Silver diamine fluoride as a proactive anti-caries tool: A review

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Abstract
The management of ECC by the regular stereotyped restorative methods alone is incapable, particularly in a vast community or developing countries like India, where we lack free availability of dental equipment and manpower. The announcement of silver diamine fluoride (SDF) as another fluoride delivery system is a breakthrough therapy with evidences of caries lesion arrest rates of about 70 percent. SDF presents as an advantageous modality and is favoured as a satisfactory interim treatment option for its less invasive nature and its inexpensiveness. Most of the researchers have reported SDF to be undeniably more potent cariostatic agent than the fluoride varnishes in arresting caries. Its anti -caries effectiveness was found to be alike on incipient dental caries, non-cavitated and cavitated lesions and no severe pulpal damage after SDF application has been reported. Hence it is justified to state that SDF is a competent, efficient, secure and a reasonable caries preventive tool which is time saving and also patient oriented.

Keywords: Silver diamine fluoride (SDF), Cariostatic agents, Fluoride delivery systems, Early childhood caries (ECC), Caries prevention, Fluoride varnishes.

Introduction
Dental caries is a widespread universal disease having a prevalence of 49% to 83% across the different countries worldwide. The disease pattern in India is distinctively variant and several studies on dental caries have documented the prevalence between 31.5% to 89%[1-3] with an overall average prevalence of Early Childhood Caries being reported as 49.6%.[4] Early childhood caries (ECC), also recognized with terms as baby bottle tooth decay, nursing caries or rampant caries,[5,6] is a global health issue and is frequently observed in underprivileged groups in developing countries.[7] Although ECC is not life-threatening, untreated caries progression may cause pain, dental abscess, severe local and systemic infections and may lead to destruction and the premature loss of primary teeth, which will influence the permanent dentition eventually.[7-9]

Even though people are now more familiar with dental treatments and also dental therapeutics modalities have also improved with time, even then early childhood caries (ECC) still remains a health concern globally[7] and untreated cases of dental caries in young children still continues to be an extensive challenge.[7,10,11] This may be because of the fact that conventional dental treatment for caries is either inaccessible or unaffordable to most of the child population.[12] Above all, getting a child's desired cooperation during dental treatment becomes difficult at times and the dental rehabilitation of such children, usually below 3 years of age, requires pharmacological behaviour management strategies, including sedation and/or general anaesthesia. Quite expectedly these modes of treatments are costly and carry the possible danger of death.[7,10,12]

Hence, to strengthen the oral health status globally, there is a need of an alternative therapy that is simple to perform, easily accessible to many and of much lower cost.[7] Not only this option should be able to fulfil the required dental needs within the scope of the desired behaviour modifications, but also results in altering the microbial biofilm in such a manner that it not only leads to arrest of further demineralization but also escalate remineralization of the dental caries.[13] Since the population expansion is ceaseless and there is a conspicuous dearth of efficient dentists, especially in developing countries, thereupon a reasonable and an acceptable passage to oral health will be an intensified spotlight on prevention and Silver fluoride compounds may somewhat fill this need to a larger extent.[14] With evidences of caries lesion arrest rates of about 70 percent, SDF presents as an advantageous modality and is favoured as a satisfactory interim treatment option for its less invasive nature a and its inexpensiveness.[15]

The broad spectrum use of SDF can be widely perceived in reference to the millennium Development Goals for Health by World Health Organization (WHO).[16,17] and in particular the oral health goals,[18] achievable with means that are able to furnish emergency care, preventive and cost-effective, in this disposition.[19]

Although the Silver compounds have been used for ages, but significant interest in these compounds emerged in the 1970s with the discovery of its favourable antimicrobial properties and low toxicity. Past studies in dental literature have also shown evidence of application of silver nitrate in the lowering of dental caries along with the cavity sterilization and dentin desensitization.[20-24]

In the 1960s fluoride was added to the silver compounds with an intention to enhance and promote its anti-caries properties and presumably for an added favourable outcome. This was apparently appertaining to the results of the preliminary studies that reported the topical application of silver fluoride curb the collateral transmission of dental caries.[25]

Silver fluoride and Silver Diamine Fluoride are two chemical formulation available and a clinical study in Western Australia has already evaluated the anti caries effect of Silver fluoride at 40% in children.[26] The combination of

ammonia and silver ions results in formation of silver-diamine ion that is more complex and stable than silver fluoride and can remain consistent for a longer time.[20-24]

SDF's effect to halt the caries process and at the same time its ability to prevent the formation of new caries makes SDF distinctive from other caries-preventive tools, such as sodium fluoride (5%) and stannous fluoride (2% to 8%).[14] Similar successes of caries reduction in coronal and root caries have been reported by several authors.[27-29] A meta-analysis by Gao et al (2016)[7] too reported a significant (81%) overall caries arrest rate post SDF application. Revised AAPD guidelines (2018) also support the incorporation of SDF in the current constituted caries management strategy with the aim of improving distinctive patient care.[30] The announcement of silver diamine fluoride (SDF) as another fluoride delivery system is a breakthrough therapy and is attracting ample considerations from many researchers and dental clinicians, however, more research is needed for the better understanding of its use in dentistry.

SDF Availability

Silver diamine fluoride (38% w/v Ag $(NH_3)_2$ F, 30% w/w) consists of two main ingredients Silver in 24.4-28.8% (w/v) and Fluoride in 5.0-5.9% and is available as a colourless solution with a pH 10. Few formulations and brands of SDF that are commercially are Advantage Arrest, (Elevate Oral Care; USA.) Fagamin (Tedequim SRL Argentina) Bioride (Densply Industria e Comericio Ltda Brazil).[21,31] Other companies have also come up with silver diamine fluoride following FDA clearance.

Fundamentals of SDF- Tooth Interaction

Although the defining framework of SDF- tooth interaction has not been clearly summarised but it is hypothesized that mainly the fluoride ions reacts with tooth surface while, silver ions, like other heavy metals, manifest their antimicrobial actions. During the topical application, SDF (Ag $(NH_3)_2F$) reacts with the tooth mineral hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) and this interaction results in the formation of CaF_2 and Ag_3PO_4 as by-products which are responsible for the caries arrest, hardening of dentin structure besides demonstrating a considerable amount of antimicrobial action against multiple types of cariogenic microbial flora.[32-39] The CaF_2 produced acts as a reservoir of fluoride and facilitate further remineralization and leads to the formation of fluorapatite ($Ca_{10}(PO_4)_6(F)_2$) which is significantly more resistant to the acid attack than hydroxyapatite.[12,30-33]

Meanwhile Ag_3PO_4 formed on the tooth surfaces is weakly soluble and its antimicrobial action is because of the presence of the bactericidal metal cations that penetrates the tubules, resulting in the partial or total, blocking of lumen, hence inhibiting the contact of cariogenic bacteria with the surface. Bacterial liquidation and the suppression of their colonies may also occur owing to the unrestricted and extensive interactions of the silver ions with sulfhydryl factions of bacterial proteins and their DNA which may alter the hydrogen bonding and result in the suppression of the respiratory mechanisms, disentangling of the DNA, disturbing cell-wall synthesis and cellular division.[12,35-37]

Besides this the alkaline property of SDF also causes the neutralization of the acidic environment and provides an unfavourable environment for collagen degradation enzyme activation like MMPs and cathepsins enzymes.[29,33]

It is also very likely that the reduced bacterial adhesion and the decreased tissue cytotoxicity with SDF[29,40,41] could be because of the formation of silver-containing hydroxyapatite. -$Ca_{10-x}Ag_x(PO_4)_6(OH)_2$ with $0.0 \leq x \leq 0.5$.[39] that is formed when a very small amount of calcium ions gets substituted with silver ions and incorporate into the crystal structure of hydroxyapatite.[39]

Although, the extracellular matrix of the oral microflora may cause a physical hindrance and impedes the antimicrobial properties of silver ions[42] but a higher concentration of silver ions, proves to be more effective in the inhibition of the bacterial growth and in the evolving of new biofilms. This has been corroborated by the results of a laboratory study[43] and by few researchers[29] where 38% SDF-treated tooth surface reported suppressed growth of S. mutans monospecies biofilm for almost 48 hours[43] including monospecies of S. mutans or Actinomyces naeslundii[36] and the dual species of S. mutans and Lactobacillus acidophilus.[29]

Technique and Guidelines on SDF Application

SDF is an acceptable therapy and its application can be safely performed by an experienced or any non-dental faculty, like dental hygienists, nurses or primary health care providers under supervision. SDF solution is usually applied topically on carious surface with an applicator tip followed by a gentle flow of compressed air to improve its effectiveness besides this, many other techniques are being evaluated clinically with an aim to augment the infiltration of silver diamine fluoride into affected dentin of the tooth. It is assumed that Pre-treatment of the cavity chemically with ethylenediaminetetraacetic acid (EDTA) may help in removing the superficial hydroxyapatite layer and opening of the dentinal tubules of the affected dentin thus accelerating the silver diamine fluoride penetration. The protocol for SDF application, adapted by the University of California San Francisco (UCSF), recommends isolation and drying of the affected teeth before the application, but does not suggests caries excavation before application.[31,44] The isolation can be performed with gauze and/or cotton rolls and the carious dentin is doused and allowed to immersed for approximately one to three minutes for greater absorption and meanwhile the surplus and residual material is wiped off with the same cotton used for the isolation.[31]

The application time may range from 10 seconds to three minutes and also the literature has not reported any correlation between application time and clinical outcome. Although Crystal YO et al (2017)[15] have suggested one-minute application of SDF to be optimal along with a moderate flux of compressed air until liquid is dry.[15] During the smaller application span, the caries should be monitored at regular intervals and consider re-application if there is no significant caries arrest since inadequate endurance is seen

with a single application. Although application every once a year results in a remarkable success, but superlative results have been seen with the semi-yearly application. It is also reasonable and justifiable to take photographs to track lesions over time.[31] There are no post application limitations for the patients and it is permissible to eat and drink shortly after the application and no changes are required in the oral hygiene practices.

There is no detailed and best protocol available for clinicians interested in SDF application. No meta-analyses have been accomplished to apprise the effect of concentration or frequency on the efficacy due to the diverse nature of the studies conducted on SDF. There is also no establishment and agreement on the frequency of application of the two clinical protocols followed at present in North America.[30,31,44]

Clinical Aspects of SDF

Inhibition and Prevention of Dental Caries

Most of the researchers involved in clinical experiments on caries prevention have presented unwavering results and reported that SDF is undeniably more potent than the fluoride varnishes in arresting caries.[7,12,14,27,28,30,32,33,45] SDF application resulted in a 52% decrease in severity of dental caries together with a 47% decline in the occurrence of fresh caries in young children in a study conducted in Japan.[33] It has been revealed in clinical trials that during the SDF topical application the amount of retained fluoride is almost 2–3 times more than the fluoride delivered by any other topical fluorides such as sodium fluoride, stannous fluoride, or acidulated phosphate fluoride (APF).[14] Additionally, the use of SDF is free from any kind of danger and can be safely applied both in adults and children and similar pattern of caries arrest is seen in primary and permanent teeth.[30,32,36] Besides this the topical application of SDF does not interfere with the adhesion of resin or glass ionomer restorative materials[12,14,27,30,33] and can also be used as an adjunctive therapy along with lasers in remineralization of dentine.[21,28,30,37]

Management of Dentin hypersensitivity

The exposure of dentinal surface leads to Dentin hypersensitivity which leads to the occurrence of pain and discomfort and may add to patient's anxiety. The symptoms may vary and can be triggered by heat, cold, sensory, chemical, or osmotic stimulation.[45,46] Topical application of SDF has been found to be effective in treating dentin hypersensitivity,[45,46] as it forms a protective squamous covering on the bare dentin, resulting in the partial occluding of the dentinal tubules.[21,31,46]

As a Root Canal Irrigant

The elimination of microorganisms is mandatory in any kind of endodontic therapy. Several antibacterial agents are routinely being used for the purpose of disinfection of the root canal but the endurance of the Enterococcus faecalis to many of root canal irrigant has been reported. In an experimental study, 3.8% SDF demonstrated a 100% decrease in E. faecalis count after 60-minutes of its introduction.[47] Nowadays SDF at 3.8% solution (a 1:10 dilution of the 38% SDF solution) is available for root canal disinfection and the manufacturer supports its application three times at 24-hour intermission.[21] As suggested by few researchers, SDF can serve as a root canal irrigant[47] or a root canal dressing[47] material in between the appointments. Still long-term evaluation of the antimicrobial properties of SDF is mandatory for its successful endorsement as there occurs a lack of sufficient clinical evidence for its recommendations.[48,49]

Limitations and Safety Concerns

SDF is not indicated in patients with a known history of silver allergy and in teeth requiring endodontic therapy. Studies reviewing the response of dental tissue to 38%SDF reported mild but brief episodes of irritability of the marginal gingiva post SDF application but no clinical signs of pulpal damage and severe erythema. Hence the prior application of vaseline over the gingival tissues is recommended to counteract any soft tissue irritation.[25,45,0,51,52] SDF should be used very carefully in individuals suffering from open sores such as in herpetic gingivostomatitis, ulcerative gingivitis. Sometimes the application may result in small, white lesion in the oral mucosa, which usually heal on its own within two days.[18,25,50-52]

Besides this SDF alone cannot restore form and function of a tooth, especially in cases with large carious lesions approximating the pulp. GIC restorations over an SDF-treated lesion adopting the silver modified atraumatic restorative technique (SMART) or interim therapeutic procedures like stainless steel crowns should be considered to augment its efficacy. Since the ammonia in SDF in the moist environment can be corrosive in nature hence these additional restorative procedures should be performed after adequate time following initial SDF application. Contradictory results have been reported with the use of SDF as an indirect pulp capping agent in deeply carious lesions. In one in-vivo study the remineralizing properties of the SDF were found to be very similar to GIC and calcium hydroxide, however the opposite was seen in an in- vitro investigation.[53,54]

SDF solution has a metallic taste and involves a high concentration of fluoride (44,800 ppm), which may invoke the concern of its acceptability and dental fluorosis in young children. However, a literature search did not reveal any case of acute toxicity, systemic adverse effects or death after professional application of SDF and also an ex vivo experiment did not promote the passage of any notable and consequential amount of fluoride into the dental pulp through dentine. Moreover, there is an insignificant chance of toxicity since only a minute amount of SDF is applied to the dental tissue at a time[12] and a single drop of the SDF during topical application, result in less fluoride ion concentration as compared to 0.25 ml of topical fluoride varnish.[15]

The most commonly proclaimed adverse effect of SDF use is the permanent black staining of carious enamel and dentine[15] but no such effect is observed in the sound tooth tissue.[26,49] It may also result in skin pigmentation if it comes in contact but it wears off with time as the silver does not penetrate the dermis.[15] Staining is because of silver phosphate

and is more prominent with the application of higher concentrations of SDF or following repeated application.[12] This may restrain its clinical application in aesthetically critical patients and in the primary maxillary incisors, which are typical sites for ECC.[32] Parental concerns about the permanent teeth staining associated with SDF application has been reported in few studies and is a major concern for many dentists.[55] Several techniques have been tried to reduce this black staining, but none was found to be successfully effective. In an in- vitro experiment potassium iodide was applied post SDF application with an aim of producing whitish silver iodide, anyhow silver iodide is photosensitive in nature and change to brown or black upon when exposed to light.[12,3] Therefore, securing an informed consent becomes crucial due to this esthetic fallout of SDF therapy and it's better and safe to present the pictures of post treatment cases to the prospective patients and the parents[10] for their better understanding.

Future Perspective

The management of ECC by the regular stereotyped restorative methods alone is incapable, particularly in a vast community or developing countries like India, where we lack free availability of dental equipment and manpower. The therapeutic access is restricted only to the people who can incur the dental expenditure and thus put a financial burden on the remaining population. It is imperative that the dentistry shifts from the traditional form of dental care, where the aim is on treating a disease, to a prevention-oriented form of care, where child-centered policies are implemented for the prevention and arrest of a disease [3,10] and enforce laying down of suitable preventive and promotional oral health programmes.[3]

Topical fluoride therapy is usually less expensive and convenient to deliver and have been used to arrest active dental caries[56] since fluorides have proven to alter plaque metabolism and composition which consequently inhibits the acid production from carbohydrates[35,57] To date, 1.23% APF Gel and fluoride Varnishes are the most commonly used topical fluoride agents, still none of them have demonstrated absolute effectiveness.[58] If SDF is introduced in the anti caries regimen of managing early childhood caries, which will reduce the urgency for sedation and general anaesthesia, then hopefully the expenses of dental care can be automatically reduced remarkably.[10] Chu et al.,2006[27] reported significant caries arrest in preschool children with annual application of 38% SDF and the results were in line with the findings of Li, 1984[59] (China), Moritani Y et al., 1970; Yamaga R et al., 1972[32,60] (Japan), and Gotjamanos, 1996[26] (Australia). The accomplishments of SDF have been evaluated in the past laboratory experiments performed in -vitro[26,32] and in vivo[59] and further clinical trials have also reported its anti caries effect in both the primary and permanent dentition.[12,25,27,50,62,63] Its anti -caries effectiveness was found to be alike on incipient dental caries (ICDAS 1 or 2), non-cavitated (ICDAS 3 or 4), and cavitated lesions (ICDAS 5 or 6)[55] and no severe pulpal damage after SDF application has been reported in the published data.[33] Hence it is justified to state that SDF is a competent, efficient, secure and a reasonable caries preventive tool which is time saving and also patient oriented.[64] (Institute of Medicine, 2001). Hence, with all the evidences of desirable properties and no incidence of toxicity or adverse events reported the main drawback associated with the esthetics due to black discoloration of the carious dentin falls behind and is outweighed.[15]

If implemented widely and wisely, SDF can become a vital aspect of the broad spectrum global anti- caries programmes that would conform to the WHO Millennium aims and Goals and improve oral health worldwide.[14]

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