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Topical silver diamine fluoride for managing dental caries in children and adults

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Topical silver diamine fluoride for managing dental caries in children and adults (Protocol)

Rajendra A, Veitz-Keenan A, Oliveira BH, Ruff RR, Wong MCM, Innes NPT, Radford J, Seifo N, Niederman R

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ABSTRACT

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

To assess the effects of silver diamine fluoride in arresting and preventing caries in deciduous and permanent teeth (coronal and root caries) compared to any other intervention including placebo or no treatment.

BACKGROUND

Description of the condition

Dental caries is the globe's most prevalent disease (Marcenes 2013; Kassebaum 2015). Scoping reviews indicate that cost-effective preventive agents, that can be applied by families or community health workers are available, but underused (Niederman 2015). Caries affects far more than a person's oral health. The range of associated issues with untreated caries and toothaches range from reduced quality of life to poor school performance (Farber 2004; Blumenshine 2008; Seirawan 2012; Detty 2014; PR Newswire July 2015). Poor oral health is also associated with inhibited growth and development, psychosocial vulnerability, lower well-being and self-efficacy, and reduced locus of control (Quiñonez 2001; Finlayson 2007; Mattheus 2010; Adair 2013; CMS 2013).

Description of the intervention

Early studies in medicine found that silver nitrate is an effective antimicrobial agent (Von Naegeli 1893). This led to the use of silver nitrate, silver foil, and silver sutures for the prevention of ocular and surgical infections (Halstead 1895). These findings led to the application of silver nitrate to treat caries, creating sclerotic or calcified dentin formation (Stebbins 1891). The hypothesized mechanism was a potent germicidal effect combined with the de-

position of silver phosphate salt (Miller 1905; Howe 1917). Dentists termed silver nitrate 'Howe's solution' after Percy Howe, who first systematically reported on its use for caries prevention.

The specific interest in silver diamine fluoride (SDF) centers around its five presumed attributes (Thibodeau 1978): (1) control of pain and infection; (2) ease and simplicity of use (paint on); (3) affordability of material (pennies per application); (4) minimal requirement for personnel time and training (one minute, once per year); and (5) the fact that it is non-invasive. In this sense, some authors refer to SDF as a potential agent to disrupt the traditional approaches to caries prevention and control (Christensen 2009). In vitro studies suggested that silver fluoride regimens inhibit *Streptococcus mutans* growth (Thibodeau 1978) and penetrate enamel to a depth of 25 microns, and that approximately two to three times more fluoride is retained than that delivered by sodium fluorophosphate (NaF-PO$_4$), sodium fluoride (NaF), or stannous fluoride (SnF$_2$) (Suzuki 1974). The in vitro studies suggest that the effect of SDF may be greater than that of NaF or SnF$_2$.

Early in vivo studies in primary teeth indicated that silver fluoride application may inhibit the lateral spread of caries (Nishino 1969). More recent, in vivo studies in permanent teeth indicated that silver fluoride may arrest approximal caries progression (Battelle 1991). These initial studies led to the use of silver diamine fluoride in Australia (Gotjamanos 1997), Japan (Yamaga 1969), and Brazil (Almeida 1994).

It is mentioned in the literature that the most effective, simplest, and least expensive caries preventive agents are silver nitrate (which kills the causative bacteria) and fluoride (which renders the teeth less soluble to bacterial acids) (Niederman 2015). The creation of a silver nitrate fluoride construct - silver diamine fluoride (SDF) - combines these two preventive agents (Rosenblatt 2009). SDF is thought to arrest and prevent decay progression by (1) killing the causative bacteria, (2) depositing a layer of protective silver phosphate that resists further decay, and (3) converting the more acid soluble hydroxyapatite to the less soluble fluorapatite (Rosenblatt 2009).

How the intervention might work

Multiple modes of action have been proposed for silver diamine fluorides (Rosenblatt 2009). This may, in part, be explained by the multiple biological organisms (e.g. bacterial, protozoan, fungal, and viral), subcellular targets (e.g. cell membranes, organelles, nuclei), and mechanisms (e.g. metabolism, replication) that have been examined. Studies indicate that silver interacts with sulfhydryl groups of proteins and with DNA, altering hydrogen bonding and inhibiting respiratory processes, DNA unwinding, cell-wall synthesis, and cell division. At the macro level, these interactions effect bacterial killing and inhibit biofilm formation (Wu 2007). The central mechanism for these diverse effects is proposed to be the interaction of silver with thiol groups (Russell 1994).

Why it is important to do this review

Several countries such as Japan, China, New Zealand, Australia, and many South American countries have been using silver diamine fluoride for many decades for arresting caries. Silver diamine fluoride is available and approved for use in multiple Asian and South American countries (Niederman 2015).

Recently in 2014 the US Food and Drug Administration (FDA) approved the use of SDF as a treatment of dentinal hypersensitivity in patients aged 21 and older, but many people have been using SDF off-label for the treatment of cavitated lesions, particularly in children. Several randomised controlled trials are showing that SDF can be used to halt the progression of caries (Rosenblatt 2009; Gao 2016).

The expanding availability of SDF and more than 100 publications cited on PubMed suggest the need for an updated systematic review examining multiple aspects of silver diamine fluoride's potential utility.

Hence, a Cochrane Review of randomised controlled trials to evaluate the effectiveness of SDF for caries arrest and prevention will provide a source of evidence for global decision making.

OBJECTIVES

To assess the effects of silver diamine fluoride in arresting and preventing caries in deciduous and permanent teeth (coronal and root caries) compared to any other intervention including placebo or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of parallel-group and split-mouth design comparing the use of silver diamine fluoride with any other intervention or placebo or no treatment, in patients with any type of carious lesions and without carious lesions. Any length in follow-up period will be considered for inclusion.

Types of participants

Children, adolescents and adults with any type of carious lesions or without carious lesions in anterior or posterior deciduous or permanent teeth or both.

Types of interventions

Topical application of any concentration or duration of application of silver diamine fluoride in anterior or posterior deciduous or permanent teeth with any type of carious lesions or without caries, treatment performed with or without caries excavation compared to any other intervention including placebo or no treatment.

Types of outcome measures

Primary outcomes

- Caries prevention, as measured by change from baseline in the number of decayed missing, filled permanent surfaces (DMFS), and decayed missing filled primary surfaces (dmfs).
- Caries arrest indicated by change from active to arrested caries, measured by visual changes in enamel and dentin or any other ways that may be used for caries arrest evaluation.

Secondary outcomes

- Adverse events (e.g. allergic reactions/taste disturbances, stains, decreased bond strength for direct restorations).
- Dental pain or sensitivity (e.g. pain and postoperative sensitivity may be measured by a visual analog scale (VAS), tested by practitioner or patient self-report).
- Aesthetics (e.g. acceptability of color changes in carious lesions assessed by patient, parent or clinician).

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. Due to the Cochrane Embase Project to identify all clinical trials on the database and add them to CENTRAL, only recent months of the Embase database will be searched. Please see the searching page on the Cochrane Oral Health website for more information. No other restrictions will be placed on the language or date of publication when searching the electronic databases.

We will search the following databases for relevant trials:
- Cochrane Oral Health's Trials Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Register of Studies;
- MEDLINE Ovid (from 1946 onwards);
- Embase Ovid (previous six months to date).

The subject strategies for databases will be modelled on the search strategy designed for MEDLINE Ovid in Appendix 1.

Searching other resources

The following trials registries will be searched:
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

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

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

The search will include online abstracts indexes of conference proceedings if available such as the abstracts from the International Association for Dental Research (IADR) or the American Association of Dental Research (AADR).

Data collection and analysis

Selection of studies

For data collection and analysis two review authors (Anjana Rajendra (AR) and Analia Veitz-Keenan (AVK)) will independently and in duplicate screen the identified titles and abstracts for possible inclusion in the review. A third author (Richard Niederman (RN)) will arbitrate disagreements. We will obtain all full-text copies of all potential eligible articles and they will be further evaluated for final inclusion in detail by the review authors (AR, AVK and RN). A PRISMA flowchart will be created to summarise the process, and excluded studies will be reported.

Data extraction and management

We will create a data extraction form for the review. Four review authors independently and in duplicate will extract data. A fifth review author will moderate disagreements. All data extracted and details of all included studies will be entered in the 'Characteristics of included studies' tables using Review Manager 5 (RevMan 5) software (RevMan 2014).

For each study the following characteristics will be reported.
- Publication details (setting/year).
- Methodology.
- Type of participants.
- Type of intervention.
- Control.
- Outcomes.
- Duration and follow-up.
- Sample size.
- Funding/conflict of interest.

Assessment of risk of bias in included studies

Two review authors (AR and AVK) will independently and in duplicate assess the risk of bias for all the included randomised controlled studies by using the criteria suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8 (Higgins 2011). A third review author will act as a moderator for disagreements.

We will grade each study for risk of bias in the seven key domains suggested:

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessor (detection bias);
5. completeness of outcome data (attrition bias);
6. risk of selective data reporting (reporting bias); and
7. other bias.

An overall judgment of 'Low risk' of bias for a study will be made when any plausible bias across all seven domains was unlikely to have altered the results. An overall judgment of 'Unclear risk' of bias for a study will be made when any plausible bias across one or more of the key domains raises some doubt that it may have altered the results. An overall judgment of 'High risk' of bias for a study will be made when any plausible bias across one or more of the key domains seriously weakens our confidence in the results reported in that study.

We will complete 'Risk of bias' tables for each included study. We will then generate a 'Risk of bias' summary graph and figure.

Measures of treatment effect

Caries prevention

For change in DMFT/DMFS from baseline comparing treatment groups, where studies use the same scale to measure the outcome, we will use mean values and standard deviations reported in studies to estimate the mean difference (MD) with 95% confidence intervals. For studies with different scales, we will express treatment effects as standardized mean differences (SMD) and 95% confidence intervals.

Caries arrest

Using standard 2 x 2 tables for the number of cavitated teeth arrested and non-arrested, we will express the estimate of treatment effects as odds ratios (OR) and 95% confidence intervals.

Unit of analysis issues

We are anticipating that the trials may randomise participants or teeth to the interventions. The number of observations in the analysis should match the number of 'units' that were randomised.

We will follow the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 9, Section 9.3 (Higgins 2011) in order to avoid unit of analysis errors.

Parallel trials will use standard meta-analytic procedures including standard random-effects models of pooled ORs and SMDs.

Analysis of data from split-mouth designs, where available, will be similar to that for cross-over trials (*Cochrane Handbook for Systematic Reviews of Interventions*, Section 16.4 (Higgins 2011)). For continuous outcomes, analysis will use effect estimates from paired t-tests and included in meta-analyses using the generic inverse variance method. For studies in which relevant information is not available to incorporate the published data into a meta-analysis, we will approximate paired analyses by imputing standard deviations. Specifically, we will consider borrowing standard deviation differences from similar studies. Alternatively, we will calculate standard deviation differences using a range of plausible correlation coefficients (see Sensitivity analysis). For dichotomous data we will calculate ORs for differences between groups about whether caries was arrested, along with appropriate standard errors and 95% confidence intervals, using RevMan 5 (RevMan 2014). For split-mouth studies, we will calculate ORs using the Becker-Balagtas method (BB OR) outlined in Curtin 2002 by R software Version 3.3.1 (R for Windows 3.3.1). We have chosen this method because we intend to pool data from split-mouth and parallel-group studies in the same meta-analyses, and this method is appropriate (as outlined by Stedman 2011). If an included study presented paired data by tooth pairs, we will calculate the intra-cluster correlation coefficient (ICC) (required for BB OR calculations) from paired data. If a split-mouth study presents data only in marginals (as parallel-group studies, not as 2 x 2 cross-classification for paired data), we will use the conservative ICC 0.05.

Dealing with missing data

We will contact authors of the selected studies for unclear methodology, missing or unclear information and missing data. For the analysis we will include only the available data. We will follow the methods suggested by Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

Clinical heterogeneity will be assessed to examine the type of participants, interventions and outcomes of each study.

We will assess heterogeneity by inspection of the point estimates and confidence intervals on the forest plots. The lack of overlap of confidence intervals may indicate heterogeneity.

Statistically heterogeneity will be assessed using Cochran's test for heterogeneity and the I^2 statistic. For the interpretation of statistical heterogeneity we will use the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will follow the guide to the interpretation of the I^2 statistic given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% considerable heterogeneity.

For the Cochran's test for heterogeneity we will consider heterogeneity for P values < 0.1.

Assessment of reporting biases

If there are more than 10 studies included in the meta-analysis, we will test for reporting bias by testing for asymmetry in a funnel plot. If reporting biases are identified, we will carry out analysis as outlined by Egger 1997 for continuous outcomes and Rucker 2008 for dichotomous outcomes.

Data synthesis

Meta-analysis will be conducted using RevMan 5 software for studies with similar comparisons and reporting the same outcome measures. We will combine ORs for dichotomous data (caries arrest) and mean differences (caries prevention) for continuous data using random-effects models.

Outcomes from studies with different scales will be converted to standardized mean differences for continuous outcomes and overall effects will be re-scaled to a common outcome type.

We will perform meta-analysis if appropriate in order to obtain a pooled relative risk (OR) for dichotomous outcomes, mean differences and standardized mean differences (SMD) for continuous outcomes to assess the effect of topical silver diamine fluoride in control of dental caries.

Subgroup analysis and investigation of heterogeneity

As described above, subgroup analysis will be considered for any outcome with an estimated I^2 of 40% to 60%, considered as possible moderate heterogeneity according to the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 9.5.2 (Higgins 2011). However, prior to any subgroup analyses we will consider both magnitude and direction of effects and strength of the evidence for heterogeneity, via confidence intervals for the I^2 statistic. Subgroup analysis will be performed for study design and by predominant age group in the study.

Sensitivity analysis

Provided there are sufficient included trials we will conduct sensitivity analysis to evaluate the impact of the following factors:

- studies of high and unclear risk of bias;
- for split-mouth designs, sensitivity analyses will be conducted to assess the impact of variation in imputed correlations for the calculation of standard deviations of differences and odds ratios.

Presentation of main results

The primary and secondary outcomes will be included in 'Summary of findings' tables using GRADEpro software (GRADEpro GDT 2014). We will assess the quality of the body of evidence with reference to the overall risk of bias of the included studies, inconsistency and directness of the evidence, the precision of the estimates, and the publications bias.

We will categorize the quality of the body of evidence for each outcome as high, moderate, low and very low.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. exp Tooth demineralization/
2. (teeth adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
3. (tooth adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
4. (dental adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
5. (enamel adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
6. (dentin adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
7. (root adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
8. Dental plaque/
9. ((dental or tooth or teeth) and plaque).mp.
10. or/1-9
11. (silver adj3 fluorid$).mp.
12. ("silver diamine" or "diamine silver" or "silver diammine" or "diammine silver").mp.
13. ((silver adj nitrate) or (silver adj3 protein$) or (nano adj3 silver)).mp.
14. ((ammonical or ammoniacal) adj2 silver).mp.
15. (SDF or AgF or AgNO3 or Ag-nano).ti,ab.

16. ("Advantage Arrest" or "Howe?s Solution" or "Riva Star" or Cariestop or Ancarie or "Salfluoraide di Walter" or (Cariostatic adj4 Inodon) or Saforide or Flurophat or Fagamin or Bioride).mp.
17. or/11-16
18. 10 and 17

CONTRIBUTIONS OF AUTHORS

All authors were responsible for writing and drafting the protocol.

DECLARATIONS OF INTEREST

Anjana Rajendra: no interests to declare.

Analia Veitz-Keenan: no interests to declare.

Branca Heloisa Oliveira: no interests to declare.

Ryan R Ruff: no interests to declare.

May CM Wong: no interests to declare.

Nicola PT Innes: no interests to declare.

John Radford: no interests to declare.

Nassar Seifo: no interests to declare.

Richard Niederman: has several articles on silver diamine fluoride and grants submitted to examine silver diamine fluoride's comparative effectiveness.

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- Cochrane Oral Health Global Alliance, Other.

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