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Comparison of the Effectiveness of Nano-Silver Fluoride with Silver Diamine Fluoride in Caries Arrest and Microbial Colonization in Children- A Systematic Review and Meta-Analysis

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Ashwin Jawdekar [1*], Mrunmayee Soman [2], Nikita Khachane [2], Pakhi Shah [2], Arati Vaiude [2]

[1, 2]Department of Pediatric and Preventive Dentistry, Bharati Vidyapeeth (Deemed-to-be University) Dental College and Hospital, Navi Mumbai, Maharashtra 410210, India.

*** Corresponding author:**
Ashwin Jawdekar
Professor and Head,
Department of Pediatric and Preventive Dentistry, Bharati Vidyapeeth (Deemed-to-be University) Dental College and Hospital, Navi Mumbai, Maharashtra 410210, India.
Phone: (+91) 9821009615
E-mail: ashwin.jawdekar@bharatividyapeeth.edu

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ABSTRACT

Background: Nano-silver fluoride (NSF) can be an alternative to silver diamine fluoride (SDF) due to its comparable caries-arresting and non-staining properties. Despite availability of primary research, no systematic review and meta-analysis (SRMA) was reported in children.

Purpose: To compare the effectiveness of NSF with SDF in caries arrest and microbial colonization.

Methods: Two investigators accessed randomized trials in English (full texts or translations) comparing NSF with SDF in children using different keyword combinations using PubMed and Cochrane Library databases. The search was extended to Google Scholar and Semantic Scholar. Data were extracted for SRMA. Risk of bias and publication bias was assessed using Cochrane tool and funnel plot, respectively. GRADE approach was used for quality appraisal.

Results: Results of twelve studies remained in the systematic review and five in the meta-analysis. Based on five studies (N=1310), Or (95% CI) were 1.13 (0.53, 2.41) favouring NSF; however, the results were statistically non-significant. Heterogeneity being high (I^2 = 86%), random effects model (REM) was used. In an additional analysis, based on eleven studies (N= 1610), the summarized proportion (95% CI) of NSF in arresting caries was 0.73 (0.71 - 0.75). Heterogeneity being high (I^2= 88%), REM was used. Risk of bias was moderate and publication bias was strongly suspected. Certainty of evidence was very low.

Conclusions: No significant difference was observed in the effectiveness of NSF compared with SDF in preventing carious lesions. NSF was effective in preventing approximately 70% of lesions. NSF had better antimicrobial activity than SDF. The quality of evidence was very low. More primary research is needed.

Key-words: Caries arrest; Dental caries; Fluoride; Lactobacilli; Minimal Intervention Dentistry; Nano-silver fluoride (NSF); Silver diamine fluoride (SDF); S. mutans

INTRODUCTION

The published literature provides clear evidence of the burden of caries which has a direct impact on the quality of life[1]. Dental caries can be prevented, and its progression can be arrested[2]. Fluoride therapy for dental caries is used by dentists as an effective preventive and management technique[3]. It thus enables management by a conservative approach to early lesions without the need for any restoration, leading to less destruction of tooth structure[2].The mechanism and mode of action of fluoride are well described in the medical literature4. Many forms of topical fluoride are available, ranging from self-applied such as toothpaste and mouth rinses to professionally applied such as fluoride varnish, sealants, and SDF (silver diamine fluoride)[5]. Two Cochrane reviews[6,7] have shown that professionally applied fluoride therapy is effective against the prevention and arrest of caries in children and adolescents with little or no toxicity concerns. Research shows that silver-containing fluorides such as silver diamine fluoride (SDF) are effective in minimally invasive dental caries management[8]. SDF applied to decayed enamel and dentin can prevent caries due to its antibacterial, remineralizing, and collagenase inhibiting properties[9,10]. The addition of nano-silver particles enhances these therapeutic properties and reduces some of the associated risks, such as discoloration of teeth in particular [11]. Despite the availability of numerous trials and some reviews assessing and comparing the effectiveness of nano-silver fluoride (NSF) with SDF, a comprehensive systematic review and meta-analysis (SRMA) was much needed which is attempted in this systematic review.

Research question and objectives

How effective is NSF compared to SDF in terms of caries arrest and microbial colonization in children?

The main objective of the SRMA was to compare the effectiveness of NSF with SDF and possibly with other agents (placebos) with respect to dental caries arrest in children. Additionally, the antimicrobial effects of NSF and SDF could be assessed.

The PICOS were identified as:

Population (P): Children with dental caries

Intervention (I): NSF

Control (C): SDF, other agents (placebos)

Outcomes (O): Caries arrest/ inactive lesions, levels of microorganisms such as S. mutans, lactobacilli

Study design (S): SRMA of RCTs and CCTs

MATERIAL AND METHODS

Registration

Research protocol for the current study using PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist was registered on PROSPERO, the study is reported using the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) checklist[12,13].

Eligibility criteria

Articles with complete text published in English or full translations available in English were included. Only randomized controlled trials (RCTs) or controlled clinical trials (CCTs) were selected. Trials reporting specific variables of interest such as % caries arrest or antimicrobial action were considered for selection. All studies in children on both primary and permanent teeth were selected.

Information sources

Complete search for published trials was performed using the information sources such as the PubMed and Cochrane Library. search engines such as Google Scholar, Semantic Scholar, etc. were used to extend the search. Cross-references were used for furthering the search. Articles published up to October 31, 2024 including the ones in online first/ pre-production stage of publication, were included. A PRISMA flow chart depicting the selection of articles is presented in Figure 1.

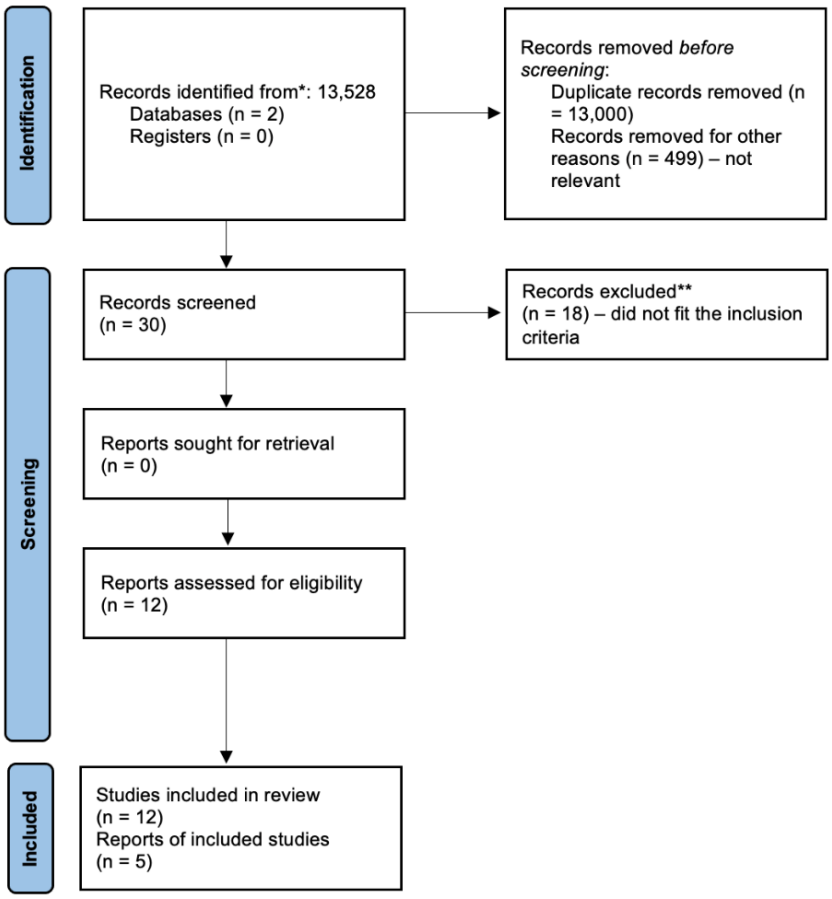

Figure 1. PRISMA flowchart depicting study selection

Search strategy

Different combinations of keywords such as Nano-silver fluoride, silver fluoride, silver diamine fluoride, nanoparticles and fluoride, silver-modified fluorides, etc. were employed. A complete PubMed search was undertaken using appropriate advanced methods and filters to include RCTs and CCTs but not the non-randomized trials, observational or in vitro studies. Titles and abstracts were screened for the same. Articles with full texts from PubMed and other sources were scrutinized to meet the eligibility, duplication removal, and availability of necessary data for the systematic review (SR) and possibly, the meta-analysis (MA).

Study records

Two independent reviewers (MS and NK) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) selected the studies, independently. A third reviewer (PS) was consulted in case of disagreements. The final selection was confirmed by the supervisor (AJ). The extracted data are presented in Table 1.

Data items

Data included several parameters starting with the authors, year, settings of the study, observation period, intervention (NSF)% success, control (SDF/placebo) % success, bacterial colonization, adjusted odds ratio (AOR) or confidence interval (CI), etc. The variables of interest were the independent variables such as interventions or comparator (NSF, SDF or other) and dependent variables such as activity/arrest of caries and changes in the microbial counts. Additionally, the sample characteristics such as age, gender type, concentrations and frequency of applications of the agents, and follow-up period were recorded as per the availability of the data. Finally, based on the merit of inclusion (the eligibility) and availability of common parameters for the meta-analysis, the studies were identified for inclusion in the SR only or both SR and MA.

Outcomes and prioritization

The independent variable was the NSF application for comparison with the SDF application or any other agent. The most important dependent

variable was the activity /arrest of dental caries followed by the levels of microorganisms such as S. mutans and lactobacilli.

Risk of bias in individual studies

Assessment of the risk of bias (ROB) of individual studies was done at study level using the Cochrane ROB tool for all trials. Risks pertaining to all domains for each study were assessed and the overall bias across the domains is reported.

Data synthesis plan

Summary proportions for comparison such as % inactive/ arrested lesions (95% confidence intervals) were analysed using the forest plot method using appropriate models (fixed or random effects) depending on the heterogeneity (I^2). Additional analysis was attempted to assess the effectiveness of NSF from the pooled data from all available studies.

Meta-bias(es)

Attempt was made to assess the publication bias using the funnel plot method for all studies on the NSF.

Confidence in cumulative evidence

The strength of the body of evidence was assessed using the GRADE approach.

Data extraction

Data were extracted from various studies including comparisons of NSF, primarily Vs SDF, and also with placebo and other agents. A total of six studies compared NSF with SDF (Table 1); three studies compared NSF with placebo: water/ saline (Table 2); one study compared NSF with NaF (Table 3) and p 11-4 while one study compared two different concentrations of NSF (Table 4). Two studies assessed the anti-microbial effects of NSF and SDF (Table 5).

RESULTS

Analyses were carried out using RevMan and an online resource metaanalysisonline.com.

Based on the extracted data, six studies were considered for inclusion in the SR and five studies were included in the MA. The risk of bias assessment using the Cochrane Risk of Bias Tool for RCTs is presented in Figures 2 and 3[14]. Two studies had high risk of bias in blinding of participants and personnel[15,16]. One study had unclear risk of bias pertaining to random sequence generation and allocation concealment[18]. Other biases were stated as unclear. Across domains, attrition and reporting biases were nil and performance bias was 33.33%. Unclear selection and detection biases were seen as about 20%.

Table 1: Effect on caries lesion arrest NSF Vs SDF

Authors / Year/ Country	Sample size	Characteristics	Observation period	Intervention (NSF) % success	Control (SDF) % success	AOR (CI)	Remarks
Quritum et al./ 2024/ Egypt[15]	1853 lesions 881 lesions (NSF) 972 lesions (SDF) 360 children (180 in each group)	1) Mean Age: 42.3 ± 8.2 months 2) ICDAS ≥ 3	6 months	78.4%	65.0%	2.57 (1.55, 4.26)	Parent satisfaction was recorded as 97.2% in NSF and 76.1% in SDF group, respectively. Included in the MA.
			12 months	71.3%	56.3%	3.27 (1.89, 5.67)	
Ammar et al./ 2022/ Egypt[16]	130 lesions 71 lesions (NSF) 59 lesions (SDF) 50 children (25 in each group)	1) Mean Age: 4.75 ± 0.76 years 2) ICDAS = 5 3) 63% posterior teeth	1 month	64.4%	63.4%	1.355	Included in the MA.
Tirupathi et al. / 2019/ India[17]	159 lesions 71 lesions (NSF) 76 lesions (SDF)	Mean Age: NSF 7.88 ± 1.3 years SDF 8.39 ± 1.41 years	1 month	67/71	71/76		Included in the MA.
			3 months	63/71	64/76		
			6 months	57/71	60/76		

	50 children 24 (NSF) 26 (SDF)		12 months	55/71	54/76	
Al-Nerabieah et al./ 2020/ Syria[18]	244 lesions (122 in each group) 118 children (59 in each group)	Mean Age: NSF 3.6 years SDF 3.9 years	3 weeks	77%	90%	Child acceptance was recorded as 85% and 91.5%, in NSF and SDF group, respectively. Included in the MA.
			6 months	67.2%	79.5%	
Al-Nerabieah et al./ (2020/ Syria[19*]	164 lesions 83 lesions (NSF) 81 lesions (SDF) 63 children 32 (NSF) 31 (SDF)	1) Mean Age: NSF+GTE 3.9 SDF 4.1 2) ICDAS = 5	21 days	77%	90%	Included in the MA.
			3 months	71%	85%	
			6 months	67.4%	79%	
Butron et al./ 2017/ Iran[20#]	44 teeth (22 in each group) 44 children (22 in each group)					Baseline fluorescence intensity was recorded as 5.68 ± 1.00 and 5.50 ± 0.8 in NSF and in NSF and SDF group, respectively. After 3 months, fluorescence intensity was recorded as 3.68 ± 1.2 and 5.09 ± 1.0 in NSF and SDF group, respectively. Not included in MA.

*Referred to as Al-Nerabieah et al. (2020) [18] in the analysis

#Study by Butron et al. (2017)[20] was excluded from the meta-analysis due to unavailability of a common parameter (% arrested caries)

Table 2: Effect on caries lesion arrest NSF Vs Placebo

Authors / Year/ Country	Sample size	Characteristics	Observation period	Intervention (NSF) % success	Control (Placebo) % success	Remarks
Santos et al. / 2014 /Brazil[21]	130 lesions 60 children	Mean Age: 6.31 ± 0.60 years	7 days	81%	0 % (water)	Included in the additional analysis.
			5 months	72.7%	27.4%	
			12 months	66.7%	34.7%	
Nagireddy et al. / 2019/ India[22]	100 lesions 60 children	1) Mean Age: 6 ± 0.6 years 2) ICDAS= 5	7 days	78%	0% (saline)	Included in the additional analysis.
			5 months	72.91%	34%	
			12 months	65.21%	28.88%	
Devi et al./ 2023 /India[23]	148 children	1) Mean Age: 6.19 ± 0.56 years 2) ICDAS = 5	1 month	56.3%	43.7% (water)	Included in the additional analysis.
			3 months	59.2%	40.8%	
			6 months	62%	38%	

Table 3: Effect on caries lesion arrest NSF different concentrations

Authors / Year/ Country	Sample size	Characteristics	Observation period	Intervention (NSF 600) % success	Intervention (NSF 400) % success	Remarks
Arnaud et al.*/ (2021) /Brazil[24]	173 lesions 68 children	1) Mean Age: 6.06 ± 0.860 NSF 600, 0.840 NSF 400 2) ICDAS = 5	6 months	NSF 600 72.7%	NSF 400 56.5%	Included in the additional analysis.

*This study is considered twice with both concentrations of NSF in the additional analysis and is referred to as Arnaud et al. (2021) and Arnaud et al. (2021) - a for NSF 600 and NSF 400 concentrations, respectively[24]

Table 4: Effect on caries lesion arrest NSF Vs NAF and p11-4

Authors / Year/ Country	Sample size	Characteristics	Observation period	Intervention (NSF) % success	Intervention (NaF) % success	Intervention (p11-4) % success	Remarks
Atteya et al./ 2023 /Egypt[25]	147 lesions 66 children	1) Mean Age: 13.46 ± 4.31 years 2) White spot lesions	1 month	11.4	6.8	18.2	Included in the additional analysis.
			3 months	31.8	10.2	40.9	
			6 months	40.9	15.3	45.5	
			12 months	47.7	30.5	54.5	

Table 5: Assessment of anti-microbial effect of NSF Vs SDF

Author/ Year/ Country	Sample size	Characteristics	Bacterial Count	Intervention (NSF)	Control (SDF)	AOR	Remarks
Ammar et al./ 2022/ Egypt[16]	130 lesions (59 in NSF and 71 in SDF group) 50 children (25 in each group)	Mean Age: 4.75 ± 0.76 years	S. mutans	21.3%	10.5%	1.281	At 1 month
			Lactobacilli	13.9%	6%	1.888	
Ghareep et al./ 2023/ Egypt[26]	60 lesions (30 in each group) 30 children	Mean age: 5.51 ± 0.96 years	Lactobacillus at 9 months (CFU)	0.37 ± 0.32	0.19 ± 0.36		At 9 months
			S. mutans (CFU)	0.6 ± 0.35	0.34 ± 0.21		

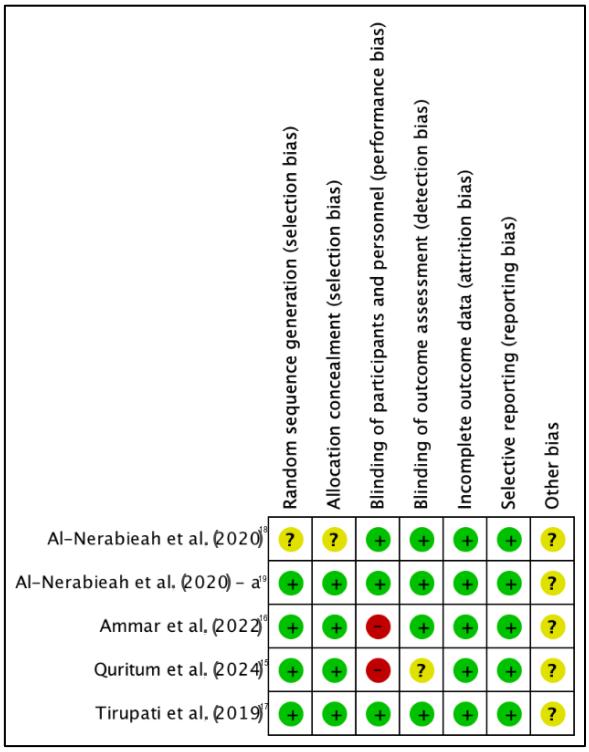

Figure 2. Risk of Bias across the studies using Cochrane Risk of Bias Tool for RCTs

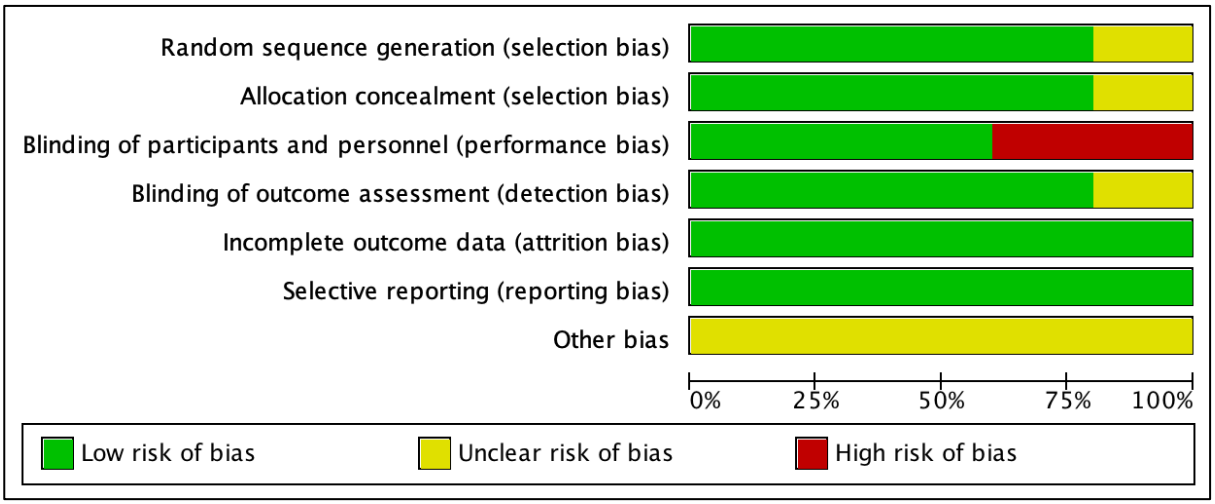

Figure 3. Risk of Bias across the domains using Cochrane Risk of Bias Tool for RCTs

The meta-analysis based on the summary statistic OR (95% CI) for the comparison of NSF and SDF in terms of caries lesion arrest are presented using the forest plot are presented in Figure 4. Based on 5 studies (N=1310), the OR (95% CI) were found to be 1.13 (0.53, 2.41) favouring NSF; however, the results were statistically non-significant. Since the heterogeneity was high (I^2 = 86%), REM was used (Figure 5).

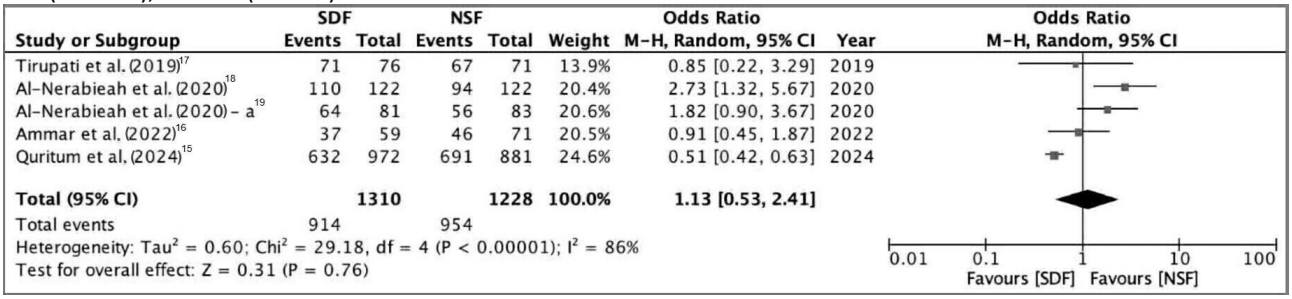

Figure 4. Meta-analysis using forest plot for the comparison of NSF and SDF in terms of caries lesion arrest

In an additional analysis based on 11 studies (N= 1610), the summarized proportion (95% CI) of NSF was effective in arresting caries was 0.73 (0.71 - 0.75). Heterogeneity was high (I^2= 88%); REM was used (Figure 5).

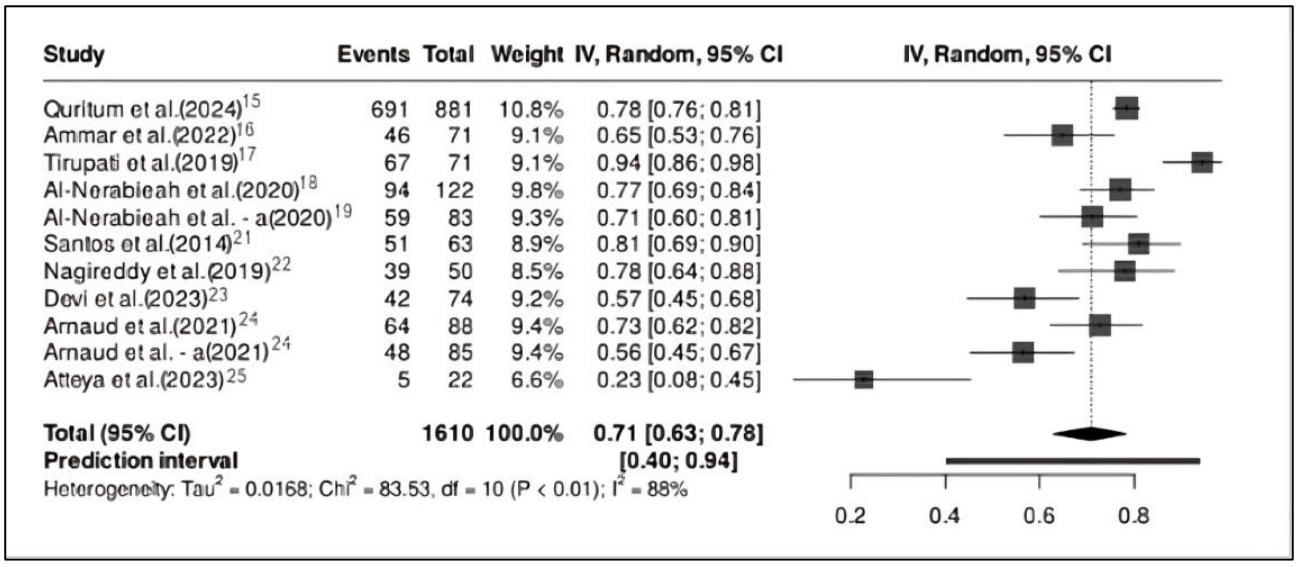

Figure 5. Meta-analysis using forest plot for the effectiveness of NSF

The publication bias was assessed using funnel plot method for all studies reporting data of NSF (Figure 6). The publication bias was found to be moderate with asymmetric dispersion of studies and the funnel excluding five studies.

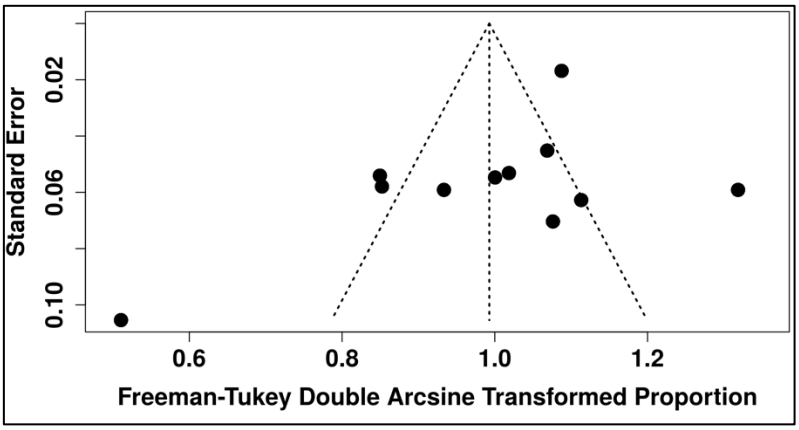

Figure 6. Funnel plot for detecting publication bias

GRADE approach was used for the assessment of overall quality. Table 6 summarizes the parameters of certainty for the GRADE assessment. The overall quality was judged as very low.

Table 6. GRADE analysis

Certainty parameters for rating down	Remark	Rating	Certainty of evidence
Risk of bias	Moderate	-1	⊕OOO Very Low
Inconsistency	Yes	-1	
Indirectness	No	0	
Imprecision	No	0	
Publication bias	Strongly suspected	-1	

DISCUSSION

Fluorine is the most electronegative and highly reactive diatomic halogen gas which is never found free as an element in nature. Fluoride or fluoride compounds are the results of chemical combination of fluorine with other elements that are widely distributed in varying amounts in various environmental sources such as water, soil, air, food, etc.[27-30]. Various studies have reported that specific levels of fluoride have a potential effect on reducing dental caries, which has been attributed to various mechanisms, such as inhibition of plaque formation, prevention of demineralization and enhancement of remineralization[31]. Evidence has also shown that exposure to optimal levels of fluoride during infancy and childhood contributes to better tooth development and a reduced incidence of tooth decay in adulthood [32]. Excessive use of topical home dentifrices, mouthwashes, foods or beverages containing fluoride can cause dental fluorosis [33,34]. Its toxic effects can be observed from the molecular level to clinical manifestations, causing developmental abnormalities[35].Thus, fluoride shows bidirectional effects on remineralization of dental lesions when applied appropriately and under the guidance of a health care professional [33,34]. SDF and NSF are specific topical formulations that do not have systemic side effects and are indicated for caries control.

A recent SRMA, based on 17 studies, having 4067 children found both NSF and SDF effective in arresting caries on primary teeth ($p < 0.05$) compared with a placebo or no treatment[36]. Another investigation, based on 584 articles, reported success with NaF varnish, NSF, and SDF; however, articles reported irreversible changes in colour of SDF-treated teeth[37]. However, the articles reported irreversible discolouration of SDF treated teeth[34]. Earlier, an extensive SRMA of a total of 2177 articles (17 RCTs) published during 1948 and 2014 reported an overall dentinal caries arrest with SDF to be 65.9 % (95 % CI: 41.2 % - 90.7 %; $p < 0.001$)[37]. However, to our knowledge until the initiation of this investigation there had been no SRMA reports comparing NSF and SDF and assessing their effect on microbial colonization.

During the last decade, SDF has been considered a gold standard for the prevention of active lesions[38] yet it has not gained popularity due to its black discoloration and metallic taste after application to carious lesions, which is a drawback especially in the treatment of anterior teeth[18]. Therefore, it is of utmost importance to find another equally effective treatment in caries prevention without the above drawbacks[39].

The main aim of our SRMA was to assess the effectiveness of NSFs compared with SDFs in preventing caries, their antimicrobial action and the reporting of harms, if any. Based on the five studies included in the MA we found no significant difference in the prevention of caries lesions. One study (not included in the MA but a part of SR) showed higher fluorescence levels indicating higher remineralization in SDF group[20], and two studies showed mixed acceptance to NSF; NSF more acceptable to SDF by parents and SDF more acceptable to NSF by children. Our findings are in agreement with a systematic review that compared SDF with other agents reporting the overall caries arrest with SDF to be 25%- 99% in comparison with that of NSF being 58.3%- 100% with NSF[40]. According to another article, NSF may be considered better than SDF because it does not leave stains and has better caries-preventive and antimicrobial properties than SDF[41]. However, we could not confirm these observations in our SRMA. Therefore, more primary research is needed before NSF should be considered an effective and acceptable alternative to SDF and deserves consideration for clinical use.

Meta-analyses of comparison of NSF with other agents (apart from SDF) was not possible due to a variety of reasons such as negative controls (water or saline), different mechanism of action (NSF Vs NaF/ p11-4) and different sample characteristics[21-23,25]. Hence, an attempt was made to assess the mean effectiveness of NSF in the additional analysis. In the additional analysis, effectiveness of NSF in arresting caries was found to be 70%. This analysis revealed that NSF was effective and its effectiveness is comparable to SDF in terms of arresting lesions.

Only one study compared different concentrations of NSF; though NSF 600 was found more efficacious, more trials are needed for a conclusive statement[23]. Although two studies were available for the comparison of antibacterial effects of NSF and SDF, there was no common variable to attempt meta-analysis. Both studies, however, favoured NSF against SDF in terms of antibacterial potential [16,26]. The main limitations were studies with small sample sizes, heterogeneity due to differences with reference to caries thresholds, age, dentition and inconsistent follow-up periods, etc. Moreover, acceptance of parents and children was not consistently reported. Additionally, costs of the intervention were not compared. Finally, both the interventions are effective; however, the overall quality of the evidence is very low while comparing the two to make a specific recommendation.

SDF may be applied without the help of any instruments thus making it an ideal material to use outside of clinical atmosphere such as in public health settings. Through our research, nano-silver fluoride a new formulation is an efficient agent against caries that does not stain tooth tissue. NSF has additional

antimicrobial properties against S. mutans and lactobacillus. Thus, with the current literature, it can be definitively said that NSF may be the next new alternative in minimally invasive dentistry.

CONCLUSIONS

Based on our SRMA (5 studies, N=1310), we conclude that there was no significant difference in the effectiveness of NSF compared to SDF in arresting carious lesions. Based on an additional analysis (11 studies, N= 1610), NSF could be effective in arresting about 70% lesions. NSF has superior antimicrobial action compared to SDF (2 studies, N= 190). The quality of evidence using GRADE approach was very low with high heterogeneity, moderate risk of bias and suspected publication bias. More primary research is needed to assess effectiveness, acceptance, and cost-effectiveness of NSF compared to SDF. NSF has potential for use in arresting caries without discolouration.

FUNDING

This was a self-funded study with no external source.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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