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Effect of Nanosilver Fluoride Varnish on Demineralized Primary Teeth: A Systematic Review

Abdulwahab Mohammed Rashed Aldubayyan[1], Ahmed Tarik Ahmed Alsuawari[1*], Bassam Mansour Alotaibi[1], Hussam Abdullah Fawaz Almalki[1], Faisal Saleh Alkhamis[1], Bader Al Hussein[2], Dr. Shahzeb H. Ansari[3]

[1]General Dentist, Riyadh, Saudi Arabia
[2]Consultant Restorative Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia
[3]Faculty Preventive Dentistry, REU, KSA College of Dentistry, University of Riyadh Elm, Riyadh, Saudi Arabia

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***Corresponding author:** Ahmed Tarik Alsuawari
General Dentist, Riyadh, Saudi Arabia

Abstract

Demineralization of teeth or caries is a common health problem among pediatric patients. It is a more serious issue among children from low-income households due to their lack of access to proper dental care. Silver diamine fluoride (SDF) is an effective agent used to treat demineralization, but experiments are being done to replace it with nanosilver fluoride (NSF). The purpose of this study was to assess the effectiveness of nanosilver fluoride varnish in containing demineralization of primary teeth. A systematic literature review method was used. About 15 articles met the inclusion criteria. Findings are conflicting, but most of the reviewed studies confirmed the effectiveness of an agent with nanoparticles compared to all other alternatives, especially SDF. Apart from suppressing microorganisms that cause demineralization at very low concentrations, agents with nanoparticles protect patients from discoloration of teeth and formation stains. Nanosilver fluoride varnish can be used to replace the current alternatives, but the findings should be used with caution since most of the present studies are experimental.

Keywords: Demineralization, NSF, SDF, varnish, teeth, caries.

INTRODUCTION

Dental caries has remained a highly prevalent chronic condition, despite the progress made in the improvement of the healthcare system. It is a multi-factorial disease, and its development is attributed to several etiological factors (such as bacteria, diet, and the host) that contribute to the demineralization that culminates in dental caries (El-Desouky *et al*., 2020, p. 155). Untreated demineralization or dental caries in primary teeth is one of the common epidemics that occur across the world (Al-Nerabieah *et al*., 2020, p. 100). Incidents of untreated demineralization of the primary teeth are common in the population of children from low-income households. The untreated condition progresses to a stage where it causes pain, increases the spread of infections, and subjects the affected children to the risk of malnutrition due to the difficulties they experience while eating (Arnaud *et al*., 2021, p. 207). These effects reduce the quality of life of the patients. This paper presents a systematic literature review of previous studies that focused on the use of nanosilver fluoride varnish in the prevention of demineralization of primary teeth.

Progression of demineralization is associated with the loss of minerals that form the teeth, leading to the development of cavitated lesions. Lessons are more difficult to contain, which creates the need for interventions that can support the process of re-mineralization. Different techniques and interventions have been developed to treat or prevent the carriers. Silver diamine fluoride (SDF) has been shown to be an effective compound that prevents and halts coronary carriers that affect the primary teeth (Nagiereddy *et al.*, 2019, p. 485). SDF is associated with serious side effects, such as the development of reversible lesions that are painful and a tendency to leave black stains on the curious tissue.

Although SDF is an effective and non-invasive intervention, there has been a need to develop

alternative agents that will control demineralization of the primary teeth without leaving black stains on the teeth. Researchers are filling this gap by introducing nanotechnology. This has led to the development of nanosilver fluoride (NSF) agent which has been shown to be effective in containing dentine caries and does not have a staining effect on the patient's teeth (Zhao *et al*., 2020, p. 2830). NSF is obtained from a reddish yellow solution that contains silver nanoparticles (AgNPs), fluoride, and chitosan, but it is currently an experimental agent (El-Desouky *et al*., 2020, p. 154). NSF combines antimicrobial and cariostatic properties, making it an effective anti-caries agent that arrests demineralization without irritating the soft tissue.

Different researchers have classified NSF as an experimental intervention (El-Desouky *et al*., 2020, p. 154; Nagiereddy *et al*., 2019, p. 484). This means that its effectiveness is not fully understood and it is still being studied. Consequently, systematic literature review studies that provide a comprehensive analysis of empirical research on the effectiveness of the new nano agent are scarce. This creates a gap that will be filled in this study. The purpose of this systematic literature review is to provide the analysis of the research articles that focused on examining the efficacy of NSF as an agent for controlling the demineralization of primary teeth.

METHODS

Study Selection

The preferred reporting items of systematic reviews and meta-analyses (PRISMA) framework will be used to present the findings of the studies considered in this paper. The articles reviewed in this paper were located online after performing a literature search through different electronic databases, including Cochrane Library, Web of Science, and PubMed. The search yielded a total of 87 relevant articles as shown in Figure 1. A keyword strategy was used to increase the chances of identifying the most relevant articles with studies linked to the topic. The most important keywords and phrases that were used include NSF and primary teeth demineralization; re-mineralization of primary teeth and NSF; treating children with dental caries and NSF; demineralization prevention and primary teeth; and effectiveness of NSF and primary teeth prevention. This was followed by a review of the titles of the identified articles to determine their relevance to the topic of the research. A total of 27 articles were excluded because of duplication as shown in Figure 1. The remaining articles were reviewed, including their abstracts as well as their full texts to determine their eligibility for this systematic literature review, whereby 15 of them were selected because they met the inclusion criteria as shown in Figure 1.

Inclusion Criteria

Articles were selected if they met all of the following criteria. First, the article must be a primary empirical study, quantitative or qualitative. Secondly, it must be a study based on a randomized controlled trial, case, or cohort control research design. Third, it must have been published in English. Fourth, participants must be humans or children with primary teeth and not animals. Fifth, children who participated in the published study must have been diagnosed with demineralization of the primary teeth and treated with NSF.

Exclusion Criteria

Articles were excluded from the systematic review based on the following criteria. First, participants were children diagnosed with demineralization of the primary teeth, but they were treated with other agents (such as SDF) only without including NSF. Secondly, all non-English articles were excluded. Third, non-empirical publications (including expert opinions and narrative reviews) did not meet the threshold for inclusion in this systematic review. Fourth, articles publishing studies of adult patients with demineralization of permanent teeth and treated with NSF were excluded.

Study Findings

The main purpose of this study was to perform a systematic review of the previous studies that assessed the effectiveness of nanosilver fluoride varnish in controlling the demineralization of primary teeth. In a randomized control trial study of 60 children aged 4-9 years, Nagiereddy *et al*. (2019, p. 484) investigated the level of effectiveness of NSF in arresting the occurrence of caries. The recruited children were randomly assigned to saline and experimental group. Treatment and monitoring occurred in intervals of seven days, five, and 12 months (Nagiereddy *et al*., 2019, p. 484). The finding indicated that the treatment had arrested caries in 78 % and 72.91 % of the participants in seven days and five months, respectively, compared to 34 % in the control group (Nagiereddy *et al*., 2019, p. 484). NSF treatment arrested demineralization in 65.21 % of the participants compared to 28.88 % in the control group (Nagiereddy *et al*., 2019, p. 484). The findings confirmed the effectiveness of NSF.

Zhao *et al*. (2020, p. 2829) investigated the effect of adding nanoparticles to silver-based agents on the re-mineralization of teeth. A sample of 36 blocks obtained from 12 dentine slices was subjected to the in vitro experiment (Zhao *et al*., 2020, p. 2829). The treatment involved subjecting the first, second, and third groups to a sodium fluoride solution, a silver agent with nanoparticles, and de-ionized water, respectively. From the results, treatment with a silver agent with nanoparticles led to re-mineralization without discoloration.

Similar to Nagiereddy *et al*. (2019, p. 484), Al-Nerabieah *et al*. (2020, p. 100) investigated the efficacy of NSF in controlling caries in children with primary

teeth. The study involved the treatment of primary teeth with NSF (60 children) and SDF (59 children), where monitoring was done in three weeks and six months. Cariostatic efficacy was 77 % and 90 % in NSF and SDF groups after three weeks, respectively, whereby $p > 0.05$ (Al-Nerabieah *et al*., 2020, p. 100). This efficacy was 79.5 % and 67.2 % in SDF and NSF groups, respectively, after six months with $p > 0.05$ (Al-Nerabieah *et al*., 2020, p. 100). Therefore, NSF was less effective than SDF

El-Desouky *et al*. (2020, p. 153) investigated the anti-cariogenic effect of a silver agent in a sample of 48 molars. The experiment involved the treatment of the intervention group with NSF. The findings revealed that the lesion depths were 36.36 and -37.30, respectively, for NSF and agents with no nanoparticles and the difference was not statistically significant (El-Desouky et al., 2020, p. 153). The results indicated that NSF and non-silver-based agents were equally effective in containing demineralization.

Arnaud *et al*. (2021, p. 207) studied the effectiveness of silver nanoparticles in arresting caries, but the study focused on comparing the efficacy of the agent at different concentrations. In this RCT, 337 children who were aged 5-7 years were recruited (Arnaud *et al*., 2021, p. 207). The study entailed the treatment of the subjects with carious lesions using NSF, which occurred in six months. Similar to Nagiereddy *et al*. (2019, p. 484), Arnaud *et al*. (2021, p. 207) found that the nano-based agent (NSF) was effective in arresting caries. However, success rates were 72.7 % and 56.5 % for NSF 600 and 400, respectively (Arnaud *et al.*, 2021, p. 207). Nanoparticles increased the effectiveness of the agents.

Similar to Arnaud *et al*. (2021, p. 207) and Nagiereddy *et al*. (2019, p. 484), Santos *et al*. (2014, p. 1) investigated the effectiveness of NSF as a relatively new agent for controlling caries. This RCT involved the treatment of primary teeth that were randomly sampled and assigned into groups with NSF and a follow-up made for seven days, five and twelve months (Santos *et al*., 2014, p. 1). The results showed that the agent arrested caries in 81 % of the primary teeth in seven days compared to zero cases in control, whereby $p < 0.001$ (Santos *et al*., 2014, p. 1). It arrested caries in 72.7 % and 66.7 % of the subjects after five and 12 months, respectively (Santos *et al*., 2014, p. 1). Therefore, the difference between the control and the intervention groups was statistically significant.

Tirupathi *et al*. (2019, p. 105), similar to Al-Nerabieah *et al.* (2020, p. 100), explored the cariostatic efficacy of NSF. The RCT involved 159 primary carious lesions of 50 children's primary molars that were treated using the NSF varnish and monitored for one, three, six, and 12 months (Tirupathi *et al*., 2019, p. 105). From the findings, the nano-based varnish was highly effective in controlling caries compared to SDF, whereby $p > 0.05$ (Tirupathi *et al*., 2019, p. 105). This success was confirmed at the end of the follow-up period.

An in vivo study involving a combination of silver nanoparticles with fluoride varnish revealed that the use of such an agent is effective in improvement of the teeth structure and promoting re-mineralization (Giron *et al.*, 2017, p. 1). Children with demineralization conditions in both maxillary teeth were recruited whereby they were treated with the varnish with and without nanoparticles three times (Giron *et al*., 2017, p. 1). The addition of nanoparticles made a significant positive difference.

El-Tekeya and El-Habashy (2020, p. 1931), similar to Giron *et al*. (2017, p. 1), compared the effectiveness of fluoride varnish with nanoparticles and one without and found that the difference between the treatment groups was not statistically significant as confirmed by the value of $p = 0.247$. The agents act as preventive interventions for teeth affected by demineralization, but they are ineffective in performing the sealing function on the affected tooth.

In an experimental study conducted to determine whether NSF can be effective in both arresting and preventing caries, it was discovered that the preventive function was 50 % with $p < 0.05$ (Ve *et al*., 2014, p. 945). Apart from arresting caries, nano-particles are highly effective in preventing its occurrence. Nozari *et al*. (2017, p. 97) and Silva *et al.* (2018, p. 509) assessed the effectiveness of nano-based silver in controlling demineralization or enhancing re-mineralization of the primary teeth. Both studies confirmed high levels of efficacy, but NSF had no statistically significant difference with NaF, whereby $p > 0.005$ (Silva *et al*., 2018, p. 509) and $p = 0.165$ (Nozari *et al*., 2017, p. 970). These findings indicated that the addition of nanoparticles did have any extra therapeutic value.

Several scholars have studied the effectiveness of NSF in reducing demineralization by comparing it with other agents, such as NaF (Teixeira *et al*., 2018, p. 1 and Soud and Elsaied, 2020, p. 153). Teixeira *et al.* (2018, p. 1) confirmed that NSF is highly effective and had a statistically significant difference compared to NaF. Soud and Elsaied (2020, p. 153) also confirmed that NSF is more effective than SDF in treating dematerialized enamel. Similarly, Nanda and Naik (2020) reported lesser demineralization when NSF was used compared to patients treated with SDF.

DISCUSSION

This systematic review study focused on the determination of the effectiveness of nanosilver fluoride varnish as an agent for treating demineralization of the primary teeth. In the past, providers used SDF, but it

resulted in staining of the teeth (Zhao *et al*., 2020, p. 2830). This created a gap that could be filled by developing agents with nanoparticles. NSF is an example of varnishes that contain nanoparticles, but it is still in the experimental stages (El-Desouky *et al*., 2020, p. 154). NSF is designed to control demineralization without causing stains on the teeth.

After a careful review of the published literature, 15 articles met the inclusion criterion. Most of the studies focused on comparing the effectiveness of NSF and SDF and confirmed that the addition of nanoparticles contributed to a higher level of success (Nagiereddy *et al*., 2019, p. 484; Tirupathi *et al*. (2019, p. 105). These findings are consistent with the previous results by Scaropelli *et al*. (2017, p. 738) indicating that Ag-nano leads to a 100 % inhibition of microorganisms at lower rate concentration levels than other agents.

However, some of the studies contradicted the previous research findings by showing that SDF is less effective than NSF (Al-Nerabieah *et al*., 2020, p. 100). A lack of statistically significant difference between agents with and those without nanoparticles was supported by the findings reported by El-Desouky *et al*. (2020, p. 153). These results contradicted the previous findings by (Zameer *et al*., 2021, p. 1) showing that NSF is a more effective alternative that addresses the limitations of NSF.

Overall, NSF is more effective and it is preferred to its SDF alternative because it protects the patient from stains during and after treatment (Zhao *et al*., 2020, p. 2830). Its effectiveness in controlling caries and containing demineralization has been supported by most of the studies (Nagiereddy *et al*., 2019, p. 484, Giron *et al*. (2017, p. 1), and Nozari *et al*. (2017, p. 97). Therefore, it should be used to treat children whose primary teeth are affected by demineralization

However, the findings of this systematic review should be used with caution due to some limitations identified in the article. For example, only Ve *et al*. (2014, p. 945) and Santos *et al*. (2014, p. 6) addressed the confounding variables. Therefore, it may not be possible to determine whether the efficacy of nano-based agents was affected by confounding variables, such as diet. In addition, the duration covered in some of the studies was short, whereby Nanda and Naik (2020), Teixeira *et al*. (2018, p. 1) Silva *et al*. (2018, p. 509) monitored the treatment for 14 days only. The duration is quite short for the assessment of an experimental agent. In addition, most of the studies, including Teixeira *et al*. (2018), Soud and Elsaied (2020), and Silva *et al*. (2018), were based on experimental design. This introduced a methodological limitation and reduced the generalization of their findings in real clinical settings.

CONCLUSION

Dental care for pediatric patients is significant because it protects children from illnesses and a poor quality of life that may result from conditions, such as caries or demineralization of the primary teeth. Although SDF has been confirmed to be effective and non-invasive, it has clinical limitations, such as staining of the patient's teeth. Based on the outcomes of this systematic literature review nano silver fluoride varnish can serve as an effective agent for the replacement of SDF in controlling demineralization of the primary teeth.

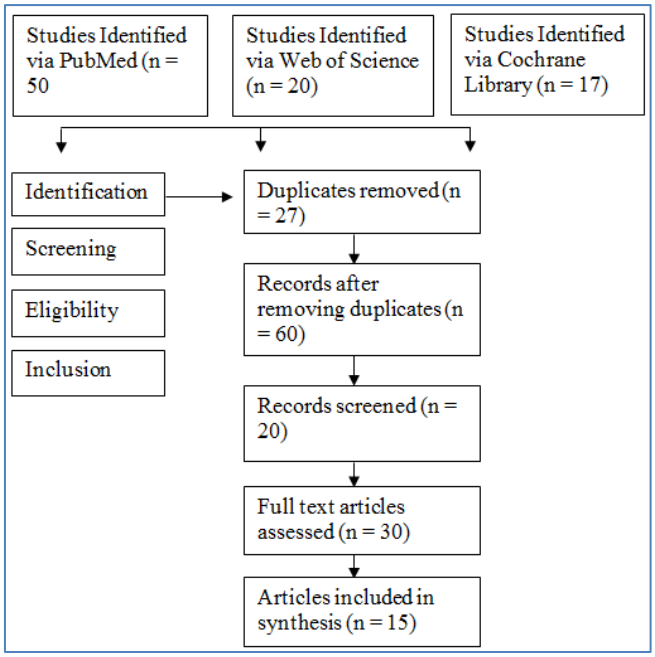

Fig-1: Flow Diagram

Table-1: Summary of the Findings

Study	Population/Sample	Design/Type of Study	Inclusion/ Exclusion Criteria	Test and control	Duration/Monitoring intervals	Results
Nanda and Naik, 2020	20 premolar teeth	RCT	-	✓	14 days	Lesser demineralization occurs with NSF treatment
Teixeira *et al.*, 2018	20 enamel fragments	Experimental design	-	✓	14 day	NSF is more effective in reducing demineralization compared to SDF
Soud and Elsaied, 2020	40 specimen	In vitro experiment	✓	✓	12 months	NSF is more effective in reducing demineralization than SDF
Silva *et al.*, 2018	33 teeth	In vitro experiment	✓	✓	14 day	NFS enhance re-mineralization, but not statistically significant difference with NaF, where $p = p > 0.005$
Nozari *et al.*, 2017	80 primary teeth	In vitro experiment	✓	✓	7 months	NFS enhance re-mineralization, but not statistically significant difference with NaF, where $p = 0.165$
Ve *et al.*, 2014	60 children with the mean age of 6.31	Experimental design	-	✓	12 months	NSF is effective in caries arresting and prevention at 50 % success rate and $p < 0.05$.
El-Tekeya, and El-Habashy, 2020	45 molars	In vitro experiment	✓	✓	6 months	The difference between nano-base and one without is statistically insignificant with $p = 0.247$
Giron *et al.*, 2017	22 children who were aged 1-6 years	An in vivo experiment	✓	✓	3 months	The addition of nanoparticles to a fluoride varnish improved the efficacy
Tirupathi *et al.*, 2019	159 primary carious lesions of 50 children's primary molars	RCT	✓	✓	1,3,6, and 12 months	NSF was effective compared to SDF with $p > 0.05$
Santos *et al.*, 2014	130 decaying primary teeth	RCT	✓	✓	7 days, 5 months, and 12 months	Success in arresting carries: 7 day – 81 % $p < 0.001$ 5 months – 72.7 % $p < 0.001$ 12 months – 66.7 % $p = 0.003$
Arnaud *et al.*, 2021	337 children aged 5-7 years	RCT	✓	✓	6 months at the intervals of 30, 60, 180 days	Success in containing caries is 72.7 % (p = 0.025) and 56.5 % for NSF 600 and 400, respectively
El-Desouky *et al.*, 2020	48 primary molars	In vitro experiment	✓	✓	7 days	lesion depths were 36.36 and -37.30, respectively, for agents with no nanoparticles, confirming equal effectiveness levels
Al-Nerabieah *et al.*, 2020	119 preschool children who had 244 dentin lesions	RCT	✓	✓	3 weeks and 6 months	Cariostatic efficacy: 77 % and 90 % in NSF and SDF, respectively after 3 weeks 79.5 % and 67.2 % in SDF and NSF groups, respectively, after 6 month
Nagiereddy *et al.*, 2019	60 children aged 4-9 years	RCT	✓	✓	Seven days, five months, and 12 month	Demineralization/ caries arresting: 78 % (34 % control) in 7 days, 72.91 % (34 % control) in 5 months, and 65.21 % (control - 28.88) % in 12 months
Zhao *et al.*, 2020	36 blocks from 12 dentine slices	In vitro experiment	-	✓	One month	PEG-AgNPs – Increase in re-mineralization with no discoloration

Table-2: Summary of Cochrane Risk of Bias Assessment

Study	Selection Bias/Appropriate control selection/baseline characteristics similarity	Selection bias in randomization	Selection bias in allocation concealment	Performance-related bias in blinding	Reporting bias/Selective reporting of outcomes	Detection bias Blinding outcome assessors	Accounting for confounding bias
Nanda and Naik, 2020	+	+	+	+	+	+	-
Teixeira *et al*., 2018	+	+	+	-	-	-	-
Soud and Elsaied, 2020	+	+	+	+	+	_	_
Silva *et al*., 2018	+	+	+	+	+	+	-
Nozari *et al*., 2017	+	+	+	+	+	+	-
Ve *et al*., 2014.	+	+	+	+	+	+	+
El-Tekeya, and El-Habashy, 2020	+	+	+	+	+	+	-
Giron *et al*., 2017	+	+	+	+	+	+	-
Tirupathi *et al*., 2019	+	+	+	+	+	+	_
Santos *et al*. (2014)	+	+	+	+	+	+	+
Arnaud *et al*., 2021		+	+	+	+	+	-
El-Desouky *et al*., 2020	+	+	+	?	+	?	-
Al-Nerabieah *et al*., 2020	+	+	+	+	+	+	-
Nagiereddy *et al*., 2019	+	+	+	+	+	+	_
Zhao *et al*., 2020	+	+	+	?	+	?	-

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