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Treatment of Dental Caries with Diamine Silver Fluoride: Literature Review

Tratamento da Cárie Dentária com Diamino Fluoreto de Prata: Revisão da Literatura

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Abstract

Brazilian health care programs recommend the use of cariostatic solutions of silver diamine fluoride (SDF) or sodium fluoride varnishes for children 0 to 3 years old with high or moderate caries activity for the control of caries lesions. SDF is a safe, economical, efficient and non-invasive coadjuvant agent, exerting an antibacterial action capable of reducing superficial mineral loss of the enamel and can be used in the treatment of deciduous and permanent teeth. The objective of this literature review was to gather current information on describing the mechanism of SDF action' and its clinical application in young children in caries prevention and paralysis. The PubMed / Medline and Cochrane Library databases were accessed by identifying the relevant studies published in English from 1960 to May 2017. The search strategy employed the keywords: "Silver diamine fluoride" and "Children "or "Infant" and "Caries prevention". Data extraction was performed in: 19 *in vitro* studies; 10 review articles and 8 *in vivo* studies. It was possible to conclude that SDF is almost twice as effective compared to fluoride varnish in caries paralysis. However, the contact time of the solution and the optimal frequency of application of the SDF are still undefined, inducing new projects and clinical studies in the search for an adequate clinical protocol of this cariostatic.

Keywords: Preventive Dentistry. Children. Dental Caries.

Resumo

Os programas de assistência à saúde brasileiros recomendam para o controle das lesões de cárie a utilização de soluções cariostáticas de diamino fluoreto de prata - DFP ou vernizes de fluoreto de sódio para crianças de 0 a 3 anos com atividade de cárie alta ou moderada. O DFP é agente coadjuvante seguro, econômico, eficiente e não invasivo, exercendo ação antibacteriana capaz de reduzir a perda mineral superficial do esmalte e, pode ser utilizado no tratamento de dentes decíduos e permanentes. O objetivo desta revisão de literatura foi reunir informações atuais sobre descrever o mecanismo de ação do DFP e sua aplicação clínica em crianças de pouca idade na prevenção e paralisação da cárie. As bases de dados PubMed/Medline e Cochane Library foram acessadas identificando os estudos relevantes publicados em inglês, no período de 1960 a maio de 2017. A estratégia de busca empregou as palavras-chave: "Silver diamine fluoride" and "Children" or "Infant" and "Caries prevention". A extração dos dados foi realizada em: 19 estudos in vitro; 10 artigos de revisão e 8 estudos in vivo. Foi possível concluir que o DFP apresenta-se quase duas vezes tão eficaz comparado ao verniz fluoretado na paralização de cárie. Porém, o tempo de contato da solução e a frequência ótima de aplicação do DFP ainda estão indefinidos, suscitando novos projetos e estudos clínicos na busca de adequado protocolo clínico deste cariostático.

Palavra-chave: *Odontologia Preventiva. Criança. Carie Dentária.*

1 Introduction

Caries is still one of the most prevalent diseases, being a paradox, the literature shows strong evidence in caries prevention measures when it is estimated that 2.5 billion people (35%) on the planet have untreated caries in their permanent dentition[1]. And in Brazil in 2010, 53.4% of the children at five years of age have an average of 2.3 teeth with dental caries, and approximately 80.0% of these cases were not treated[2].

To better understand the prevention and paralysis of caries, it is necessary to remember that for its development, it is necessary the interaction of essential factors (substrate, host,microbiota and time) to biological modulating factors (saliva, fluorine, biofilm, dental anatomy/position, Nutrition/ diet and age) and social ones[3,4].

The American Academy of Pediatric Dentistry - AAPD, 2008 sets the early childhood caries (CPI) as the presence of one or more decayed, missing or filledf surfaces in the deciduous teeth of a child of 71 months (equivalent to 6 years) of age or less[5]. Its prevalence varies in different populations due to socioeconomic differences that lead to inequalities in the distribution of wealth, in the availability of technological advances and in access to education and health services[2].

Almeida et al.[6] show that 27% of 18-month children (1 year and 6 months) to 36 months (3 years) of age have at least one deciduous element with caries. Thus, the prevention and control of dental caries should be started already in the first years of age by preventing or, at least, minimizing the progression in cases where the lesion has already been

detected. Since 1994, the Brazilian health care programs recommend the use of cariostatic solutions of silver diamine fluoride (SDF) or sodium fluoride varnishes for children 0 to 3 years old with high or moderate caries activity for the control of caries lesions[7]. Even so the dentistry professional is faced with difficulty treating dental caries lesions in young children[8].

DFP is presented as an effective therapeutic in preventing and stopping the caries and can be considered a preventive agent that meets the criteria/objectives of t WHO and American Medical Institute for medical care in the 21st century[6,9], becoming great promise for the surgery dentistry[10] it is considred is a safe, economical, efficient and non-invasive coadjuvant agent, exerting an antibacterial action capable of reducing superficial mineral loss of the enamel and can be used in the treatment of deciduous and permanent teeth[11–14]

Being considered an efficient therapeutic agent, it is necessary to understand its mechanism of action and its clinical application in children of young age, thus we will begin by reviewing the DFP literature in preventing and stopping of caries.

2 Development

The PubMed / Medline and Cochrane Library databases were accessed by identifying the relevant studies published in English from 1960 to May 2017. The search strategies used the keywords: "Silver diamine fluoride" and "Children" or "Infant" and "Caries prevention". The aspects observed among the studies were: clinical evaluation, radiographic examination, diagnostic measures, reduction of the biofilm count, alteration of the microhardness of surface, reduction of bacterial colony forming units (CFU) and surface changes in the levels of F^- and ratio Ca/P. The data extraction was performed in : 19 studies *in vitro*; 10 review articles and 8 studies *in vivo*.

To facilitate the understanding of this subject, it wil be subdivided into topics, namely: History of cariostiatics substances in dentistry; Mechanism of DFP action; and clinical application of the DFP in young children.

2.1 History of cariostatic substances in dentistry

The historical use of silver-basaed compounds dates back approximately 1000 years, in Japan, where it was the custom of the ladies to stain their teeth in black, with "OHAGURO" (powder puff of walnut and solution of iron ion), demonstrating that they were married[15]. Although it was a cosmetic dental, at the same time, prevented the dental caries[16]. Data from Russel and Hugo[17], show that silver compounds in medicine have been used in the application of silver nitrate, silver leaves and sutures, since 1893 Von Naegeli, noting that silver nitrate was a very effective antimicrobial agent. Opportunely, Howe[18], applying silver nitrate directly on the carious lesions showed similar results, calling it the "Howe", and this, began to be used in the stoppage of caries during the 50 years following. Craig et al.[19] reported that the silver fluoride solutions (AgF) has been used in dentistry since the decade of 1970.

DFP recommended by Yamaga[20] and approved by the Central Pharmaceutical Council of the Ministry of Health and Welfare of Japan for treatment of dental caries since the decade of 1960, has been used in several countries for stoppage of caries, being named anticaries or cariostatic agent. It is presented with pronounced antimicrobial action, effective in preventing/paralizing dental caries in young children, root caries in elderly patients, dental caries in pits and fissures, as well as secondary caries and dental desensitization[21]. This carisotatic agent has easy application, low cost and large-scale use[9,22,23], but its disadvantage is the anti-aesthetic result after application, because it darkens the region demineralized by dental caries process in activity, even so, it is an option for the prevention and treatment in young children, especially in public health, where working conditions are often limited.

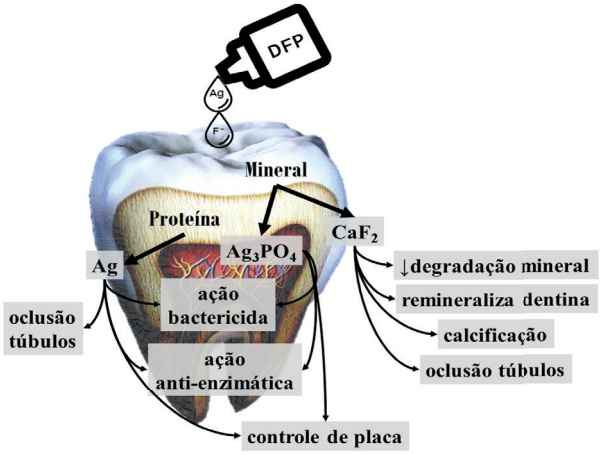
2.2 Mechanism of the DFP action

The use of fluoride in dentistry is one of preventive health measures more successful in the history of dental carie. Current clinical and laboratory studies show that the mode of fluoride action in caries prevention, is mainly topic, demonstrating significant effect in the demineralization and remineralization of dental tissue. Mei et al.[24] and Savas et al.[12] emphasize the efficiency of the DFP in laboratory studies in the increase of the enamel microhardness[14,25,26] and mineral content of dentin caries[14,27,28].

The source of this fluoride can be fluorapatite (formed by the incorporation of fluoride in enamel) or precipitate of calcium fluoride (CaF_2) which are formed in the enamel and on board after the application of topical fluoride. The deposits of calcium fluoride are protected against the quick dissolution by a protein/phosphate coating of salivary origin. At lower pH, the coating is lost occurring increase in the rate of calcium fluoride dissolution. This, therefore, acts as an efficient source of free fluoride ions during the cariogenic challenge. The current evidence indicates that fluoride has a direct and indirect effect on the bacterial cells, however, the mechanism of action of fluorine and DFP are still not clearly elucidated[29].

Elucidating the DFP action on dental components (enamel and dentin) the interaction of its components is observed (Ag and F^-) as shown in Figure 1.

Figure 1 - Schematic redesign of the action of the DFP components on the tooth structure. (adapted from Shah et al.[23]). *Mineral portion* = dental enamel, *protein portion*dentin = *thick arrows* = reaction of the DFP with mineral and protein portions, *thin arrows* = action of the products of reaction on the dentin and enamel.



Yamaga et al.[16] and Chu et al.[30] reported that DFP reacts with the hydroxyapatite, mineral component of dental enamel, releasing calcium fluoride (CaF_2) and silver phosphate (Ag_3PO_4), responsible for the prevention and hardening of dental caries. The calcium fluoride formed on the tooth surface is unstable and can be removed by daily brushing; however small amount of fluoride is retained on the enamel surface. This calcium fluoride is converted into insoluble fluorapatite, because the calcium and fluorine ions react slowly with the phosphate ion in the saliva, forming fluorapatite. The formed calcium fluoride becomes a fluoride reservoir for the formation of fluorapatite, being thus, more resistant to the acids[31]. Being extremely stable and resists to decalcification during cariogenic challenge[16,20].

Okamoto et al.[32] observed macro and microglobular deposits of silver phosphate and calcium fluoride on the enamel surface after application of DFP and currently, Mei et al[33] demonstrated the alteration of the crystalline structure of precipitated minerals (longer and thicker), allowing the formation of fluorhidroyiapatite, explaining the role of the DFP in the dental caries remineralisation. In addition, it is known that the fluorine (F^-) promotes calcification, restores the surface imperfection and improves the crystallinity of hydroxyapatite, being its action mainly post-eruptive[23,29].

Studies of Shah et al.[23] and Zhao et al.[34], show that the silver ions, component of the DFP, have antimicrobial effects, because they interact with the sulphydryl groups of proteins and with the deoxyribonucleic acid (DNA). They destroy the cellular structure of the bacterium wall; inhibit the enzyme activity/metabolic processes and the replication of bacterial DNA, with this on the macroscopic level, these interactions promote bacterial death and inhibit the of biofilm formation[35].

Anti-enzymatic actions of reaction products (phosphate of silver and silver ion) between the protein and mineral component of the tooth/DFP are a consequence of the bactericidal action of silver ions inhibiting the colonization of *S. mutans* on the enamel surface, with proven anti-plaque action of the product[14,28,36,37]. Regarding the enamel DFP promotes significant remineralisation [38] forming fluorhydroxiapatite, with reduced solubility, which may be the main factor of paralization of caries lesions[33]; although, when comparing DFP and fluoride varnish, this releases more fluoride with greater interaction to enamel, and thus promotes less mineral loss when compared to the DFP solution [7].

Concerning the dentin, the silver ion promotes the obliteration of the dentinal tubules[39] by the decrease of dentinal permeability , therefore the dissemination of acid and invasion of microorganisms through the dentinal tubules can be blocked, and even if they invade the dentinal tubules, their growth will be inhibited by the oligodynamic action of the silver[20]. It is known that the superficial area of dentin caries is attacked by the most easily demineralized part, therefore, if it is covered by DFP and associated to the dentinal tubules obliteration, there will be the increase to resistance to secondary caries. Studies of Mei et al.[37] demonstrated in a comprehensive way that DFP 38% inhibits demineralization and preserves the collagen degradation in demineralized dentin, besides presenting anti-microbial activity against *S. mutans* and *L. acidophilus* in cariogenic biofilm on dentinal surfaces. Furthermore, the ion F^- DFP applied to the dentin under *in vivo* conditions can penetrate to a depth of 50-100μm[40].

Currently, studies of Mei et al.[28.37] demonstrate that DFP 38% applied on caries reduces the demineralization process, minimizing the loss of mineral content and slowing down the destruction of collagen type I. Furthermore, concentrations of silver ions and fluorine, inhibit the growth of cariogenic biofilms in multi-species, being DFP highly effective against cariogenic biofilm of *S. mutans*[12]. DFP strongly inhibited the proteolytic activity of metalloproteinases (MMPs) participating in the collagen degradation upon the dental caries[41].

Mei et al.[38] demonstrated the presence of dense superficial layer and highly mineralized in the dentinal cavitated lesion of deciduous teeth after applying DFP 38% biannualy for 24 months, finding greater mineral content of calcium and phosphate, with more aligned and organized crystallites in the lesion, obseving thus that the collagen was protected in paralyzed lesions. Therefore, the treatment with DFP increases the bone mineral density of the enamel and dentin microhardness caries lesion. Chu et al.[14]; Mei et al.[28] and Shimizu[39] conclude that on the dentin subjected to pH cycling DFP presented antimicrobial activity against the cariogenic biofilms and reduction of the demineralization, being effective in the preservation of the dentinal collagen [31.34], reducing the depth of the dentinal lesions, by the obliteration of the dentinal tubules with silver chloride and metallic silver[32].

2.3 Clinical application of the DFP in young children.

The caries manifestations in children under three years of age is a critical condition and the resolution of early childhood caries, as it is known, is a challenging task for the Pediatric Dentistry. The lesions present an acute aspect rapidly evolving and affecting several teeth. Started in the first years of life causes serious future damages, because the deciduous teeth play an important role in the development/eruption of permanent teeth and the growth/development of the face. The list of possible sequelae of early childhood caries is long, including a lot of pain, reduced quality of life, lost time of children in school and parents at work or other activities and the increase of costs[22].

The behavioral issues complicate or prevent the restoration of early childhood caries in young children, due to barriers to access in vulnerable populations, caries starts not to be treated. In developed countries, non-cooperative children have options for the care under conscious sedation or in a hospital environment under general anesthesia, but with increased risks and costs of treatment, in addition to high recurrence of lesions after the restorative treatment[42].

Many systematic reviews of current controlled trials suggest preventive interventions as an alternative, associated with the traditional restorative methods[10,42], according to *in vivno* studies about paralization/prevention of dental caries with DFP, as it can be observed in Table 1.

Table 1 - Clinical studies with application of DFP in different concentrations, percentage (%) of caries paralization and contact time of the solution.

Author	Study period/ concentration of the DFP (%)	SDF application	Caries Paralization (%)	Contact Time of the solution with the carious surface
Lo et al.[43]	18 months/38%	Annual/anterior teeth	97.70%	**
Chu et al.[30]	30 months/38%	Annual/anterior teeth	70%	**
Llodra et al.[44]	36 months/38%	Semester/deciduous canines and molars and 1st permanent molar	77%	**
Yee et al.[45]	24 months/38% and 12%	Unique/deciduous teeth	50%	2 minutes
Braga et al.[46]	30 months/10%	G1= CTT	Clinical evaluation (3,6,12,18 and 30 months)	Not mentioned
		G2= DFP		
		G3= CIV sealant		
		1st Permanent Molar Consecutive Weekly (for 3 weeks)		
Zhi et al.[47]	24 months/38% and CIV	G1= Annual DFP	G1= 79%	**
		G2= Semester DFP	G2= 91%	
		G3= Annual CIV	G3= 82%	
Dos Santos Jr et al.[48]	12 months/30%	Annual	6 months=84.7%	**
			12 months=66.9%	
Duangthip et al.[49]	18 months/30%	G1= Annual	G1= 40%	10 seconds
		G2=Consecutive Weekly (for 3 weeks)	G2= 35%	
Fung et al.[50]	18 months/38% and 12%	G1= Annual 12%	G1 =50% G2 =55% G3 =64% G4 =74%	Not mentioned
		G2= Semester 12%		
		G3= Annual 38%		
		G4= Semester 38%		

(**) The time of application of product indicated by the manufacturer = 3 minutes; *CTT* = control group; *CIV* = glass ionomer cement; *G1, G2, G3 and G4* = experimental groups of studies.

3 Conclusion

Based on the collected references, it was possible to conclude that:

DFP is effective both as a bactericide, and provides the hardening of carious dentin, acting in paralyzing and preventing caries.

It is almost twice as effective as the varnish fluorised in the paralysis of caries,

The application of DFP in children with behavioral problems reduces the costs of legal risks to the professional;

The contact time of the solution and the optimal frequency of application of DFP are still undefined

Reference

1. Marcenes W, Kassebaum NJ, Bernabe E, Flaxman A, Naghavi M, Lopez A, et al. Global burden of oral conditions in 1990-2010: a systematic analysis. J Dent Res 2013;92(7):592–7.

2. Corrêa-Faria P, Martins-Júnior PA, Vieira-Andrade RG, Marques LS, Ramos-Jorge ML. Factors associated with the development of early childhood caries among Brazilian preschoolers. Braz Oral Res. 2013;27(4):356-62.

3. Tenuta A, Cury J. Fluoride: its role in dentistry. Cariol Braz Oral Res 2010;24(1):9-17.

4. Sheiham A, James WPT. Diet and dental caries: the pivotal role of free sugars reemphasized. J Dent Res 2015;94(10):1341-7.

5. Chu C-H, Gao SS, Li SK, Wong MC, Lo EC. The effectiveness of the biannual application of silver nitrate solution followed by sodium fluoride varnish in arresting early childhood caries in preschool children: study protocol for a randomised controlled trial. Trials 2015;16(1):426.

6. Almeida LFD, Cavalcanti YW, Valenca AMG. In vitro antibacterial activity of silver diamine fluoride in different concentrations. Acta Odontol Latinoam 2011;24(2):127-31.

7. Delbem ACB, Bergamaschi M, Sassaki 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.

8. Frencken JE, Peters MC, Manton DJ, Leal SC, Gordan V V., Eden E. Minimal intervention dentistry for managing dental caries: a review: Report of a FDI task group. Int Dental J 2012;62:223-43.

9. Rosenblatt A, Stamford TCM, Niederman R. Silver Diamine fluoride: a caries silver-fluoride bullet. J Dent Res 2009;88(2):116-25.

10. Quock RL. Silver diamine fluoride: an operative dentistry perspective. J Oper Esthet Dent 2016;1(2):6-9.

11. Sharma G, Puranik MP, K R S. Approaches to arresting dental caries: an update. J Clin Diagn Res 2015;9(5):8-11.

12. Savas S, Kucukyilmaz E, Celik EU, Ates M. Effects of different antibacterial agents on enamel in a biofilm caries model. J Oral Sci 2015;57(4):367-72.

13. Nantanee R, Santiwong B, Trairatvorakul C, Hamba H, Tagami J. Silver diamine fluoride and glass ionomer differentially remineralize early caries lesions, in situ. Clin Oral Investig 2016;20(6):1151-7.

14. Chu CH, Mei L, Seneviratne CJ, Lo ECM. Effects of silver diamine fluoride on dentine carious lesions induced by Streptococcus mutans and Actinomyces naeslundii biofilms. Int J Paediatr Dent 2012;22(1):2-10.

15. Ishikawa T, Seino A. "Ohaguro" traditional tooth staining custom in Japan. Int Dent J 1965;15(4):426-41.

16. Yamaga R, Nishino M, Yoshida S, Yokomizo I. Diammine silver fluoride and its clinical application. J Osaka Univ Dent Sch 1972;12:1-20.

17. Russell AD, Hugo WB. Antimicrobial activity and action of silver. Prog Med Chem 1994;31:351-70.

18. Howe PR. A Study of the microörganisms of dental caries. J Med Res 1917;36(3):481-92

19. Craig EW, Suckling GW, Pearce EI. The effect of a preventive programme on dental plaque and caries in school children. N Z Dent J 1981;77(349):89-93.

20. Yamaga R. Mechanisms of action of diammine silver fluoride and its use. Nippon Dent Rev 1970;328:180-7.

21. Mei ML, Chin-Man Lo E, Chu C-H. Clinical use of silver diamine fluoride in dental treatment. Compend Contin Educ Dent 2016;37(2):93-8.

22. Bhaskar V, McGraw KA, Divaris K. The importance of preventive dental visits from a young age: systematic review and current perspectives. Clin Cosmet Investig Dent 2014;6:21-7.

23. Shah S, Bhaskar V, Venkatraghavan K, Choudhary PMG, Trivedi K. Silver diamine fluoride: a review and current applications. J Advaced Oral Res 2014;5(1):25-35.

24. Mei ML, Ito L, Cao Y, Li QL, Chu CH, Lo ECM. The inhibitory effects of silver diamine fluorides on cysteine cathepsins. J Dent 2014;42(3):329-35.

25. Liu BY, Lo ECM, Li CMT. Effect of silver and fluoride ions on enamel demineralization: A quantitative study using micro-computed tomography. Aust Dent J 2012;57(1):65-70.

26. Chu CH, Lo ECM. Promoting caries arrest in children with silver diamine fluoride: a review. Oral Health Prev Dent 2008;6(4):315-21.

27. Lou YL, Botelho MG, Darvell BW. Reaction of silver diamine fluoride with hydroxyapatite and protein. J Dent 2011;39(9):612-8.

28. Mei M, Li Q, Chu C-H, Lo EC-M, Samaranayake L. Antibacterial effects of silver diamine fluoride on multi-species cariogenic biofilm on caries. Ann Clin Microbiol Antimicrob 2013;12(1):4.

29. Rošin-Grget K. The cariostatic mechanisms of fluoride. Acta Med Acad 2013;42(2):179-88.

30. Chu CH, Lo ECM, 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):767-70.

31. Suzuki T, Nishida M, Sobue S, Moriwaki Y. Effects of diammine silver fluoride on tooth enamel. J Osaka Univ Dent Sch 1974;14:61-72.

32. Okamoto M, Monomura E, Sobue S. Scanning electron microscopy studies on intact enamel surface after application of diamine silver fluoride. Jap J Pedod 1975;13(1):78-84.

33. Mei ML, Nudelman F, Marzec B, Walker JM, Lo ECM, Walls AW, et al. Formation of Fluorohydroxyapatite with Silver Diamine Fluoride. J Dent Res 2017;2203451770973.

34. Zhao IS, Gao SS, Hiraishi N, Burrow MF, Duangthip D, Mei ML, et al. Mechanisms of silver diamine fluoride on arresting caries: a literature review. Int Dent J 2017;1-10.

35. Wu M Y, Suryanarayanan K, van Ooij W J ODB. Using microbial genomics to evaluate the effectiveness of silver to prevent biofilm formation. Water Scien Technol 2007;55:413-9.

36. Suzuki TSS, Suginaka H. Mechanism of antiplaque action of diamine silver fluoride. J Osaka Univ Dent Sch 1976;16:87-95.

37. Mei ML, Chu CH, Low KH, Che CM, Lo ECM. Caries arresting effect of silver diamine fluoride on dentine carious lesion with S. mutans and L. acidophilus dual-species cariogenic biofilm. Med Oral Patol Oral Cir Bucal 2013;18(6):2-9.

38. Mei ML, Ito L, Cao Y, Lo ECM, 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.

39. Shimizu A. Effect of diammine silver fluoride on recurrent caries. Jap J Conserv Dent 1974;17:183-201.

40. Shimooka S. On the penetration of silver nitrate and ammoniacal silver fluoride into microstructure of the sound dentin. Shigaku. 1972;59(6):534-66.

41. Mei ML, Li QL, Chu CH, Yiu CKY, Lo ECM. The inhibitory effects of silver diamine fluoride at different concentrations on matrix metalloproteinases. Dent Mater 2012;28(8):903-8.

42. Crystal Y, Niederman DDSR, Dm D. Silver Diamine Fluoride

Treatment Considerations in Children's Caries Management. Pediatr Dent 2016;38(7):466-72.

43. Lo EC, Chu CH, Lin HC. A community-based caries control program for pre-school children using topical fluorides: 18-months results. J Dent Res 2001;80(12):2071-4.
44. Llodra J c, Rodriguez A, Ferrer B, Menardia V, Ramos T, Morato M. Efficacy of silver diamine fluoride for caries reduction in primary teeth and first permanent molar of schoolchildren: 36-month clinical trial. J Dent Res 2005;84(8):721-4.
45. Yee R, Holmgren C, Mulder J, Lama D, Walker D, Hederman W van P. Efficacy of silver diamine fluoride for arresting caries treatment. J Dent Res 2009;88(7):644-7.
46. Braga MM, Mendes FM, Benedetto MS, Imparato JC. Effect of silver diamine fluoride on incipient caries lesions in erupting permanent first molars: a pilot study. J Dent Child 2009;76(1):28-33.
47. Zhi QH, Lo EC, Lin HC. Randomized clinical trial on effectiveness of silver diamine fluoride and glass ionomer in arresting dentine caries in preschool children. J Dent 2012;40(11):962-7.
48. Santos VE Dos, Vasconcelos FM, Ribeiro AG, Rosenblatt A. Paradigm shift in the effective treatment of caries in schoolchildren at risk. Int Dent J 2012;62(1):47-51.
49. Duangthip D, Chu CH, Lo EC. A randomized clinical trial on arresting dentine caries in preschool children by topical fluorides - 18 months results. J Dent 2016;44:57-63.
50. Fung MD, Wong MCM, Lo ECM, Chu CH. Arresting dentine caries with different concentration and periodicity of silver diamine fluoride. JDR Clin Transl Res 2016;1-10.