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REVIEW ARTICLE

Effectiveness of Silver Diamine Fluoride in Children with Early Childhood Caries: A Systematic Review and Meta-analysis

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ABSTRACT

Aim: Silver diamine fluoride (SDF) has been used globally in several countries and there are many published reports stating its effectiveness against dental caries. However, dosage and timing of application are controversial, as many authors have recommended various treatment protocols. The objective of this review was to evaluate the effectiveness of SDF in children with early childhood caries (ECC).

Materials and methods: Literature searches involved PubMed, ScienceDirect, and Cochrane Library from January 2005 to December 2016. The search generated 146 articles for screening (69 from PubMed, 71 from ScienceDirect, and 6 from Cochrane Library). From the imported references, 133 were screened against title and abstract by the two reviewers after duplicates were removed. Out of these, 126 studies were excluded based upon the inclusion criteria and seven were assessed for full-text eligibility in which one study was excluded (*ex vivo* study). Finally, six articles were selected for the full-text analysis and quality assessment. The meta-analysis was performed with Review Manager (version 5.3). Only studies that reported the results as dichotomous data were analyzed with Cochran–Mantel–Haenszel test.

Results: In the overall meta-analysis, there was an association between caries arrest in the groups using SDF and the other control groups [odds ratio = 0.66 (0.5–0.78)]. Subgroup analysis showed the following associations at 3 months interval [odds ratio = 0.55 (00.43–0.73)] and 6 months interval [odds ratio = 0.56 (00.43–0.74)]. At 18 months and above, however, there was no association seen [odds ratio = 1.01 (0.75–1.36)].

Conclusion: Early childhood caries is a global health issue that should be addressed in the primitive stages. Silver diamine fluoride is a material that is effective in caries arrest and progression and thus is useful in halting the spread of the disease. Its rationale is justified as compared with other materials used in the treatment of ECC due to the higher percentage of caries arrest seen.

Clinical significance: At concentrations of 30 and 38%, SDF shows potential caries arrest in children suffering from ECC.

Keywords: Caries arrest, Early childhood caries, Meta-analysis, Silver diamine fluoride, Silver diammine fluoride, Systematic review.

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INTRODUCTION

The disease of ECC is the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces in any primary tooth in a child 71 months of age or younger.[1] Early childhood caries is a global oral health problem that continues to affect infants and preschool children causing pain, poor esthetics, dietary deficiency, malocclusion, psychological derangement and financial loss, thus leading to a poor quality of life.

In an era of prevention where the primary focus is on prevention of extension rather than an extension for prevention, the solution lies in SDF's hypothesized potential to terminate the caries process and simultaneously prevent the formation of new caries.[2]

The definitive interest in SDF centers around its favorable attributes, i.e., regulation of pain and infection, the simplicity of use (paint on), the cost-effectiveness of material (pennies per application), the minimal requirement for staff time and training (one minute, once per year), and that it is noninvasive. Thus, in the context of prevention, SDF has been labeled to be a "silver fluoride bullet."[3]

Apart from caries arrest, SDF is used for the treatment of root caries, pit and fissure caries, as a root canal irrigant and as a desensitizing agent.[4] The discovery of silver nitrate as a useful antimicrobial by Percy Howe was a milestone in medicine. Over the years, Howe's solution has endured various experimental alterations to extract its beneficial effects and is now cleared by the Food and Drug Administration for reducing tooth sensitivity defined under the UCSF protocol by Horst et al.[5]

Documented studies on SDF show that authors have used it in various concentrations and application intervals. Comparing the study results systematically will help to formulate an effective treatment plan for future use.

MATERIALS AND METHODS

This review was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www. prismastatement.org).[6] The concept of the study was first registered in the International Prospective Register of Systematic Reviews, "PROSPERO" (CRD42017081531).

Search Strategy

The search strategy was based on the following Medical Subject Heading (MeSH) terms in different combination strategies: "Silver diammine fluoride" or "Silver diamine fluoride" and "Early childhood caries."

Sources Used

The literature searches involved PubMed MEDLINE, ScienceDirect, and Cochrane Library. The studies were from January 2005 to December 2016. The preferred language was English and studies in this language were included. Two examiners (SKK and SDG) evaluated titles, abstracts, and full text. All decisions were made unanimously by the authors.

Inclusion Criteria

The review design is presented in Table 1, following the Patient, Intervention, Comparison, Outcome (PICO) strategy, which denotes the inclusion criteria. Only the studies that followed the PICO criteria were included. Duplicate publications were removed.

Exclusion Criteria

- Literature reviews
- Case reports
- Laboratory studies
- Clinical treatment guidelines
- Participants above 6 years of age
- *Ex vivo* studies
- *In vitro* studies
- Follow-up period less than 3 months.

Qualitative Assessment

Qualitative assessment of the included studies were done using the Cochrane Tool for Assessing Risk of Bias.[7]

Table 1: Patient, intervention, comparison, outcome strategy

Criteria	*Description*
Participants	Children of mean age 5.9 years (71 months)
Intervention	SDF to arrest/prevent dental caries in primary/permanent dentition
Comparison groups	Control groups, other topical fluorides, sealants, annual and biannual application, modification with tannic acid
Outcome	Caries arrest/prevention
Study	Clinical trials

Risk of bias was assessed for each included study from six aspects:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias.

The percentage of dental caries arrested after SDF treatment in each study was calculated with respect to the number of teeth or tooth surfaces with active caries at baseline and the number of teeth or tooth surfaces with arrested caries at follow-up.

The meta-analysis was performed using the Review Manager software (version 5.3). Only studies that reported the results as dichotomous data were analyzed with Cochran–Mantel–Haenszel test. Fixed-effects model was used to evaluate the association between SDF and caries arrest at different follow-up examinations. The pooled odds ratio was used to compare the relative odds of the caries arrest by usage of SDF (confidence interval = 95%). The I^2 statistic was used to assess statistical heterogeneity between studies, where I^2 values of 25, 50, and 75% indicated low, medium, and high heterogeneity respectively.

REVIEW RESULTS

Study Identification and Characteristics

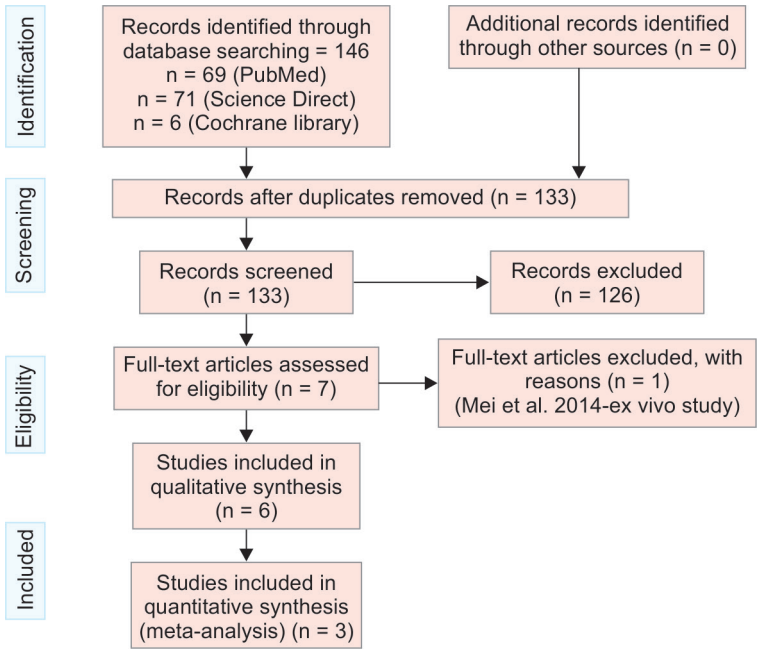
Flow diagram describing the process of studies selection related to caries arrest by SDF as seen in Flow Chart 1. The search generated 146 articles for screening (69 from PubMed, 71 from ScienceDirect, and 6 from Cochrane Library). From the imported references, 133 were screened against title and abstract by the two reviewers after duplicates were removed. Out of these, 126 studies were excluded based upon the inclusion criteria and 7 were assessed for full-text eligibility in which 1 study was excluded (*ex vivo* study). Finally, six articles were selected for the full-text analysis and quality assessment.

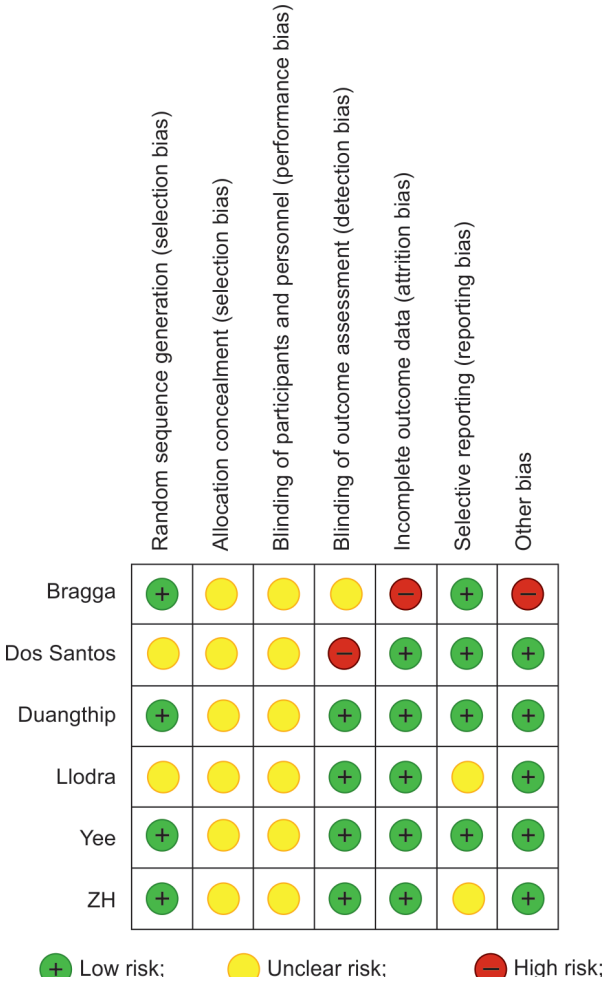
Qualitative assessment was done for each study and overall showed a low risk of bias (Graph 1). Only three studies presented with dichotomous type of data and thus were used for meta-analysis.

Overall Summary

The data from the studies which were included for the meta-analysis were divided into three subgroups according to the time intervals for application of SDF, i.e., at 3, 6, and 18 months and above.

Flow Chart 1: Preferred reporting items for systematic reviews and meta-analyses 2009 flow diagram for study selection





Graph 1: Risk of bias summary

In the overall meta-analysis (Graph 2), there was an association between caries arrest in the groups using SDF and the other control groups [odds ratio= 0.66 (0.5–0.78)].

Subgroup analysis showed the following associations at the 3-month interval [odds ratio = 0.55 (00.43–0.73)] and 6-month interval [odds ratio= 0.56 (00.43–0.74)]. At 18 months and above; however, there was no association seen [odds ratio = 1.01(0.75–1.36)].

Substantial quantitative heterogeneity was found on the multiplicative scale (I^2 = 83%, p < 0.00001) owing to the fact that SDF was used in various concentrations and at various treatment time intervals.

DISCUSSION

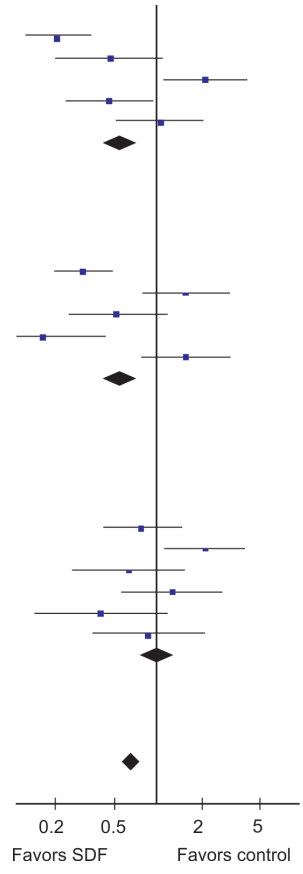
Dental caries is a significant disease that affects children worldwide. The global average of decayed-missing-filled teeth is 2.4. International data confirm that dental caries still remains a serious disease of childhood that is observed in children from both developing and developed countries.[8]

Since 1969, there have been inaccuracies in the nomenclature for SDF (Ag $[NH_3]_2F$). Silver diamine fluoride contains an "ammine" (NH_3) group and not an "amine" ($-NH_2$) group. "Amine" denotes a covalently bound $-NH_2$ group, while an "ammine" is a chemical species in which one or more ammonia molecules (NH_3) are bound in a coordination complex with a metal ion. This distinction is important and should be kept in mind to prevent future errors.[9]

The safe, effective, patient-centered, time efficient, and widely implemented use of SDF meets the WHO millennium goals. Silver diamine fluoride could possibly increase access to care for remote areas, boost oral health, and, in due time, reduce the need for emergency care and treatment.[10]

1.1 Caries arrest

Study or subgroup	SDF Events	SDF Total	Control Events	Control Total	Weight	Odds ratio M-H, Fixed, 95% CI
1.1.1 Caries arrest at 6 months						
Dos santos	28	183	76	162	19.0%	0.20 [0.12, 0.34]
Duangthip (1)	82	100	97	107	4.7%	0.47 [0.21, 1.07]
Duangthip (2)	82	100	66	97	3.4%	2.14 [1.10, 4.16]
Zhi (3)	31	71	43	69	6.8%	0.47 [0.24, 0.92]
Zhi (4)	31	71	31	72	4.8%	1.02 [0.53, 1.99]
Subtotal (95% CI)		525		507	38.7%	0.55 [0.42, 0.73]
Total events	254		313			
Heterogeneity: $Chi^2 = 34.41$, df = 4 ($p < 0.00001$); $I^2 = 88\%$						
Test for overall effect Z = 4.24 ($p < 0.0001$)						
1.1.2 Caries arrest at 12 months						
Dos santos	56	169	94	153	18.3%	0.31 [0.20, 0.49]
Duangthip (5)	70	90	62	90	3.8%	1.58 [0.81, 3.08]
Duangthip (6)	70	90	87	100	5.1%	0.52 [0.24, 1.12]
Zhi (7)	37	67	53	60	7.0%	0.16 [0.06, 0.41]
Zhi (8)	37	67	28	64	3.6%	1.59 [0.80, 3.16]
Subtotal (95% CI)		483		467	37.8%	0.56 [0.43, 0.74]
Total events	270		324			
Heterogeneity: $Chi^2 = 31.28$, df = 4 ($p < 0.00001$); $I^2 = 87\%$						
Test for overall effect: Z = 4.11 ($p < 0.0001$)						
1.1.3 Caries arrest at 18 months and above						
Dos santos	0	0	0	0		Not estimable
Duangthip (9)	49	89	54	89	6.7%	0.79 [0.44, 1.44]
Duangthip (10)	40	89	27	97	4.0%	2.12 [1.15, 3.89]
Zhi (11)	51	67	50	60	3.5%	0.64 [0.26, 1.54]
Zhi (12)	51	67	46	64	3.1%	1.25 [0.57, 2.73]
Zhi (13)	47	60	53	59	3.2%	0.41 [0.14, 1.16]
Zhi (14)	47	60	50	62	3.0%	0.87 [0.36, 2.09]
Subtotal (95% CI)		432		431	23.5%	1.01 [0.75, 1.36]
Total events	285		280			
Heterogeneity: $Chi^2 = 10.60$, df = 5 (p = 0.06); $I^2 = 53\%$						
Test for overall effect: Z = 0.06 (p = 0.95)						
Total (95% CI)		1440		1405	100.0%	0.66 [0.56, 0.78]
Total events	809		917			
Heterogeneity: $Chi^2 = 86.34$, df = 15 ($p < 0.00001$); $I^2 = 83\%$						
Test for overall effect: Z = 4.95 ($p < 0.00001$)						
Test for subgroup differences: $Chi^2 = 10.62$, df = 2 (p = 0.005), $I^2 = 81.2\%$						



Graph 2: Forest plot: (1) group I *vs* control; (2) group I *vs* II; (3) group I *vs* II; (4) group *vs* control; (5) group I *vs* II; (6) group I *vs* control; (7) group I *vs* II; (8) group I *vs* control; (9) group I *vs* II; (10) group I *vs* control; (11) 18 months: group I *vs* II; (12) 18 months: group I *vs* control; (13) 24 months: group I *vs* II; (14) 24 months: group I *vs* control

The included studies for the quality assessment with different concentrations and time intervals are depicted in Table 2. Studies showing clinically better outcomes are highlighted in blue, whereas studies showing clinically low outcomes are highlighted in red.

In the study by Zhi et al[11] where a comparison was done to evaluate the effectiveness of the annual topical application of SDF solution, semiannual topical application of SDF solution, and an annual application of a flowable high fluoride-releasing glass ionomer in primary teeth for arresting active dentin caries. Results of the study showed that application of SDF 38% semiannually was favorable compared with application annually and/or glass ionomer.

The tannic acid from boiled tea does not appear to have any significant additional effect on arresting caries compared with 38% SDF alone, but it helps in the reduction of the black staining caused due to SDF. Results from the study conducted by Yee et al[12] showed that single application of 38% SDF, with or without the use of tea as a reducing agent, was more effective in arresting dental caries in all primary teeth of young children than 12% SDF or no application (control); nevertheless, the arresting caries effect of 38% SDF diminishes slowly over time.

The clinical outcomes at 36 months by Llodra et al[13] depicted that the 6-monthly application of a 38% SDF solution is beneficial to control caries in deciduous teeth

Table 2: Summary of the included studies

Author/year	*Study design*	*Age*	*Intervention*	*Control*	*Follow-up*	*Outcome*
Duangthip et al 2016	Randomized controlled trials	3–4 yrs	Group I: 30% SDF, annually Group II: 30% SDF at weekly interval	Group III: 5% sodium fluoride	6, 12, and 18 months	Group I (40%) > group II (35%) > group III (27%)
Dos Santos et al 2012	Randomized controlled trials	5–6 yrs	Group I: 30% SDF	Group II: glass ionomer as IRT	6 and 12 months	Group I (67%) > group II (39%)
Zhi et al 2012	Randomized controlled trials	3–4 yrs	Group I: 38% SDF, annually Group II: 38% SDF, semiannually	Group III: glass ionomer, annually	6, 12, 18, and 24 months	Group II (91%) > group III (82%) > group I (79%)
Yee et al 2009	Randomized controlled trials	5.2 (mean)	Group I: 38% SDF Group II: 38% SDF + tea Group III: 12% SDF	Group IV: no treatment	6, 12, and 18 months	Group II (32%) > group I (31%) > group III (22%) > group IV (15%)
Braga et al 2009	Randomized controlled trials	5–7 yrs	Group I: 10% application of SDF	Group II: CTT Group III: GIC fissure sealant	Baseline and after 3, 6, 12, 18, and 30 months	No significant difference among groups at 30 months
Llodra et al 2005	Randomized controlled trials	6 yrs	Group I: 38% SDF	Group II: no treatment	36 months	Group I (97%) > group II (48%)

and the approach is also advantageous to prevent caries in erupting first permanent molars.

The 38% SDF contains 44,800 ppm fluoride. The average dosage of SDF applied with a micro-applicator is 0.22 mg (8.8 μg F). Dental fluorosis can be considered a theoretical risk since the quantity of SDF applied on numerous carious teeth is distant from reaching the acute toxic levels.[14] If there is accidental ingestion of voluminous amount of SDF, it is best to seek for medical assistance. Emesis may be induced to avoid absorption in the body; 10% calcium gluconate (10 mL) solution is beneficial since insoluble calcium fluoride (CaF_2) is formed, which is not absorbed in the gastrointestinal tract.[4]

Few studies like Dos Santos et al[15] and Duangthip et al[16] have shown that SDF used in the concentration of 30% is effective. According to Dos Santos et al,[15] follow-up at 12 months revealed that SDF 30% was more effective than interim restorative treatment (IRT) using glass ionomer cement (GIC) for the arrest of caries. Duangthip et al[16] devised a study with the following groups where the application of 30% SDF solution was done every 12 months, applications of 30% SDF solution done at a weekly interval, and three applications of 5% sodium fluoride (NaF) varnish at a weekly interval at baseline. The conclusions made were that the two SDF solution application protocols (groups I and II) significantly reduced the time to caries arrest when compared with the NaF varnish application protocol (group III). Between the two SDF solutions, no significant differences were observed at the 18-month follow-up.

Routine preventive treatment comprises of topical fluoride treatment for smooth surface caries and GIC for pit and fissure caries, but in comparison, the carries arresting outcome is seen to be superior in the case of SDF. Future preventive therapies for children suffering from ECC can include SDF as an adjunct for the treatment.

Few of the studies like Braga et al[17] and Yee et al[12] have used SDF in the concentration, such as 10 and 12% respectively. These studies have shown to have reduced caries arresting rate as compared with control groups when compared with the percentage of caries arrest seen with 38 or 30% SDF application. Braga et al[17] conducted a study involving following groups: Cross tooth-brushing technique (CTT), application of SDF, and glass ionomer fissure sealant. Observations after 12 months revealed that both SDF and GIC treatments were more effective than CTT in controlling occlusal caries. Longer than 18 months, all noninvasive techniques were similar in controlling enamel caries in erupting permanent molars. Therefore, usage of SDF in low concentrations is seen to have no significant outcome in caries-arresting effect.

The major drawback of silver compounds is the black staining effect on carious tissue. This discoloration is caused by the oxidation of ionized silver into metallic silver; which possibly hinders the acceptance in patients who value esthetics.[14] Usage in higher concentrations or repeated application of SDF leads to the formation of silver phosphate, which produces black staining of carious enamel and dentin, but not sound tooth tissue.[9] To combat the staining problem, potassium iodide can be administered to form a creamy white substance of silver iodide.[4]

The usage of SDF can be substantiated for the treatment of the primary tooth that will eventually shed and also in minimal intervention strategies where tooth-colored restorative materials can mask the discoloration. Social acceptance may be low for esthetically demanding patients, especially over the upper anterior teeth facial surfaces, a common site for ECC.[14] In developing countries where health care is not adequate due to the lack of economy and awareness, SDF can serve as an effective material in caries arresting and prevention. Tannic acid from boiled tea has been suggested as an inexpensive substitute for stain removal.[12]

There are some limitations of this study, as only studies published in the English language were included, whereas many clinical trials have been performed and reported in non-English languages. Also, most studies used various concentrations and various treatment intervals, thus the caries surfaces arrested were taken into account rather than the number of teeth to overcome the vast heterogeneity. Considering the following limitations, future research should try to incorporate studies showing significant results in all possible languages.

CONCLUSION

In conclusion, SDF used in concentrations of 38 and 30% have been shown to effectively arrest caries lesions in children suffering from ECC. Considering the clinical significance, the cost per application of SDF is comparable to GIC and topical fluoride treatment, it can be an adjunct to preventive care in rural areas and also in urban areas where esthetic is not the highest demand of the patient and parents.

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