Review Article

Effect of 38% silver diamine fluoride on control of dental caries in primary dentition: A Systematic review

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Abstract

Silver diamine fluoride (SDF) has been extensively researched and proven effective for caries prevention and arrest in children. Limited studies support its effectiveness in primary dentition at 38%. This systematic review examines the effectiveness of 38% silver diamine fluoride on control of dental caries in primary dentition. Multiple search engines and databases were searched in accordance with predefined inclusion-exclusion criteria. Quality assessment was done using Centre for Evidence-Based Medicine worksheets. Scientific works of literature were searched in October 2019 for articles. Four studies were identified that addressed the effectiveness of 38% SDF on deciduous dentition in children. All the four studies selected were controlled clinical trials. The cumulative results of the studies showed that 38% SDF application is efficacious and safe for the control of dental caries in primary teeth. Its advantages over different other techniques or placebo have been demonstrated. Based on this systematic review, 38% SDF is one of the best treatment approaches in control of dental caries in primary dentition.

Keywords: Arrest, caries, children, primary dentition, safety, silver diamine fluoride, systematic review

Introduction

One of every two children in India suffers from dental caries. With a pooled prevalence rate ranging from 50.8% to 62.4% in children, dental caries is still the most common dental problem.[1] In recent years, even though overall caries indicators have shown a marked reduction, an increase in early childhood caries (ECC) has been documented. ECC is the presence of 1 or more decayed, missing due to caries, or filled tooth surfaces (DMFS) in any primary tooth in a child at 71 months of age or younger. Prevalence of ECC in India at 5 years of age is found to be 49%.[2]

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In spite of a recent mild declining trend, dental caries prevention and control in children remains one of the most daunting problems faced by the primary care dentist. Wide urban-rural variations in dental caries, along with cultural and age-related variations make caries prevention and control a challenging task.

This challenge of prevention and control of dental caries in children is bound to rise in the future. Even at present, children below 14 years of age make up 30.7% of India's population.[3] This percentage is poised to increase and peak in the near future. Therefore, there is a forthcoming need to find a solution for control of dental caries that is quick, inexpensive, and painless.

One such solution that has been recently postulated and tested is the use of silver diamine fluoride (SDF). SDF is a colorless alkaline solution containing silver and fluoride, which forms a

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mixed heavy-metal halide coordination complex with ammonia. The combined effects of silver and fluorides can simultaneously arrest caries progression and prevent the development of new caries by reducing the CFU (Colony Forming Units) counts of mono-species strains of *S. mutans* and *Actinomyces naeslundii*.[4] Further, SDF also enhances the mineral content of dental hard tissues and promotes the absorption of calcium. Hence, carious lesions treated with SDF are known to have a significantly higher surface microhardness.[5-7]

SDF was approved for use as a therapeutic agent in Japan in the 1960s.[5] It has also been used in Argentina, Australia, Brazil, and China for many years to treat dental caries.[8] In 2014, the US Food and Drug Administration (FDA) cleared the first SDF product for use in the USA.[9] Various uses of SDF that have been documented in the literature so far are to arrest caries of the primary teeth in children[5] to prevent pit and fissure caries of the erupting permanent molar[10] and prevent root caries in elderly people.[11] However, until now, the evidence about the clinical efficacy of SDF for control of dental caries among children is not clear. Hence, the present study aims at determining the efficacy of 38% SDF application in the control of dental caries among children with primary dentition.[12-14]

Materials and Methods

PRISMA (Preferred reporting items for systematic reviews and meta-analysis) reporting guidelines were followed to conduct this review systematically.

Eligibility criteria

The design of this systematic review was conducted by referring to PICOS (Participants, Intervention, Comparison, Outcomes, Study Design) schema. We included studies meeting the following inclusion criteria:

- Participants: children with primary dentition;
- Intervention: topical 38% SDF solution (any frequency) applied by any health care worker at whichever sites;
- Comparisons: no intervention, placebo, other concentrations of SDF, any topical cariostatic agents, resin or glass ionomer pit and fissure sealants or restorative materials;
- Outcomes: the primary outcome was the development of new dentin caries lesions at the surface. Adverse events reported have been reported as secondary outcomes;
- Study Design: all parallel-group, clinical trials with a follow-up of at least 1 year.

Another inclusion criterion was the articles in the English language only. Studies that did not meet one of these criteria such as case series, animal studies, systematic reviews, narrative reviews, expert opinions, Delphi studies, guidelines by various organizations, and letters to the editor were excluded.

Search strategy

The literature searches were performed in October 2019 and were searched from January 1998 to October 2019. Articles were searched in Medline via PubMed, EMBASE, SCOPUS, Web of Science, Lilacs, and Cochrane library. In addition, ClinicalTrials.gov and Clinical Trials Register of India were searched for unpublished studies. The search was restricted to the English Language. A planned search strategy was developed for PubMed and later adapted for other databases. The literature search was carried under three broad sections:

Search #1: "Silver Diamine Fluoride" OR "Diammine Silver Fluoride" OR "Ammonical Silver Fluoride" OR Silver Ammonia Fluoride" OR "Silver Fluoride" OR "Quaternary Ammonium Compounds"[MeSH Terms] OR "Silver Nitrate + Caries"

Search #2: "Children + Caries + Silver" OR "Dental Caries + Therapy + Silver" OR "young children + Care Management + Dental" OR "Cariostatic Agents + Therapeutic + Children" OR "Dental Atraumatic Restorative Treatment/Methods" OR "Dental Caries + Prevention + Control + Silver" OR "Dental Caries + Drug Therapy" OR "Primary dentition."

Further, references of various reviews on SDF were used to find any possible articles.

Search 3: #1AND#2

All the data generated from the search was uploaded to End-Note X7 (Thomson Reuters, San Francisco, CA, USA) to remove duplicate articles. Two reviewers independently screened all the studies and selected studies after the application of inclusion and exclusion criteria.

Two reviewers pilot tested the eligibility criteria on a sample of 10 reports. After independently assessing these studies, they discussed the problems met in the application of the defined eligibility criteria. After a thorough discussion, they independently examined the titles and abstracts of each of the remaining articles.

Study selection

A total of 2936 papers were identified through the electronic searches as shown in Figure 1. After removal of duplicated and initial screening, 201 papers were evaluated for eligibility from which 146 papers were not eligible. Seventeen studies were assessed for eligibility criteria. Only four studies could be included for data synthesis after the application of inclusion and exclusion criteria.

All six authors independently read all the selected studies, extracted the information, and assessed their quality and risk of bias in an assessment table [Table 1] by using the critical appraisal worksheet for controlled clinical trials from the Oxford Centre for Evidence-based Medicine (CEBM 2005).[15] All the authors

argued on differences in critical appraisal worksheet until they attained a consensus.

Results

Four studies were selected for review after inclusion and exclusion criteria and are shown in Table 2. All the studies showed that 38% SDF is superior for caries arrest in comparison to other interventions. 38% SDF showed higher caries arrest compared to other lower percentages of SDF but the difference was not statistically significant. Sample size estimation was described in all the studies. Fung *et al.* (2018) studied a sample of 888 children from kindergartens of Hong Kong.[16] Yee *et al.* (2009) studied 976 children from kindergarten and primary schools in Nepal.[17] Chu *et al.* (2003) conducted their study on 375 children and Llodra *et al.* 2004 conducted the study on 452 school children in Cuba.[7,18] One of the included trials was registered in the US clinical trials registry.[16]

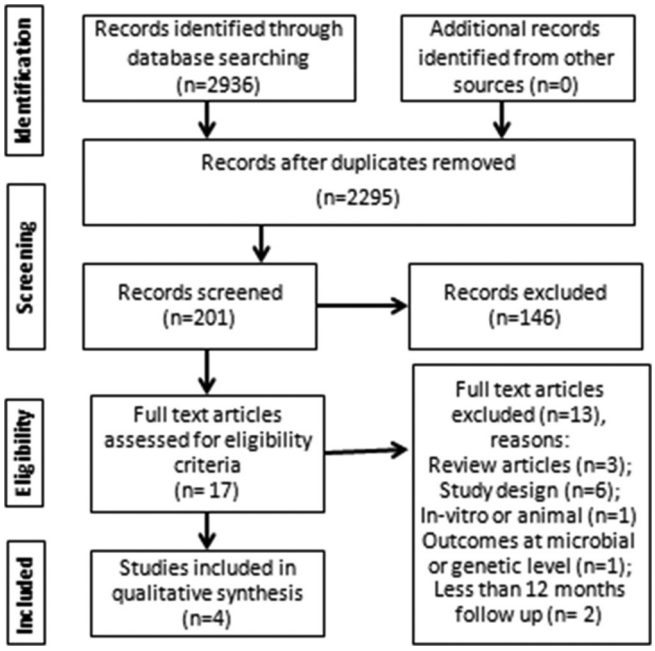

Figure 1: Flow Diagram showing the process of study selection for eligibility

One study by Fung *et al.* recorded adverse effects.[16] These were telephonically confirmed in case of short-term adverse events, while long-term effects were discovered on the examination of the participant. Adverse events determined were nausea, not eating, dysphagia, dyspnea, swelling around lips and face, itchiness, rashes, stomach ache, and diarrhea. They found that there was a difference of 0.6% between adverse events recorded between test and control groups. The effects examined were gingival or mucosal ulceration or swelling and black discoloration. In the study by Llodra *et al.*, 3 patients developed white mucosal lesions that were mildly painful.[18] The reason for the development of these lesions was inadvertent contact with SDF solution.

A study by Fung *et al.* (2018) showed that 38% SDF applied after 12 months and 6 months showed a caries arrest rate of 66.9% and 75.7%.[16] This was considerably higher than caries arrest by 12%SDF. A study by Yee *et al.* (2009) in Nepal evaluated the mean number of arrested caries, which was found to be significantly greater in 38% SDF with (4.5 ± 0.4) or without (4.2 ± 0.3) tea extracts.[17] In a study by Llodra *et al.* in 2005, there was a significant difference between the mean number of inactive caries among 38% SDF (2.8 ± 0.3) and control group (1.8 ± 0.3).[18]

The lost to follow-up was evaluated by all the studies as outlined in Table 2. For Fung *et al.*, the main reason for lost to follow-up was found to be moving to another Kindergarten.[16] Other studies have not mentioned the reason for lost to follow-up.

Quality of studies was evaluated using the modified Centre for Evidence-Based Medicine (CEBM) criteria [Table 1]. One study by Fung *et al.* showed a high quality of evidence as they fulfilled 8 out of 9 criteria.[16] A study by Llodra *et al.* (2003)[18] was evaluated to provide moderate level of evidence with CEBM score of 6, while the two studies by Chu *et al.* (2002)[7] and Yee *et al.* (2009)[17] were found to have low-quality evidence with scores 5 and 4, respectively.

Discussion

This review is based on evidence from four clinical trials that assessed the role of 38% SDF in the control of dental caries in primary teeth.

Table 1: Critical appraisal worksheet summary for clinical trial

Author, Year, Country	Randomized assignment of subjects	Similar groups at baseline	Equal treatment of groups	Intention to treat analysis	Double blinded study design	Examiners calibrated	Large effect size	Precision of estimate	External validity	Extent to which criteria were met
Fung *et al.*[16]; 2018, Hong Kong	Yes	Yes	Yes	Not mentioned	Yes	Yes	Yes	Yes	Yes	8 out of 9 criteria met
Yee *et al.*[17]; 2009, Nepal	Done, method of random allocation not described	Yes	No	No	Not mentioned	Yes	No	Yes	Yes	4 out of 9 criteria met
Chu *et al.*[7]; 2002, China	Not mentioned	Yes	No	No	No. Single blind	Yes	Yes	Yes	Yes	5 out of 9 criteria met
Llodra *et al.*[18]; 2005, Cuba	Done, method of random allocation not described	Yes	Yes	No	No. Single blind	Yes	Yes	Yes	Yes	6 out of 9 criteria met

Table 2: Summary of studies included for systematic review

Author/ Year/ Country	Setting/Study design/duration of Follow-up (in months)	Inclusion criteria; Age range (years)/ Mean±SD	Sample size/ Lost to follow-up	Treatment Protocols included	Clinical Outcome measures	Clinical Outcomes
Fung *et al.*[16]; 2018; Hong Kong	37 kindergartens; Randomized clinical trial; 30 months	Healthy children aged - 3 to 4 years, Minimum one soft carious lesion in dentin; 3-4/3.8±0.6	Baseline *n*=888; Lost to follow-up *n*=89 (10%) at 30 months	Group 1: 12% Silver diamine fluoride every 12 months. Group 2: 12% Silver diamine fluoride every 6 months. Group 3: 38% Silver diamine fluoride every 12 months. Group 4: 38% Silver diamine fluoride every 6 months	1) Difference in caries arrest rate from baseline. (2) Changes in oral hygiene-related behaviors from baseline. (3) Effect of SDF on plaque.	(1) Caries arrest rate: Group 1-55.2%, Group 2-58.6%, Group 3-66.9%, Group 4-75.7% (2) All groups showed a change in oral hygiene behaviors from baseline, with no significant difference among groups. (3) Concentration of SDF and frequency of application significantly affected Visual Plaque Index scores.
Yee *et al.*[17]; 2009; Nepal	Kindergarten and primary school; Randomized Controlled Trial; 24 months	Not mentioned 3 to 9/5.2±1.2	Baseline *n*=976; Lost to follow-up *n*=68 (7%) at 6 months *n*=208 (21.3%) at 12 months *n*=342 (35%) at 24 months	Group 1: Single application of 38% SDF alone. Group 2: Single application of 38% SDF with tannic acid as reducing agent. Group 3: Single application of 12% SDF alone. Group 4: (Control) No treatment.	Change in active carious surfaces to arrested caries surfaces post-treatment	Mean number of arrested caries: Group 1-2.1, Group 2-2.2, Group 3-1.5, Group 4-1. There was no significant difference between 38% SDF with or without reducing agent in arresting active caries
Chu *et al.*[7]; 2002; China	8 kindergartens; Controlled clinical trial; 30 months	Not mentioned 3-5/4±0.8	Baseline *n*=375; Lost to follow-up *n*=67 (18%) at 30 months	Group 1: 38% SDF with caries excavation. Group 2: 38% SDF without caries excavation. Group 3: 5% sodium fluoride with caries excavation. Group 4: 5% sodium fluoride without caries excavation. Group 5: water (Control)	(1) Number of new and arrested carious tooth surface. (2) Black and nonblack arrested carious lesion	(1) Mean numbers of arrested carious tooth surfaces: Group 1-2.5, Group 2-2.8, Group 3-1.5, Group 4-1.5, Group 5-1.3. There were statistically significant differences in the mean number of arrested carious tooth surfaces among the five treatment groups. (2) Children who received an annual application of SDF had a higher proportion of their arrested caries appearing black.
Llodra *et al.*[18]; 2005; Cuba	Schools; Controlled clinical trial; 36 months	Children above 6 years of age; 6 or more/6.29±0.48	Baseline *n*=452; Lost to follow-up *n*=79 (17.5%) at 36 months	Group 1: 38% SDF group. Group 2: Regular group on Sodium fluoride applications.	Mean number of new decayed surfaces appearing in primary teeth	Mean number of new decayed surfaces: Group 1-0.29, Group 2-1.43

A concentration of 38% SDF has been studied widely in the recent past and has shown promising results in the arrest of dental caries. The studies selected showed the varying levels of evidence regarding safety and efficacy of 38% SDF in dental caries control. Reviews have been done on the effects of SDF application on mixed and permanent dentition; however, limited evidence exists on the efficacy of 38% SDF in primary teeth. One of the most important outcome evaluators was the number and rate of teeth showing arrested caries post-treatment. Studies also considered other outcomes such as the number of new caries and oral hygiene-related behaviors. The studies also included adverse effects and events as markers of the safety of treatment by 38% SDF.

The cumulative results of the studies showed that 38% SDF application is efficacious and safe for the control of dental caries in primary teeth. Its advantages over different other techniques as well as placebo have been demonstrated. We chose 38% SDF application as one of the eligibility criteria because there are studies showing the difference in caries arrest in different percentages of SDF.[16,19]

Two studies showed similar arrest rates for dental caries.[16,17] In all the studies, there was a significant difference between caries arrest shown in the treatment and the control arms. The study by Fung *et al.* (2018) showed that 38% SDF had application led

to an increase of 18%–20% in caries arrest rate as compared to control of 12% SDF.[16]

Whereas studies have shown a comparison between 38% SDF with other materials and lower concentrations of SDF, these trials do not compare with higher concentrations of SDF to assess the efficacy and safety of higher concentrations. The mechanism of action of SDF is not clear and studies should be carried out to determine the mechanism of action of SDF. Further, the reasons why 38% SDF has greater efficacy when compared to lower concentrations have not been probed. There is a need to determine the cause of increased efficacy of SDF with increased concentration. It is important to actively collect and describe patient or parent perceived outcomes in clinical trials as well.

The free fluoride concentration of SDF is around 44,800 ppm and silver concentrations maybe 255,000 ppm. Therefore, these solutions should be used cautiously to prevent acute reactions and allergies in pediatric patients. In addition, proper isolation of gingival tissues is necessary as some adverse reactions have been reported with the contact of SDF with gingiva. Another important adverse reaction that has been reported with SDF is the black staining of surfaces where it is applied. Black staining of the carious surface is often a concern with the parents of the child patients in anterior teeth. However, in posterior teeth, it is not a cause of concern. The concern of parents about discoloration and staining may be a culturally dependent factor. Perceptions of parents belonging to different cultural backgrounds about the acceptability of black staining of carious lesions in different parts of the mouth may be an important area of future research. Irrespective of parents' perception about the staining, it is a significant aberration from the normal and should be corrected. Future studies should also emphasize prevention and correction of this discoloration.

Even though a comprehensive search was carried out, only a few clinical trials were found to report efficacy and safety of 38% SDF application in primary teeth. Even as early childhood caries continues to be an important problem in pediatric dentistry, there has been limited emphasis on the use of 38% SDF in primary teeth. A greater number of clinical trials should be carried out on this to create a stronger evidence base. In addition, further studies are required to investigate whether a different percentage of SDF can be applied to noncarious teeth for the prevention of dental caries without causing staining. The application of SDF as an effective public health tool at the community level also needs more exploration. Using SDF may be useful as an important part of care of dental caries in children and may become an integrated part of primary dental care as evidenced by earlier studies in dentistry.[20,21]

This review considers 38% SDF application to be useful in arresting dental caries in primary teeth based on the evidence collected by three studies. Even though the studies differ in quality, there is a consistency among the results of all the studies on the effect of SDF in arresting dental caries in primary teeth. Therefore, 38% SDF can be considered as a potent agent for arresting dental caries spread in primary teeth.

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Conflicts of interest

There are no conflicts of interest.

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