



Effectiveness of Silver Diamine Fluoride compared with Sodium Fluoride Varnish on Oral Saliva pH in the Children with Sever- Early Childhood Caries (S-ECC)

Bahareh Nazemi Salman¹, Amir Ali Bakhtiari², Seyede Solmaz Taheri^{3*}

¹ Associate Professor of Pediatric, School of Dentistry, Zanjan University of Medical Sciences, Zanjan, Iran

² Dentist (DDS), School of Dentistry, Zanjan University of Medical Sciences, Zanjan, Iran

³ PhD candidate, Department of Biostatistics, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Corresponding author:** Seyede Solmaz Taheri, **Address:** Department of Biostatistics, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, **Email:** Solmaz.taheri.1990@gmail.com, **Tel:** +982122718531

Abstract

Background & Aims: Colorless Silver Diamine Fluoride (SDF) solution is effective in increasing the remineralization of hard tooth tissue, and the silver ion in it has antibacterial properties. The aim of this study was to compare the effect of Sodium Fluoride (NaF) varnish with SDF on oral saliva pH in children with premature dental caries.

Materials & Methods: In this clinical trial study, 25 children with the age group of 3-6 years old were randomly selected, and then randomly divided to two groups of receiving NaF and receiving SDF. The rate of salivary pH change in both study groups was measured and recorded before treatment (baseline time), 5, 10, 20, and 30 minutes after treatment, using digital pH meter. The results were evaluated using repeated measures and independent t-test at a significance level of 0.05%.

Results: The mean salivary pH level of the SDF group in the fifth ($p = 0.018$), tenth ($p = 0.022$), and twentieth ($p = 0.039$) minutes after treatment was significantly higher than it in the NaF group. In the SDF group, saliva pH at 5 ($p = 0.001$), 10 ($p < 0.001$), 20 ($p < 0.001$) and 30 minutes ($p = 0.002$) was significantly higher than the baseline time.

Conclusion: The saliva pH of children increased significantly after using SDF compared to NaF. Due to the other positive effects of SDF in preventing caries compared to NaF, this substance is recommended for oral pH control in ECC and S-ECC treatment plans, especially in the cases where anesthesia is not possible.

Keywords: Saliva, Saliva Ph, Silver Diamine Fluoride, Sodium Fluoride Varnish, Remineralization

Received 10 June 2022; accepted for publication 25 November 2022

Introduction

As a global problem, deciduous teeth are more prone to decay due to their mineral compositions and less thickness of enamel (1). In this area, premature caries in

children (ECC) and its severe form (S-ECC) have double importance (2). Preventing dental caries is more critical than treating them (3). For this purpose, it is very useful to know the factors influencing the caries process.

Ecologically, dental caries, like other diseases, depends on the balance or imbalance between invasive factors, acquired factors, and moderating factors, namely plaque and saliva (4). In this process, the pH of saliva decreases faster than the rate of remineralization (5). Any change in the amount or quality of saliva can endanger oral health (6, 7). The anti-decay properties of saliva are influenced by several factors, the most important of them are the pH of saliva and its tampon strength, which counteracts the demineralization of the mineral part of the tooth due to buffering of the oral environment (8). Caries resistance is also related to the part of saliva power in controlling oral pH (6, 8). If the pH of the mouth stays below 5.5 for a long time, demineralization may turn into caries (9). Knowledge of saliva composition including fluoride concentration and saliva pH can play an important role in assessing the condition of the mouth and controlling both the activity of bacteria and the mineral content of the teeth (10). Therefore, measuring the pH difference is used to study the effect of fluoride on reducing enamel demineralization or improving remineralization in caries (1). The use of fluoride-containing substances to prevent caries began about 50 years ago (11, 12), and fluoride gels and varnishes were used as two common methods of fluoride therapy (13). Varnish has been increasingly welcomed by dentists for reasons such as low risk, ease of use especially in young and uncooperative children, saving time, and preventing fluoride ingestion (14, 15). One of the newest products containing fluoride is Silver Diamond Fluoride (SDF) (16). It is a colorless solution containing silver ions and was first introduced in Japan in 1970 (17). Clinical studies suggest that SDF also helps prevent and stop coronary caries in children's deciduous teeth. It is also used to control caries in children, to stop root caries and caries of grooves, to prevent secondary caries, to desensitize the treatment of infectious canals, and to prevent fractures of teeth undergoing root canal treatment (18-20). This solution can be effective in increasing the remineralization of hard tooth tissue, and the silver ion in it acts as an antibacterial agent (19, 20). This treatment is effective due to its non-invasiveness and ease of implementation

in young children and those who need special care (19, 21). In the cases that the child is too small to cooperate for restorative treatment, the dental treatment is not economically viable, or when there is a significant shortage of dental staff, the SDF is used to stop or slow down the caries (22, 23). Apart from staining of caries caused by the deposition of silver phosphate and silver sulfide, no significant side effects of SDF use have been reported in children (17, 24, 25). Given the dual importance of caries prevention in children and the popularity of non-invasive methods for treatment of the carious lesions, it is important to identify the consequences of using newer materials to prevent caries in children (26, 27). In Iran, the effects of SDF and its common application are not very generalized, so it is necessary to study the short-term changes of SDF due to the effects of its remineralization on caries and changes in oral pH. The aim of this study was to investigate the effect of SDF consumption on pH and compare it with the old fluoride varnish method.

Materials & Methods

This was a randomized clinical trial study with study population of 26 children in the age group of 3-6 years with S-ECC or ECC at a private pediatric dentistry center (Tabassom) in Zanjan, Iran. This research was approved by the Ethics Committee of the Zanjan University of Medical Sciences (IR.ZUMS.REC.1400.145) with IRCT code of IRCT20210718051926N1. Using repeated measure formula (90% power and 5% error), the sample size was measured 12 children for each group. For this, 13 children were included in the study, taking into account of the 5% probable loss in each group. We used systematic one-in-5 random sampling method. In this method, in the list prepared by the clinic secretary, one child was randomly selected from the first 5 patients of the list, then the fifth child was selected from the list after him. Random allocation process was also followed. Samples were assigned to two random groups using the random number generation method by random number generation software. In this way, random numbers in the range (0 to 1) were generated in the software and

numbers less than 0.5 were assigned to the SDF group and numbers greater than 0.5 to the NaF group. Although it seemed that the socioeconomic status of the families of children referred to the private clinic was close to each other, but to reduce the error of the results, the researcher used the existing socioeconomic status (SES) questionnaire (28) to match the two groups (questionnaire was completed by one of the parents). The group matching method was used to match the SES status, gender, and age in this study; the researcher always checked the distribution of these three variables in terms of group matching with the opinion of a statistical consultant when randomly assigning children to two groups. Due to the fact that the intervention process was performed by one person, this study could not be blinded. The parents of these children were informed of the complications of SDF and entered the study if they agreed (signing a written consent). We take this fact into account that the parents are not satisfied with the dental operation under their child's anesthesia.

Inclusion criteria: Children with deciduous tooth systems (3 to 6 years old), with SECC (any sign of caries on the smooth surfaces of the teeth of children under 3 years of age (2)) or ECC (presence of one or more decayed teeth with or without cavities, lost due to caries or filled in any of the baby teeth in a 71-month-old or younger child is called premature caries in the children) (2).

Exclusions criteria: Systemic disease or dry mouth, intellectual disability, Herpes, colds, poor cooperation of the child or parents, impatience, having more than 5 decayed teeth.

Saliva sampling methods: Parents were asked to refrain from giving any drinks or food to their children at least one hour before the start of sampling. The surface of the teeth in all specimens was cleaned with a sterile gauze, plaques were removed, and the tooth surfaces were decontaminated. The children were asked with the help of their parents to pour their saliva into a disposable glass. As this did not cause any pain or discomfort to the children, they gained more trust in the researcher. Immediately after collecting the children's saliva in a disposable glass, salivary pH measurements

were carried out using a digital pH meter (Orion Star A221/Stara 2215-Thermo Scientific) and then entered in a pre-designed checklist. The samples were then divided randomly into two groups. For the varnish group, 5% fluoride varnish (V-varnish / Korea / fluoride varnish / 4.0 ml) with V-varnish brand was applied. For the second group, 30% silver diamine fluoride (caries top 30% / Iran / biodinamica / 5 ml) was applied. These two substances were purchased from Pooyesh Teb Atieh Company. In both groups, children were asked to pour their saliva into a disposable glass at 5, 10, 20, and 30 minutes after the intervention. Then the oral pH was measured and recorded. The researcher advised parents to use 5% sodium fluoride varnish or 30% SDF after examination to prevent caries and even treatment for children with severe caries, especially maxilla. Conditions were the same for all samples (Saliva was collected between 3 p.m and 7 p.m), and all tests were performed by one person. After collecting data, to compare the effect of sodium fluoride and silver diamine fluoride on oral pH in the period of deciduous teeth, the data were analyzed by a statistical consultant and the difference in their effects was determined.

Statistical analysis: Individual information was entered into SPSS software ver. 22 after initial registration on checklist papers by the researcher. Then Chi-square test, repeated measures analysis, Bonferroni pairwise comparison, and independent t-test were used to analyze the data. Paired t-test was used to study between group.

Results

In this study, children were examined in two groups of 13. There was a drop in the SDF group and finally 12 and 13 children were in the SDF and NaF groups, respectively. The results of Chi-square test showed that there was no difference in terms of gender ($p=0.832$) and Sex ($p=0.641$) in the study groups. The results of independent t-test showed that the age distribution was the same in the two groups (and group matching is completed) ($p=0.857$). After examining the normality of the data, the Mochley sphericity test showed that the sphericity assumption is valid in the data. One-way

repeated measures of the pH in 5, 10, 20, and 30 minutes after using SDF or NaF revealed no significant interaction between time of measurements and groups of study ($p = 0.098$), but the effect of time was significant ($p < 0.001$). Therefore, the data of each group were evaluated separately at five times using simple repeated measures analysis. The results showed that the pH of the mouth after SDF consumption at 5, 10, 20, and 30 minutes were significantly different ($p = 0.018$). Nevertheless, the pH of the mouth at 5, 10, 20, and 30 minutes after using fluoride varnish are not much different from each other ($p = 0.167$). (Table 1) Due to the significant effect of time in the silver diamine fluoride group, pairwise time comparisons in this group were performed using Bonferroni pairwise comparison tests. In the SDF group, the mean pH before the intervention was significantly different from the mean pH at 5 minutes after the intervention ($p < 0.001$), and the mean pH at 5 minutes was approximately 1.5 units more than it before the intervention. Also, the mean pH

at 10 minutes was approximately 1.3 units higher ($p < 0.001$), 1.2 units higher at 20 minutes ($P < 0.001$), and 0.75 units higher at 30 minutes ($p = 0.002$) after the intervention. That is, the change in pH after the intervention at all times compared to it before the intervention was significant. On the other hand, the pH at 5 minutes after the intervention was approximately 0.708 units higher than it after 30 minutes of intervention ($p = 0.003$). Also the pH at 10 minutes after the intervention was approximately 0.542 units higher than the pH at 30 minutes ($p = 0.002$) and the pH at 20 minutes after the intervention was approximately 0.458 units more than it at 30 minutes after the intervention ($p = 0.020$) (Table 2). The pH increases from 5 minutes onwards and in 10 and 20 minutes was significantly higher in the SDF group than the fluoride varnish group. From 10 minutes onwards, the pH decreases, although this decrease was significantly lower in the SDF group than it in the fluoride varnish group (Figure 1).

Table 1. general trend and the effects of each group over time

Test name	Categories	p-value
Check the general trend*	Time effect (intrapersonal measurements)	<0.001
	Time effect \times groups (intergroup)	0.098
Comparing the effects of each group over time**	NaF	0.167
	SDF	0.018

*: one-way repeated measure test

** : simple repeated measure test

Table 2. Test of comparing the effects of SDF group over time

paired repeated times	Mean difference	P-value*
pH before intervention	pH 5 minutes after intervention	-1.458
	pH 10 minutes after intervention	-1.292
	pH 20 minutes after intervention	-1.208
	pH 30 minutes after intervention	-0.750
pH 5 minutes after intervention	pH 10 minutes after intervention	0.167
	pH 20 minutes after intervention	0.250
	pH 30 minutes after intervention	0.708
pH 10 minutes after intervention	pH 20 minutes after intervention	0.083
	pH 30 minutes after intervention	0.542
pH 20 minutes after intervention	pH 30 minutes after intervention	0.458

*: Bonferroni paired test

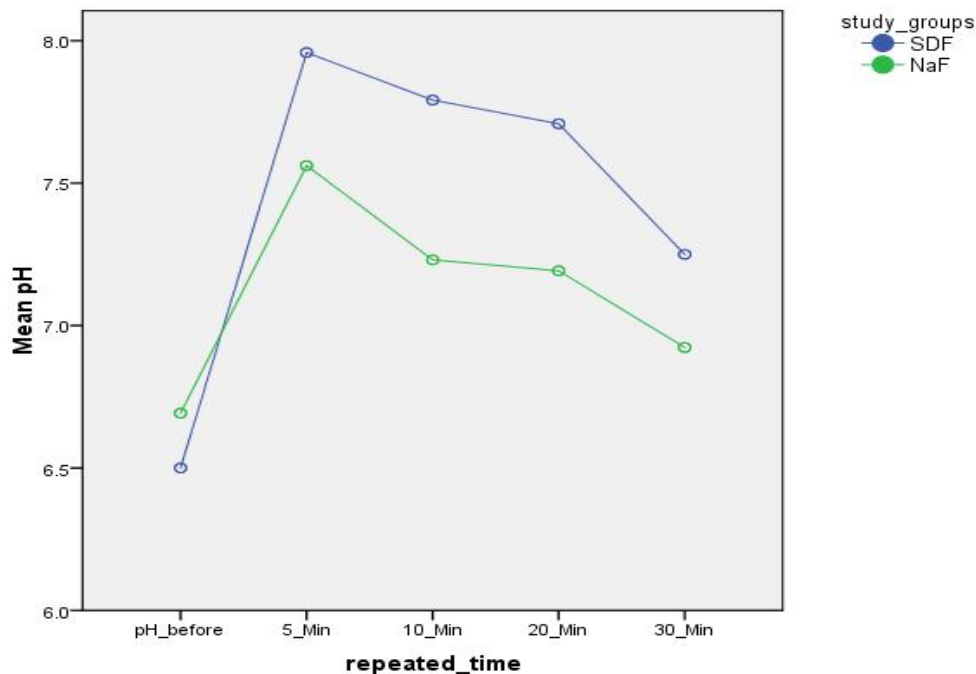


Fig. 1. Linear graph of mean pH in NaF and SDF groups

Discussion

Topical application of fluoride is one of the most important ways to prevent caries. The combination of fluoride reduces the solubility of minerals. Although the specific mechanism of action of fluoride in the prevention of caries is not fully understood, it is generally accepted that topically applied fluorides have an effect on tooth rigidity (29). The aim of this study was to compare the effect of fluoride varnish with SDF on oral pH in saliva of children with ECC and S-ECC. The results of the present study showed that from 5 minutes onwards, the pH of saliva in both groups, including SDF and NaF, increased and salivary acidity decreased. However, this increase over time was significant only in the SDF group. In the study by Apriani et al. which examined the 6 months' effects of fluoride varnish and casein phosphopeptide sulfur calcium phosphate (CPP-ACP) on saliva pH and caries in children aged 8-9 years, participants' salivary pH increases after 1 month of using fluoride varnish (once a week), although the results were not significant (5). Chhabra et al. also examined the salivary pH of children aged 8-9 years after treatment with CPP-ACP and concluded that treatment once a

week for 1 month could increase salivary pH in these children (30). Llorda et al. reported that the SDF was 80% effective in preventing new caries in deciduous teeth and 65% in permanent first molars, and could be useful in preventing and stopping caries on all teeth and surfaces (24). There is not any specific advice or method on how to use SDF (24). Some recommend annual use, others recommend six months, and the others recommend three months' use, and there is no documented evidence that which method is preferable. Nevertheless, the results show that three 6-month uses can be effective and the effect of SDF on reducing caries in the long run seems to be greater than fluoride varnish. Prolonged contact to SDF may increase the amount of fluoride absorbed by the decay. It also increases the formation of hydroxyapatite fluoride and decreases the solubility of enamel against acid (25). In two other clinical trials conducted to evaluate the effectiveness of SDF in Japan and England, it was reported that SDF administration resulted in a 47% reduction in the incidence of new dental caries (31, 32). In two systematic reviews study both done in 2016, SDF treatment was suggested as a non-invasive method and

easy implementation as a promising strategy for managing tooth decay in young children or those with special needs (24, 27). Among fluoride products to treat dentin caries, SDF can stop almost 68% of the caries (33). Its slower inactivation and dissolution than NaF enhance the anti-corrosion effects of this substance compared to conventional sodium fluoride varnishes. On the other hand, cost effectiveness, ease of use, less time to use, and stopping dentin allergy (which is very common in ECC) are the factors that make SDF a more suitable alternative for use in pediatric dentistry, especially in the weak economic zones (34, 35). After treatment with SDF, a highly remineralized surface area rich in calcium and phosphate could be detected in the cavity lesions. Silver ion also acts as an antibacterial agent in SDF (19). According to the results of the present study and some studies that have shown the effect of SDF 38% in preventing the progression of dentin caries lesions in deciduous teeth (25, 36), root caries (37), occlusal surfaces of permanent first premolars (25), studies that have shown annual use of SDF effectively stops dentin caries (22, 38), studies on antibacterial properties that prevent the growth of cariogenic biofilms (39), study of the different dimensions of this material and its effect on the teeth deserves much more in-depth studies. Although this study investigated the effect of SDF and fluoride varnish on the pH of children's saliva and there are not many studies in this field, but one of the weaknesses of the present study is the lack of time and currency to evaluate the rate of caries cessation in six-month or one-year follow-up. However, due to the report of minor side effects of this substance and its effective role in comparison with NaF in preventing caries, the present study suggests the use of this substance to control saliva pH and prevent caries.

Conclusion

SDF leads to a significant increase in saliva pH about 5 minutes after use. Due to the important role of saliva pH in oral health and the uncommon use of this substance in Iran, topical application of SDF is recommended. It is suggested that in future studies, the

pH of the mouth should be evaluated after a few hours and 24 hours after treatment with higher sample size and also the patients should refer to follow up after treatment.

Limitations of the project

Lack of active participation of some parents in the study and difficulty of finding samples led to a prolongation of the sampling period. Due to the age of the evaluated samples, it was very difficult to get their and their parents cooperation as well as to examine the 5 stages of oral saliva pH. It was not possible to prepare a 38% SDF solution in Iran and the researcher had to use the only solution available in the market, SDF 30%.

Acknowledgments

We warmly thank all the children and their parents for their patience and participation in this study. We express our very grateful thanks to Tabassom clinic staffs for their most useful advice on the saliva sample analysis procedures.

Ethical statement

All the implementation steps and objectives of the research were explained to the patients' parents and written consent was received from them to participate in the research. No costs were incurred for patients and participation in the study did not change their standard treatment and they had the opportunity to opt out at any stage of the study.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Conflict of interest

None declared

References

1. De Mello Vieira AE, Botazzo Delbem AC, Sasaki KT, Rodrigues E, Cury JA, Cunha RF. Fluoride dose response in pH-cycling models using bovine enamel. *Caries Res* 2005;39(6):514-20.

2. Emadian M, Malekzadeh Shafaroudi A, Mesgarani A, Afkhaminia F, Nahvi A. Mother's Knowledge Regarding Oral Health among Their Preschool Children. *Int J Pediatr* 2020;8(8):11681-9.
3. Burke FJT. From Extension for Prevention to Prevention of Extension: (Minimal Intervention Dentistry). *Dent Update* 2003;30(9):492-502.
4. Eidelman AI, Schanler RJ. Breastfeeding and the use of human milk. *Pediatrics* 2012;129(3):e827-e41.
5. Apriani A, Widyarman A, Budiyantri E, Roeslan B. Caries activity and ph level changes after fluoride varnish and casein phosphopeptides-amorphous calcium phosphate application on children's saliva. *Contemp Clin Dent* 2020;11(2):126-30.
6. Sköld UM, Petersson LG, Birkhed D, Norlund A. Cost-analysis of school-based fluoride varnish and fluoride rinsing programs. *Acta Odontol Scand* 2008;66(5):286-92.
7. dos Santos APP, Nadanovsky P, de Oliveira BH. A systematic review and meta-analysis of the effects of fluoride toothpastes on the prevention of dental caries in the primary dentition of preschool children. *Community Dent Oral Epidemiol* 2013;41(1):1-12.
8. Duckworth RM, Knoop DTM, Stephen KW. Effect of mouthrinsing after toothbrushing with a fluoride dentifrice on human salivary fluoride levels. *Caries Res* 1991;25(4):287-91.
9. Hicks J, Wild T, Flaitz CM, Seybold S. Fluoride varnishes and caries development in primary tooth enamel: an in vitro study. *ASDC J Dent Child* 2001;68(5-6):300,304-10.
10. Duckworth RM, Morgan SN. Oral fluoride retention after use of fluoride dentifrices. *Caries Res* 1991;25(2):123-9.
11. Mei ML, Chu CH, Lo ECM, Samaranayake LP. Fluoride and silver concentrations of silver diamine fluoride solutions for dental use. *Int J Paediatr Dent* 2013;23(4):279-85.
12. Chu CH, Mei ML, Lo EC. Use of fluorides in dental caries management. *Gen Dent* 2010;58(1):35-7
13. Pinkham JR, Casamassimo PS, Fields HW, McTigue DJ, Nowak A. Pediatric dentistry. *Infancy through Adolesc* 2005;4.
14. McDonald RE, Avery DR, Dean JA. *Dentistry for the child and adolescent* 9th ed. St Louis Mosby co. Published online 2011:28-43.
15. Miller EK, Vann WF. The use of fluoride varnish in children: A critical review with treatment recommendations. *J Clin Pediatr Dent* 2008;32(4):259-64.
16. Pinkham JR, Casamassimo P, Fields H, McTigue D, Nowak A. *Infancy through adolescence* 4th ed. *Pediatr Dent*. Published online 2005:594-5.
17. McDonald RE, Avery DR, Dean J. *Dentistry for the child and adolescent*. St Louis Mosby. Published online 2008:11-2.
18. Chen A, Cho M, Kichler S. Silver Diamine Fluoride : An Alternative to Topical Fluorides. *J Can Dent Assoc* 2012;20(10):1-14.
19. Delbem ACB, Bergamaschi M, Sasaki KT, Cunha RF. Effect of fluoridated varnish and silver diamine fluoride solution on enamel demineralization: pH-cycling study. *J Appl Oral Sci* 2006;14(2):88-92.
20. Chu CH, Lo ECM. Microhardness of dentine in primary teeth after topical fluoride applications. *J Dent* 2008;36(6):387-91.
21. Lo ECM, Chu CH, Lin HC. A community-based caries control program for pre-school children using topical fluorides: 18-month results. *J Dent Res* 2001;80(12):2071-4.
22. Chu CH, Lo ECM. Promoting caries arrest in children with silver diamine fluoride: a review. *Oral Health Prev Dent* 2008;6(4):315-21.
23. Lou YL, Botelho MG, Darvell BW. Reaction of silver diamine fluoride with hydroxyapatite and protein. *J Dent* 2011;39(9):612-8.
24. Gao SS, Zhao IS, Hiraishi N, et al. Clinical Trials of Silver Diamine Fluoride in Arresting Caries among Children: A Systematic Review. *JDR Clin Trans Res* 2016;1(3):201-10.
25. Llodra JC, Rodriguez A, Ferrer B, Menardia V, Ramos T, Morato M. Efficacy of silver diamine fluoride for caries reduction in primary teeth and first permanent molars of schoolchildren: 36-month clinical trial. *J Dent Res* 2005;84(8):721-4.

26. Salehzadeh Esfahani K, Mazaheri R, Pishavar L. Effects of Treatment with Various Remineralizing Agents on the Microhardness of Demineralized Enamel Surface. *J Dent Res Dent Clin Dent Prospects* 2015;9(4):239-45.
27. Gao SS, Zhang S, Mei ML, Lo EC-M, Chu C-H. Caries remineralisation and arresting effect in children by professionally applied fluoride treatment—a systematic review. *BMC Oral Health* 2016;16(1):12.
28. Kazemi Karyani A, Karimi Matin B, Soltani S, et al. Socioeconomic gradient in physical activity: Findings from the PERSIAN cohort study. *BMC Public Health* 2019;19(1):1-11.
29. Divaris K, Preisser JS, Slade GD. Surface-specific efficacy of fluoride varnish in caries prevention in the primary dentition: results of a community randomized clinical trial. *Caries Res* 2013;47(1):78-87.
30. Chhabra N, Chhabra A. Enhanced Remineralisation of Tooth Enamel Using Casein Phosphopeptide-Amorphous Calcium Phosphate Complex: A Review. *Int J Clin Prev Dent* 2018;14(1):1-10.
31. Shimizu A, Kawagoe M. A clinical study of effect of diamine silver fluoride on recurrence caries. *J Osaka Univ Dent Sch* 1976;16:103-9.
32. Bedi R S-IJ. Oral health care in disadvantaged communities, London: FDI world press. London FDI World. Published online 1999.
33. Li Y, Liu Y, Psoter WJ, et al. Assessment of the Silver Penetration and Distribution in Carious Lesions of Deciduous Teeth Treated with Silver Diamine Fluoride. *Caries Res* 2019;53(4):431-40.
34. Suzuki T, Nishida M, Sobue S, Moriwaki Y. Effects of diamine silver fluoride on tooth enamel. *J Osaka Univ Dent Sch* 1974;14:61-72.
35. Santos L de M, dos Reis JIL, de Medeiros MP, Ramos SM, de Araújo JM. In vitro evaluation of fluoride products in the development of carious lesions in deciduous teeth. *Braz Oral Res* 2009;23(3):296-301.
36. Chu CH, Lo EC, Lin HC. Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children. *J Dent Res* 2002;81(11):767-770.
37. Li R, Lo ECM, Liu BY, Wong MCM, Chu CH. Randomized clinical trial on arresting dental root caries through silver diamine fluoride applications in community-dwelling elders. *J Dent* 2016;51:15-20.
38. Rosenblatt A, Stamford TCM, Niederman R. Silver diamine fluoride: A caries “silver-fluoride bullet.” *J Dent Res* 2009;88(2):116-25.
39. Mei ML, Ito L, Cao Y, Lo EC, Li QL, Chu CH. An ex vivo study of arrested primary teeth caries with silver diamine fluoride therapy. *J Dent* 2014;42(4):395-402.

Copyright © 2022 Journal of Research in Applied and Basic Medical Sciences

This is an open-access article distributed under the terms of the [Creative Commons Attribution-noncommercial 4.0 International License](https://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, as long as the original work is properly cited.