE et al.* (2006) [22] | 05 | Parallel group | ART criteria | 7.5 | | | Class I | 1.3 years | Fuji IXGP / Ketac Molar |
| | 06 | | | | | | | 2.3 years | |
| | 07 | | | | | | | 3.3 years | |
| | 08 | | | | | | | 4.3 years | |
| | 09 | | | | | | | 5.3 years | |
| | 10 | | | | | | | 6.3 years | |
| | 11 | | | | | | Class II | 1.3 years | |
| | 12 | | | | | | | 2.3 years | |
| | 13 | | | | | | | 3.3 years | |
| | 14 | | | | | | | 4.3 years | |
| | 15 | | | | | | | 5.3 years | |
| | 16 | | | | | | | 6.3 years | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Gao W et al. (2003)[#] [24] | 17 | Splitmouth | USPHS criteria | 7-9 | | | Class I | 30 months | Fuji IXGP / Ketac Molar |
| Yip H-K et al. (2002)[#] [32] | 18<br>19 | Splitmouth | USPHS criteria | 7-9 | | | Class I | 12 months | Fuji IXGP<br>Ketac Molar |
| Yu C et al. (2004) [34] | 20<br>21<br>22<br>23 | Splitmouth | ART criteria | 7.4 | Primary | Not reported | Class I | 12 months<br>24 months | Fuji IXGP<br>Ketac Molar<br>Fuji IXGP<br>Ketac Molar |
| Honkala E et al. (2003) [4] | 24<br>25 | Splitmouth | ART criteria | 5.7 | | | Class I<br>Class II | 22 months | ChemFlex |
| Taifour D et al. (2002) [30] | 26<br>27 | Parallel group | ART criteria | 6-7 | | Yes | Class I<br>Class II | 36 months | Fuji IXGP / Ketac Molar |

*/ [#] 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

| Article | DS | ART | | Amalgam | | RR | 95% CI |
|---|---|---|---|---|---|---|---|
| | | n | N | n | N | | |
| **Permanent dentition** | | | | | | | |
| | 01 | 230 | 355 | 173 | 295 | 1.10 | 0.98 – 1.25 |
| Frencken JE et | 02 | 106 | 132 | 68 | 108 | 1.28* | 1.08 – 1.51* |
| al. (2007) [23] | 03 | 154 | 222 | 74 | 116 | 1.09 | 0.92 – 1.28 |
| | 04 | 39 | 70 | 57 | 108 | 1.06 | 0.80 – 1.39 |
| | 05 | 454 | 487 | 370 | 403 | 1.02 | 0.98 – 1.05 |
| | 06 | 375 | 397 | 289 | 323 | 1.06* | 1.01 – 1.10* |
| | 07 | 334 | 348 | 258 | 267 | 0.99 | 0.96 – 1.02 |
| | 08 | 274 | 288 | 191 | 218 | 1.09* | 1.03 – 1.15* |
| | 09 | 153 | 161 | 108 | 113 | 0.99 | 0.94 – 1.05 |
| Frencken JE et | 10 | 138 | 153 | 97 | 108 | 1.00 | 0.92 – 1.09 |
| al. (2006) [22] | 11 | 41 | 52 | 26 | 33 | 1.00 | 0.80 – 1.25 |
| | 12 | 31 | 34 | 13 | 23 | 1.61* | 1.11 – 2.34* |
| | 13 | 25 | 29 | 9 | 12 | 1.15 | 0.80 – 1.64 |
| | 14 | 18 | 21 | 7 | 9 | 1.10 | 0.75 – 1.63 |
| | 15 | 12 | 12 | 2 | 2 | 1.00 | - |
| | 16 | 9 | 12 | 2 | 2 | 0.88 | 0.48 – 1.60 |
| Gao W et al. (2003) [24] | 17 | 16 | 17 | 6 | 6 | 0.99 | 0.77 – 1.27 |
| Yip H-K et al. | 18 | 21 | 21 | 22 | 22 | 1.00 | - |
| (2002) [32] | 19 | 17 | 17 | 22 | 22 | 1.00 | - |
| **Primary dentition** | | | | | | | |
| | 20 | 17 | 18 | 17 | 17 | 0.95 | 0.81 – 1.10 |
| Yu C et al. (2004) | 21 | 12 | 13 | 17 | 17 | 0.92 | 0.75 – 1.12 |
| [34] | 22 | 5 | 6 | 5 | 7 | 1.17 | 0.65 – 2.10 |
| | 23 | 5 | 5 | 5 | 7 | 1.33 | 0.79 – 2.26 |
| Honkala E et al. | 24 | 24 | 26 | 23 | 25 | 1.00 | 0.85 – 1.18 |
| (2003) [4] | 25 | 8 | 9 | 10 | 10 | 0.89 | 0.67 – 1.19 |
| | 26 | 322 | 376 | 316 | 380 | 1.03 | 0.97 – 1.09 |
| Taifour D et al. (2002) [30] | 27 | 360 | 610 | 224 | 425 | 1.12 | 1.0 – 1.25 |

* Significant difference in favour of ART ($p<0.05$); DS = Dataset number; RR = Relative Risk; CI = Confidence Interval; n = Number of successful restorations; N = Total number of evaluated restorations

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.

| Evaluation period (Numbers of combined datasets) | | | Test of statistical heterogeneity | | | RR | 95% CI | Statistical difference (P-value) |
|---|---|---|---|---|---|---|---|---|
| | | | $Chi^2$ | df | $I^2$ | | | |
| | Dataset | Weight % | | | | | | |
| 12 months | 020 | 54.0 | 0.06 | 1 | 0% | 0.93 | 0.83 – 1.06 | 0.28 |
| | 021 | 46.0 | | | | | | |
| 24 months | 022 | 14.1 | 1.42 | 2 | 0% | 1.07 | 0.91 – 1.27 | 0.39 |
| | 023 | 14.4 | | | | | | |
| | 024 | 71.5 | | | | | | |

RR = Relative Risk; CI = Confidence Interval; df = Degree of freedom; $I^2$ = 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.

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*Acta Odontologica Scandinavica*
2009, 1–12, iFirst article

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**ORIGINAL ARTICLE**

# 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 enamel 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 10.0 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 xylitol-based chewing gum [3,4,7]. Other vehicles include milk [9], mouth-rinses [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

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*(Received 7 March 2009; accepted 3 July 2009)*

ISSN 0001-6357 print/ISSN 1502-3850 online 
DOI: 10.1080/00016350903160563

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

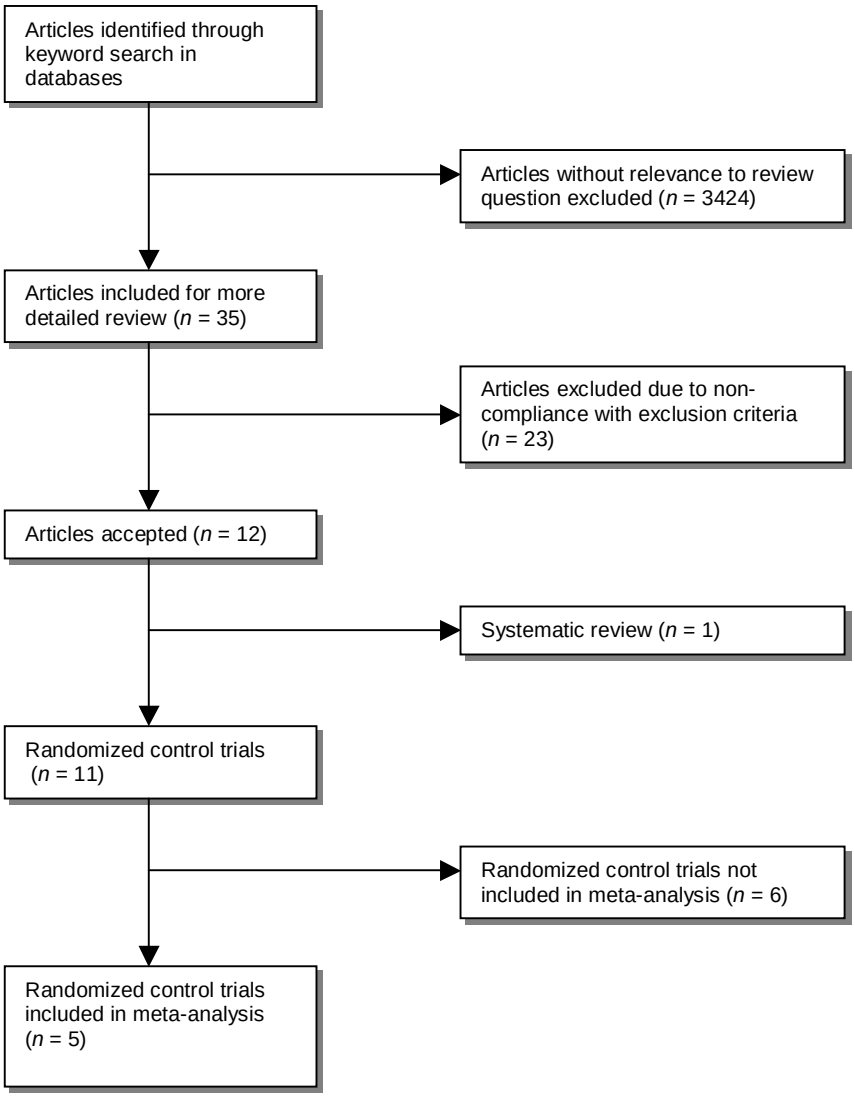


**Table 1.** Excluded articles and main reasons for exclusion

| Authors | Reason for Exclusion |
|---|---|
| Aimutis WR 2004 [42] | Narrative review |
| Ardu S et al. 2007 [34] | Case report |
| Cochrane NJ et al. 2008 [31] | In vitro study |
| Hay et al. 2005 [11] | Investigated casein derivatives such as calcium phosphate but not CPP-ACP |
| Hicks J et al. 2004 [41] | Narrative review |
| Mazzaoui SA et al. 2003 [43] | In vitro study |
| Milnar FJ et al. 2007 [36] | Case report |
| Oshiro M et al. 2007 [2] | Study on animal tissues |
| Pai D et al. 2008 [29] | In vitro study |
| Piekarz C et al. 2008 [30] | In vitro study |
| Rahiotis C et al. 2007 [34] | In vitro study |
| Ramalingam L et al. 2005 [40] | In vitro study |
| Reynolds EC 1997 [5] | In vitro study |
| Reynolds EC 1998 [44] | Narrative review |
| Schirrmeister JF et al. 2007 [45] | Study on animal tissues |
| Slayton RL 2006 [47] | Narrative review |
| Sudjalim TR et al. 2006 [38] | Narrative review |
| Sudjalim TR et al. 2007 [37] | In vitro study |
| Tantbirojn D et al. 2008 [32] | In vitro study |
| Vlacic J et al. 2007 [33] | Case report |
| Yamaguchi K et al. 2006 [39] | Study on animal tissues |
| Yamaguchi K et al. 2007 [1] | Study on animal tissues |
| Zero DT 2006 [46] | Narrative review |

*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 2.** Details of included studies

| Author/year | Population | Intervention | Comparative intervention/controls | Outcome/s | Study design |
|---|---|---|---|---|---|
| Iijima et al. 2004 [7] | 10 healthy subjects, (mean age 32.3; SD +/- 7.9 years) | 2 Gum treatments:<br>1.Dental chewing gum in slabs containing CPP – ACP (18.8 mg)<br>2. Sugar free gum in slabs without CPP-ACP | Crossover design with 14-day test period followed by 7-day washouts between interventions.<br>In-vitro acid challenge of enamel slabs done for 8 and 16 hours | % Subsurface remineralization [%R] (CPP-ACP versus Control)<br>3 measures reported<br>1. %R with no acid challenge (17.88 ± 0.97 vs 9.02 ± 0.74)<br>2. %R after 8hr acid challenge (12.43 ± 0.90 vs 3.12 ± 0.88)<br>3. %R after 16-hr acid challenge (10.40 ± 1.19 vs 1.08 ± 1.02 | Double blinded in-situ and in-vitro RCT with crossover |
| Itthagarun et al. 2005 [25] | 12 healthy subjects (5 males; 7 females; age range 20-47 years) | 3 types of sugar free gum containing<br>1. 30 mg urea<br>2. 30 mg urea + 25 mg dicalcium phosphate dehydrate<br>3. 30 mg urea + 47 mg CPP-ACP. | Crossover design with 21 day test period for each type of gum followed by 5 day washouts after each test period | Two outcomes reported<br>1. Mean % change in lesion depth of the samples<br>2. Mean % change in the mineral content of the samples | Double blinded in-situ RCT with crossover |
| Shen et al. 2001 [24] | 30 healthy subjects<br>(30 +/- 7; 33 +/- 7 and<br>34 +/- 6 years) | 3 types of gum<br>1. Sorbitol based pellet gum containing 4 different doses of CPP-APP<br>2. Sorbitol based slab gum containing 4 different doses of CPP-APP<br>3. Xylitol based pellet gum containing 4 different doses of CPP-APP<br><br>Doses in mg of CPP-ACP were 0, 0.19, 18.8 & 56.4 mg | Crossover design with 14 day test period for each type of gum followed by at least one week washout period between interventions | % Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover |

**Table 2.** Details of included studies (contd.)

| Author/year | Population | Intervention | Comparative intervention/controls | Outcome/s | Study design |
|---|---|---|---|---|---|
| Reynolds et al. 2003 [6] | 30 healthy adults (age range 22-44 years) | Consisted of 2 parts/;- A. Mouth-rinse trial – 4 interventions tested<br>1. 2% CPP-ACP<br>2. 6% CPP-ACP,<br>3. Calcium + phosphate slurry mixed as mouth rinse 4. de-ionized water<br><br>B. Chewing gum trial with 2 parts<br>(1) Gum either in pellet or slab form contained a calcium additive<br>$CaCO_3$ or $CaHPO_4/CaCO_3$ or CPP-ACP<br>(two types of gum with 3 different additives)<br>(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.<br>Chewing gum trial – crossover in design; no washout period stated; in-situ study | For mouth rinse trial- Calcium and phosphate levels in supragingival plaque<br><br>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:<br>1. Sugar-free pellet gum containing 20mg citric acid + 18.8 mg CPP-ACP<br>2. Gum with 20 mg citric acid<br>3. Gum with neither citric acid or CPP-ACP | Crossover trial with 2 week treatment periods followed by 7 day washout | 1. % Subsurface remineralization<br>2. % Remineralization after 16 hour acid challenge | Double blinded in-situ RCT with crossover |
| Walker et al. 2006 [9] | 10 healthy adults | Three treatments:<br>1. 200 ml milk containing 2.0 g CPP-ACP/l<br>2. 200 ml milk containing 5.0 g CPP-ACP/l<br>3. 200 ml milk containing no CPP-ACP | Crossover trial with 15 day treatment periods<br>(200 ml milk consumed over 60 s) followed by 7 day washout | % Subsurface remineralization (%R) | 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) | Four treatments consisting of 1.75g lozenge with:<br>1. 18.8 mg CPP-ACP<br>2. 56.4 mg CPP-ACP<br>3. No CPP-ACP<br>4. No lozenge; nil treatment; control | 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 | % Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover |
| Manton et al. 2008 [8] | 10 healthy subjects (6 males; 4 female) | 3 types of gum:<br>1. Sorbitol/ Xylitol based 2.0 g slab gum containing no CPP-APP<br>2.Sorbitol/Xylitol based 1.5 g pellet (x2) gum containing no CPP-APP<br>3. Two gum pellets containing 10 mg CPP-ACP | Crossover design with 14 day test period for each type of gum (4x daily use) followed by 7 day washout period between interventions | % Subsurface remineralization (%R) | Double blinded in-situ RCT with crossover |

**Table 2.** Details of included studies (contd.)

| Author/year | Population | Intervention | Comparative intervention/controls | Outcome/s | Study design |
|---|---|---|---|---|---|
| Morgan et al. 2008 [4] | 2720 healthy children randomized into test (n = 1369) and control (n = 1351) | Gum with 54 mg CPP-ACP chewed 3X daily for 10 minutes per session.<br>926 children completed trial. 439 dropped out | Sorbitol based gum- chewed 3x daily for 10 minutes per session.<br>894 children completed trial. 452 dropped out. | Caries progression or regression at 24 months. Approximal caries diagnosed via digital bitewing x-rays. | Double blind RCT |
| Reynolds et al. 2008 [10] | 14 healthy subjects (7 males; 7 females; age range 21 to 45 years) | 2 RCTs:<br>A. Three mouth rinses containing either<br>1. 2% w/v CPP-ACP + 450 ppm F as NaF in deionized water<br>2. 450 ppm F as NaF in deionized water<br>3. Placebo control rinse as deionized water<br>B. Toothpaste trial. Each toothpaste slurry contained either<br>1. Placebo<br>2. 1100 ppm F as NaF<br>3. 2800 ppm F as NaF<br>4. 2% CPP-ACP<br>5. 2% CPP-ACP + 1100 ppm F as NaF | 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.<br>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 | 1. Plaque fluoride levels<br>2. % Subsurface remineralization (%R)<br>3. % Remineralization after acid challenge | Double blinded in-situ and in-vitro RCT with crossover |
| Andersson et al. 2007 [13] | 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 | Test group consisted of 13 subjects; 70 sites.<br>Treatment: Brush x2 daily with dental cream containing CPP-ACP for 3 months followed by use of 1100 ppm F toothpaste for 3 months | Control group consisted of 13 subjects; 62 sites.<br>Treatment: 0.05% NaF mouthwash + 1100 ppm F toothpaste for 6 months | Regression of White spot lesions diagnosed via visual inspection and laser fluorescence over 1, 3, 6 and 12 months | RCT |

**Table 3.** Quality assessment of included studies

| Author/year | Randomization | Allocation concealment | Blinding | Sample size (n) | Drop-outs | Follow-up period |
|---|---|---|---|---|---|---|
| Iijima et al. 2004 [7] | A-Adequate<br>Central randomization | A-Adequate<br>Central randomization | A-Yes<br>Double-blind | 10 | A- None | Crossover design<br>14 days x2 with 7x 2 day washouts |
| Itthagarun et al. 2005 [25] | A-Adequate<br>Central randomization | A-Adequate<br>Central randomization | A-Yes<br>Double-blind | 12 | A- 3 | Crossover design<br>21 days x 3 with 5 x3 day washouts |
| Shen et al. 2001 [24] | A-Adequate<br>Central randomization | A-Adequate<br>Central randomization | A-Yes<br>Double-blind | 10 | A- None | Crossover design<br>14 days x3 with 7 x3 day washouts |
| Reynolds et al. 2003 [6] | A-Adequate<br>Central randomization | A-Adequate<br>Central randomization | A-Yes<br>Double-blind | 30 | A- None | Crossover design<br>14 days x3 with unknown washout period |
| Cai et al. 2007 [3] | A- Adequate<br>Central randomization | A- Adequate<br>Central randomization | A-Yes<br>Double-blind | 10 | A- None | Crossover design<br>14 days x3 with 7 x3 day washout period |
| Walker et al. 2006 [9] | A-Adequate<br>Coded randomization | B- Unclear | A-Yes<br>Double-blind | 10 | A- None | Crossover design<br>15 days x3 with 7 x3 day washout period |
| Cai et al. 2003 [12] | A- Adequate<br>Central randomization | A- Adequate<br>Central randomization | A-Yes<br>Double-blind | 10 | A- None | Crossover design<br>14 days x4 with 7 x4 day washout period |
| Manton et al. 2008 [8] | A- Adequate<br>Central randomization | A- Adequate<br>Central randomization | A-Yes<br>Double-blind | 10 | A- None | Crossover design<br>14 days x3 with 7 x3 day washout period |
| Morgan et al. 2008 [4] | A-Block randomization | A- Sealed coded envelopes | A-Yes<br>Double-blind | 2720<br>Test Group (n = 1369)<br>Control group (n = 1351) | Test Group -439<br>Control group – 452<br><br>B- dropouts >30% (33%) | 24 months |
| Reynolds et al. 2008 [10] | A- Adequate<br>Central randomization | A- Adequate<br>Central randomization | A-Yes<br>Double-blind | 14 | A- None | Crossover design<br>14 days x5 with 7 x5 day washout period |
| Andersson et al. 2007 [13] | A- Adequate<br>Assignment made by use of dice | B- Unclear | A- Blinded examiner | 26 | A- None | 12 months |

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

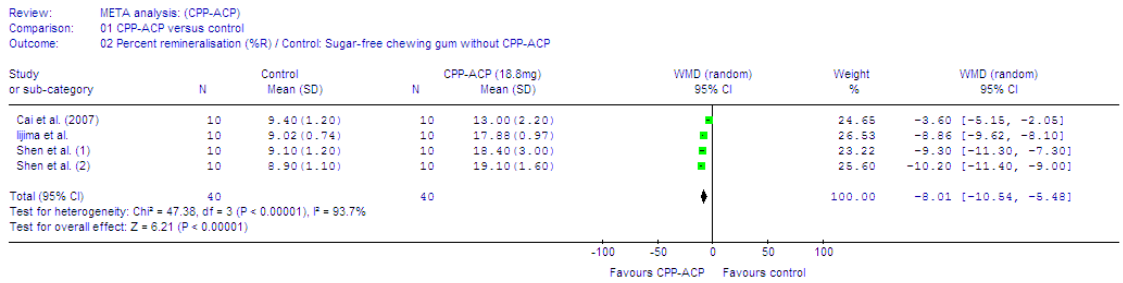



**Figure 3.** Percent remineralization (%R) – Subgroup 2

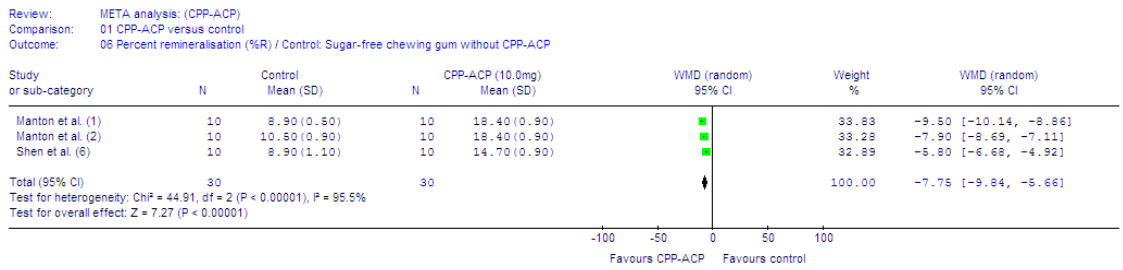
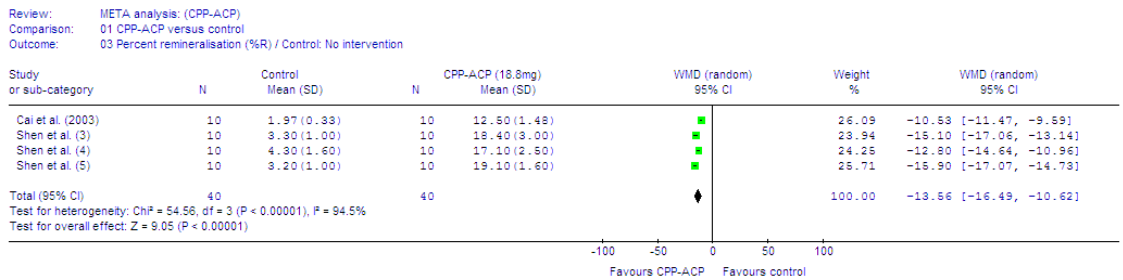



**Figure 4.** Percent remineralization (%R) – Subgroup 3




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 3$^{rd}$ 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.

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