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Use of Silver Diamine Fluoride in Dentistry

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Abstract

Silver diamine fluoride (SDF) is an alternative to traditional surgical and restorative treatment approaches in caries management. Although it stains teeth and has a metallic taste, SDF is a non-invasive, simple and affordable dental treatment which improves children's oral health, increases their access to care, controls pain and infection, and requires minimal personnel time and training. It is also recommended for uncooperative child patients. SDF can be applied with a simple applicator or microbrush without the need of complicated equipment or instruments. Studies have shown that SDF's triple mechanism of action against bacteria and augmentation of the mineral and organic content of dental hard tissues results in a reduction in tooth tissue solubility against chemical acid challenge and facilitates tissue remineralisation. This may be the reason for SDF's effectiveness in preventing and arresting caries. SDF may become a safe and efficient caries control agent which can fulfil the World Health Organization's Millennium Goals and the US Institute of Medicine's criteria for 21st-century medical care. Further studies have investigated its effectiveness in endodontic and hypersensitivity treatment.

Use of silver compounds in dentistry

Silver has been used for its medical properties for centuries, especially in the prevention of microbial infections [1]. Interest in silver nitrate solution was revived by Moyer in 1965 [2]. He demonstrated that it works as an antiseptic agent due to the presence of silver. Since then, silver has been used as a major therapeutic agent in medicine. In dentistry, the use of silver compounds was introduced for clinical treatment more than 170 years ago. However, in Japan, a similar traditional practice existed from ancient times until the Edo Period, which ended in 1868. This traditional custom, called "ohaguro," was practiced by women and some noblemen [3]. They dyed their teeth black by blending gallnut powder with acetic acid solution and iron (as an aesthetic agent). In addition to the blackening effect, this practice also protected the teeth from caries and periodontal problems. The presumed first report of the use of silver compound in dentistry was of silver nitrate ($AgNO_3$) used for arresting caries in the 1840s [4]. In 1917, Howe added ammonia water to make the solution alkaline. He used this solution, ammonical silver nitrate ($[Ag(NH_3)_2]NO_3$), to sterilize root canals. It was later applied to enamel pits and dentine to prevent caries [5]. Although silver nitrate stained the teeth black, it was still used in the 1960s [6, 7]. However, silver nitrate could not promote dentine remineralisation due to the formation of soluble calcium nitrate and the consequent loss of calcium.

Silver fluoride (AgF) achieved better results in this particular aspect. It both prevented [8] and arrested caries [9] resulting in tissue which was more calcified due to the reaction of fluoride with calcium [10, 11]. However, it needed to be followed by stannous fluoride solution as a reducing agent to stabilize the reaction. Silver diamine fluoride ($Ag(NH_3)_2F$), or SDF, was developed in consideration of the actions of fluoride and silver [3]. It was accepted as a therapeutic agent for dental treatment in Japan since 1960s [12]. SDF has also been used for many years in countries other than Japan [13]. In the 1980s, the Brazilian Ministry of Health, influenced by the Scandinavian movement, adopted a national oral health prevention program with widespread SDF use [14]. It has also been used in Australia [15], China [16, 17], Argentina [18] and Spain [19]. In Cuba [20, 21], Peru [22], Venezuela [23] and Nepal [24], SDF was used to arrest caries in community projects. The US Food and Drug Administration cleared SDF in 2014 for off-label use as a fluoride to desensitize teeth roots.

Since SDF's introduction in dentistry, it has been used to boost remineralisation of dental hard tissues and to act against cariogenic bacteria. As a safe and efficient caries control agent, it has been used to prevent and arrest caries in both primary and permanent teeth [16, 21, 24-27]. A review concluded that it may fulfil the World Health Organization's Millennium Goals [28] and the US Institute of Medicine's criteria for 21st-century medical care [29]. SDF is also used to prevent root fracture [30], as a dentine desensitizer prior to cementing procedures and for tooth hypersensitivity [31, 32]. It can also be use combined with laser irradiation to increase the acid-resistance of enamel and dentine [33-35]. SDF is compatible with glass ionomer cement and resin composites [36], as studies have reported that SDF does not affect these materials' bond strength [37]. The use of SDF as a root canal disinfectant has been investigated in several in vitro studies. Studies have shown that SDF was effective against Enterococcus faecalis, which is associated with root canal treatment failure [38, 39]. This review aims to provide an overview of SDF's escalating use in dentistry.

Identification and mode of use

SDF is a stable and alkaline solution containing fluoride ions, ammonia and silver ions. Table 1 shows different concentrations of commercially available preparations of SDF used for these diverse applications. Their concentrations of SDF vary between 3.8% and

38%. The 3.8% concentration is most commonly used for root canal treatment, the higher concentrations are used for caries management and the 38% concentration is used for hypersensitivity management.
The most common direction of use of SDF for caries arrest is once or twice per year [16, 21]. A more intensive regimen of fluoride application has been suggested to increase the proportion of caries arrest [40]. One study demonstrated that both an annual application and three consecutive weekly applications of 38% SDF solution are more effective in arresting dentine caries in primary teeth than three consecutive weekly applications of 5% sodium fluoride varnish [41].

For dentine hypersensitivity treatment, application varies from one to five applications within different periods of time. The highest percentage of pain reduction (99%) was achieved with five applications within three months [42]. However, there are no clear guidelines for choosing a mode of application or a concentration [43]. Similarly, for endodontic treatment, no standard mode of application has been determined. Therefore, the proper concentrations and usage directions for each specific clinical use should be further investigated.

Table 1 : SDF products and their manufacturers

Product	Manufacturer and Country	Contact
Advantage Arrest SDF 38%	Elevate Oral Care, USA	(+8) 77 866-9113 (Florida, USA) http://www.elevateoralcare.com/dentist/AdvantageArrest
Cariestop 12% and Cariestop 30%	BiodinamicaQuimica e Farmaceutica Ltda, Brazil	(+55) 43 3178-7000 http://www.biodinamica.com.br/
Fagamin 38%	Tedequim SRL, Argentina	(+54) 35 43 44-8260 http://www.tedequim.com.ar/productos-eng.html
Fluoroplat 38%	NAF Laboratorios, Argentina	(+54) 11 4865-9096 http://www.nafonline.com.ar/
Riva Star SDF 38%	SDI, Australia	(+61) 3 8727 7111 http://www.sdi.com.au/es/riva-star/riva-star
Saforide 3.8% and Saforide 38%	Toyo Seiyaku Kasei Co. Ltd. Japan	(+81)75-605-2300 (J. Morita MFG. Corp) http://www.morita.com/

Actions on plaque and teeth

The mechanism behind SDF's actions has yet to be determined. Studies have, however, investigated SDF and reported its antimicrobial activity and its effects on dental hard tissues such as enamel and dentin. In this study, the discussion of SDF's efects is grouped into 3 parts: antimicrobial activity, effect on the mineral (inorganic) content of dental hard tissues and effect on collagen and proteases (organic content) in dentine.

Antimicrobial effects (in cariogenic and endodontic treatment for associated bacteria)

Although SDF's mechanism against cariogenic bacteria is still not fully understood, studies have demonstrated that SDF is effective against mono- and multi-species coronal cariogenic biofilm [44-46]. SDF also inhibits the growth of bacteria associated with root caries [47] and is effective against *E. faecalis* [38, 39]. Silver ion has been found to be the main biofilm inhibitory element in SDF [48]. Silver ions can cause structural changes and damage to the bacterial membranes, causing cellular distortions and even bacteria death [49]. Silver ions have been suggested to interfere with the synthesis of glucans (from sucrose). Thus, SDF affects the adhesion of the bacteria to the surface [50, 51] and disables bacterial cell division [52]. According to the fundamental mechanism suggested by Russel and Hugo [53], the process of killing bacteria or inhibiting biofilm formation is due to silver ions' inhibition or induction of genes and transporter systems [54]. Besides the antibacterial effect of silver ions, the fluoride ions, such as those released from SDF application, may also exercise an inhibitory effect on bacteria [55]. SDF has a high concentration of fluoride, which can inhibit biofilm formation [46]. Fluoride acts at the cellular and/or dental plaque level, reducing carbohydrate metabolism and the sugar uptake of acidogenic bacteria by inhibiting enolase and proton-extruding adenosine triphosphatase (ATPase). Fluoride also increases the bacteria's acquisition of protons, resulting in diminished tolerance, growth and metabolism in acidic environments [56].

Effects on the mineral content of dentine and enamel

Suzuki [57] proposed a simplified chemical reaction scheme for the interaction of SDF and dental hard tissues. Calcium fluoride and silver phosphate are the major products in the reaction of SDF with dental hard tissue. Calcium fluoride is an essential reaction product. It works as a fluoride reservoir during cariogenic challenges. The precipitated silver phosphate forms an insoluble layer on the tooth's surface and provides a reservoir of phosphate ions [57]. SDF is alkaline, so it provides a favourable pH for the formation of covalent bonds between the phosphates from saliva and the proteins in dentine [58, 59]. Once the phosphate is incorporated into the dentine collagen, the phosphorylated dentine collagen attracts calcium ions, facilitating the nucleation of apatite for the remineralisation needed for crystal growth [60]. Calcium and phosphate from saliva and the demineralization process diffuse into the tooth; at the same time, fluoride (especially from the dissociation of CaF_2) binds to the existing crystal remnants, forming fluorapatite [61]. Fluorapatite is significantly less soluble and more acid-resistant than hydroxyapatite or calcium fluoride [3], so it is also more resistant to caries.

In vitro analysis of mineral content has shown that SDF can prevent caries [27], re-harden and remineralise decayed dentine [47, 62] and reduce mineral loss in dentine caries [47, 58]. However, another in vitro study found that fluoride varnish was more effective than SDF in reducing enamel surface demineralization [63]. SDF application has also been demonstrated to possibly contribute to dentine tubule orifice occlusion [64]. Precipitates containing high phosphorous and silver content occluded the dentinal tubules [46] and decreased their dye permeability [65] after SDF application. Silver ions can precipitate proteins in the dentinal tubules [66], and fluoride ions can react with free calcium ions. The products of the latter reaction are deposits of calcium fluoride which can block dentinal tubules [67].

Effects on organic content of dentine

Studies have shown that SDF treatment can protect dentine collagen [46, 47]. SDF's mechanism of action on the dentine's organic content is not clear. SDF has been found to have a high concentration of silver ion may cause physio-chemical or morphological changes, resulting in a more degradation-resistant collagen structure [58, 68] and increased inhibition of bacterial collagenase activity [69]. In addition, although SDF's mechanism on endopeptidases is not totally elucidated, it has been demonstrated that SDF may inhibit the activity of matrix metalloproteinases [33, 70] and cysteine cathepsins present in dentine [71]. SDF inhibits these enzymes' endogenous proteolytic activity on dentin, which leads to collagen degradation in the caries process [72]. The suggested mechanisms for the inhibitory effect against dentine endopeptidases may explain SDF's arresting effect.

Applications

SDF's triple action mechanism results in more than just clinical efficacy in caries management. In addition, studies have demonstrated that SDF can be used to manage hypersensitivity and for endodontic treatment. Three major clinical applications for SDF were identified:

Caries management

SDF can prevent and arrest caries in primary teeth, in permanent premolars and in children's molars [20, 73], including incipient caries [27]. It can also be used in rampant caries treatment [74] and to arrest caries in primary molars for very young children who are difficult to manage [13]. SDF's effectiveness in preventing the development of new root caries in adults has been demonstrated in clinical trials [75-77]. SDF has also been used as an indirect pulp-capping material to stimulate dentine remineralisation [18].

SDF treatment can be combined with laser irradiation to enhance its efficacy in preventing primary and secondary caries, providing a more resistant coronal and root dentine surface, both chemically and mechanically [58]. A review concluded that SDF can prevent secondary caries [15]. SDF conditioning does not affect the bond strength of resin composites, and it even enhances the strength of glass-ionomer cement [78]. SDF has been accepted as an effective tool due to its simple application, effectiveness in preventing and arresting caries and lower cost, especially in field settings.

Treatment of Hypersensitivity

Dentine hypersensitivity is a common clinical problem. The aetiology seems to be vigorous oral hygiene, diet and tooth wear that leads to open dentinal tubules. Recent clinical trials have also shown SDF's effectiveness as a tooth desensitizer in patients of various ages [32]. These studies evaluated tooth sensitivity for up to 12 months and showed a high level of effectiveness [42, 79-82]. The suggested mechanisms are the blockage of the dentinal tubules and the promotion of dentine remineralisation. A combination of SDF and potassium iodide (KI) were also used to desensitize teeth in a clinical trial [31]. KI could prevent the staining caused by SDF. Desensitization with Saforide also showed positive results without affecting the bond strength of a luting agent [83]. In short, SDF has proven to be an effective tooth desensitizer, although examination of its outcomes over a longer period of time and in comparison with other products is warranted.

Endodontic treatment

The elimination of microorganisms from the dentinal tubules in endodontic treatment is fundamental for successful treatment. In this regard, the removal of the smear layer to promote the flow of the intracanal medicaments is important. Many different antibacterial agents have been used, but failures due to the resistance of E. faecalis have been frequently reported [84]. Studies have demonstrated SDF's potential to reduce root dentinal permeability and increase dentine hardness and its effectiveness as an inter-appointment dressing and antimicrobial root canal irrigant [38]. It has been found to be effective against common root canal bacteria [85], including *E. faecalis* [39]. A CO_2 laser has been proven to be an effective method to remove or melt the smear layer on root canal walls after treatment with 38% SDF solution [86]. In addition, Nd:YAG laser irradiation in combination with SDF, has promoted increased fracture resistance in endodontically treated teeth [30] and decreased permeability in dentinal tubules [87]. Laser treatment closes dentinal tubules by rapid melting and recrystallization. This may induce the incorporation of the silver in the SDF solution onto the surface of the dentine root.

Advantages and disadvantages

SDF promotes a non-invasive, simple and affordable dental treatment. Moreover, it increases children's and adults' access to care and improves their oral health in developing countries, helps control pain and infection and requires minimal time and training for personnel. SDF's low cost was also recognized in a report about the current use of professionally administered topical fluorides in Asian countries [88]. This study reported that SDF use may not correlate with the level of need in these populations, so it suggested that governments should pursue low-cost SDF treatment. In addition, SDF has been shown to offer superior efficacy compared to other means for preventing and arresting caries. It was identified as the "best choice" for root caries prevention in adults when compared to three other preventive agents (fluoride, chlorhexidine and amorphous calcium phosphate) presented in different formulations, concentrations and routes of administration [89]. SDF was also compared to glass-ionomer cement for arresting treatment on primary teeth [25, 90] and to sodium fluoride varnish for preventing [26, 27] and arresting caries on permanent first molars in children [16, 17, 29, 41], with SDF in each case showing a significant higher effectiveness. SDF also showed a longer-term preventive effect, and consequently lower cost, relative to sealants [23].

The disadvantages of using SDF in arresting caries are the staining of the carious tissue and the metallic taste. Recent studies in Australia have suggested that a combined use with KI can prevent staining [36, 91], but further studies should be done to corroborate this evidence for clinical practice. Another suggestion to overcome the staining problem is the restoration of SDF-treated teeth with glass ionomer cement [92] and ammonium hexafluorosilicate. Nevertheless, the acid resistance of the teeth after application of the latter was shown to be inferior to those treated with SDF [13]. The problem of staining was also reported in root canal treatments, so SDF should be recommended especially for locations in which staining is not a major concern. However, no significant patient complaints have been reported, and SDF's benefits in caries treatment seem to outweigh the problem.

Safety concerns and precautions of use

The safety concerns associated with SDF are related to fluorosis, soft tissue irritation and potential cytotoxicity in periapical host cells.

Fluorosis

The possibility of acute toxicity or fluorosis through SDF use has been debated, especially in Australia [93]. However, the Dental Services of the Health Department of Western Australia reported no evidence to support the view that use of neutral 40% silver fluoride would cause fluorosis [94]. On the contrary, over 90% of the teeth treated with 40% silver fluoride from an ex-vivo study showed a favourable histological pulp response [15]. However, without data and with results based only on pulpal histology, the risk can be neither excluded nor supported. Studies in rat teeth have also demonstrated that SDF applications did not cause pulpal damage or severe reactions [57, 95], and only mild pulpal histological inflammatory changes were found up to six days [96]. Clinical studies have shown no pulp lesions in children [21], and no clinical reports of side effects have been reported in other clinical trials [24], up to 30 months [16].

Soft tissue irritation

Many studies have demonstrated SDF's effectiveness without reports of severe or relevant complications [16, 17, 21, 24, 27]. Reversible, small, whitish and mildly painful lesions in the oral mucosa were reported due to inadvertent contact with SDF solution in three individuals out of 225 children. However, these lesions disappeared within 48 hours without treatment [21]. SDF has been clinically proven to be free of severe long-term side effects, although some laboratory studies have raised the issue of SDF's safety for clinical practice. Further studies can investigate the mode of application that makes SDF most clinically effective.

Cytotoxicity to periapical host cells

Regarding SDF's effects on periapical lesions, a study showed that iontophoresis treatment using direct current and SDF as an antibacterial agent, though effective in the management of apical periodontitis [97], may induce necrotic cytotoxicity in host cells around periapical lesions after use in endodontic treatment [98]. The clinical effectiveness of this combination is still arguable. Therefore, further studies are necessary to determine the ideal methodology for iontophoresis with SDF in endodontic treatment.

Conclusion

Available studies suggest that SDF is a promising therapeutic agent for preventing and arresting caries in both primary and permanent dentition. SDF's anti-cariogenic mechanism and its ability to increase dentine mineralization have been recognized. SDF is a quick, simple and cost-effective therapeutic agent. It can be used in patients with acute caries lesions and for those who are difficult to manage. Studies have also reported that SDF may be effective as a dentine desensitizer and considered its use as an intracanal medication.

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