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RESEARCH ARTICLE

AN INSIGHT INTO THE MECHANISM OF ACTION AND USES OF THE MYSTERY FLUID-SILVER DIAMMINE FLUORIDE

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ABSTRACT

Despite numerous advances in dentistry over the past few decades, dental caries remains one of the most widespread diseases worldwide. Children from lower socio-economic classes or those with special needs are often affected and generally lack access to conventional restorative dental care. The caries management ideology has thus shifted from typical restorative treatment to arresting dental decay using fluoride therapies to provide more inclusive care. Silver diamine fluoride can arrest dental caries and prevent its progression. Although silver diamine fluoride had been used as a caries preventive measure in 1970s in Japan, it had not become popular in the other part of the world. Now, many countries have recommended the use of 38% silver diamine fluoride solution for caries prevention as well as for caries arrest.

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INTRODUCTION

Dental caries is probably a disease of modern civilization.It is a complex and dynamic process where a multitude of factors initiate and influence the progression of disease. It is seen in all the geographic areas in the world and affects persons of both genders in all races, socioeconomic strata and every age group.[1]At any given site, over time the action of micro-organisms on fermentable carbohydrate results in a disturbance of the equilibrium between the hard tissues (enamel, dentine, cementum) and the fluid immediately surrounding them. This leads to a net loss of mineral and eventually a localised destruction of the mineralized tissues of the tooth.[2]The traditional treatment approach to cure dental caries involves restoration of the tooth after proper cavity preparation.[3] This requires both operator skill and patient co-operation which may not be feasible all the time especially in case of pediatric patients.[4]The quest for newer materials to be used in dentistry has always been paramount which enables the dental surgeons to upgrade the clinical practice with the new materials. It dates back to 1891 when Stebbins first reported the halt of caries progression by using silver nitrate solution combined with amalgam scraps.[5] Silver Diammine Fluoride can serve as an effective solution that has the ability to both prevent and arrest caries.[6]This paper presents an overview of how silver diamine fluoride exerts its action.

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History: Silver diamine fluoride was first investigated by Mizuho Nishino in 1969 who wished to combine the antimicrobial properties of silver with the beneficial effects of high dose of fluoride.[7] The formulate resulted in a precipitate that blocked the dentinal tubules and reduced hypersensivity.[8] In the 1970s Silver fluoride was applied followed by stannous fluoride application in New South Wales population and it showed promising results to arrest caries.[9]Silver Diammine Fluoride(SDF) gained clearance from the U.S. Food and Drug Administration (FDA) in August 2014. Its physical ability to block dentin tubules allowed it to be classified as a medical device, rather than a drug, paving the way for expedited approval. October 2016 marked the beginning of a new era as SDF was awarded the designation of "breakthrough therapy" based on its ability to arrest dental dental decay in both children and adults, a first of its kind in oral healthcare therapy. This distinction identified SDF as a drug "to treat a serious or life-threatening disease or condition" and affirmed that "preliminary clinical evidence indicates that the drug may

demonstrate substantial improvement over existing therapies."[10]

Medical Management Of Dental Caries: Over the past few years there has been a paradigm shift in the management of dental caries. While earlier treatment options were mainly tertiary care, that is, operating on the tooth after the caries progression had taken place; recent treatment involves assessing the caries risk for a patient and taking the preventive measures based on the risk involved.[11] Primary care, including oral hygiene instruction, dietary counseling and fluoride supplementation has been formally included to address specific patient risk factors. Dental chemotherapeutics (e.g., high concentration fluorides, pellicle-inhibiting drugs such as chlorhexidine and silver ion compounds) act as adjunct options to the surgical treatment of these lesions as caries-inhibiting and caries-arresting medications.[12] Currently, SDF is covered under the Current Dental Terminology code D1354 as set forth by the American Dental Association. This is designated for a caries-arresting medicament to topically treat an existing asymptomatic carious lesion without removal of tooth structure and can be used by all properly trained dental professionals.

Mechanism of Action: The first medicinal use of silver dates back to 1000 B.C. when it was used to store potable water.[13] However the recent uses of Silver includes application of silver nitrate, silver foils and silver sutures in order to prevent ocular and surgical infections.[14,15]As silver has high polarizing power because of its small ionic size and larger charge on the ion and being a soft lew is acid it can interact with other soft lew is bases. By virtue of this property it may be thought to react with the sulphur and nitrogen containing amino acids like cysteine and histidine in the proteins of the bacteria and other microorganisms.[6] Silver interacts with the sulphahydryl group of amino acids or nucleic acids in the proteins and DNA that leads to altered hydrogen bonding and inhibition of the respiratory process, DNA unwinding, cell-wall synthesis, and cell division.[16,17] This is manifested as bacterial killing and reduced biofilm formation.[18] What led to the understanding of the mechanism of silver diamine fluoride can be said from a few chemical reactions. Yamaga and Yokomizo in 1969 and Yamaga in 1972 studied the effect of sodium fluoride and silver nitrate on the tooth structure.[19,20]

$$Ca_{10}(PO_4)_6(OH)_2 + NaF \rightarrow Ca_{10}(PO4)_6F_2 + NaOH \quad (1)$$

$$Ca_{10}(PO_4)_6(OH)_2 + NaF \rightarrow CaF_2 + Na_3O_4 + NaOH \quad (2)$$

$$Ca_{10}(PO_4)_6(OH)_2 + Ag(NO_3) \rightarrow Ca(NO_3)_2 + Ag_3PO4 + Ag_2O + H_2O\ Ag(NO_3)_2 \quad (3)$$

From the third reaction, silver phosphate that was formed led to the development of silver diamine fluoride. The basic reaction of Silver diamine fluoride on the tooth structure is represented below. It reacts with the hydroxyapatite of tooth to form silver phosphate and the fluoroapatite formed may result in the resistance against caries.

$$Ca_{10}(PO_4)_6(OH)_2 + Ag(NH_3)_2F \rightarrow CaF_2 + Ag_3PO_4 + NH_4OH$$
$$CaF_2 \rightarrow Ca^{++} + 2F^-$$

$$Ca_{10}(PO_4)_6(OH)_2 + 2F_- \rightarrow Ca_{10}(PO_4)_6F_2 + 2OH^-$$

The silver phosphate formed blocks the dentinal tubules and results in the caries arrest. Young and Elliot in 1966 suggested the probable changes brought about by the fluoride in the hydroxyapatite crystal lattice that leads to lesser solubility of the enamel in acidic environment. They suggested that apatite crystal has a calcium plane and the hydroxyl ions lies in a configuration such that it is either below or above the calcium plane. When the hydroxyl ion is located below one calcium plane and the subsequent calcium plane has its hydroxyl ion located above it, steric hindrance occurs and the hydroxyl ion is eliminated creating reversal points or voids. There are many such voids in the hydroxyapatite crystal lattice which results in increased solubility in acidic environment. Fluoride ion when comes in contact with the hydroxyapatite crystals, due to its similar ionic radii as that of the hydroxyl ions it fills these voids and results in a more compact fluorohydroxyapatite crystal lattice which is less susceptible to acid dissolution. Also hydroxyapatite becomes less reactive when it is converted to fluorohydroxyapatite resulting in reduced surface energy and reduced biofilm accumulation.[21]Besides the high concentration of fluoride in Silver diamine fluoride has the ability to form fluoroapatite crystals. Matrix metalloproteinases (MMPs) are metal-dependent endopeptidases commonly known as matrixins.[22] It is found that MMPs are present in dentin matrix[23,24] or in saliva.[25] They can be activated in an acidic environment or by lactate released by cariogenic bacteria. In the presence of zinc ion (Zn2+) which acts as a co-factor, MMPs mediate the degradation of practically all extracellular matrix molecules, including native and denatured collagen.[26] Recent studies suggest that the activation of MMP-2, MMP- 8 and MMP-9 have a crucial role in the destruction of dentin collagen in caries lesions.[25] MMP-8 (neutrophil collagenase) is capable of degrading triple-helical fibrillar collagens into distinctive 3/4 and ¼ fragments. MMP-2 and MMP-9 are gelatinase, which degrades type IV collagen. The activation of MMP-2, MMP-8 and MMP-9 has been shown to have a crucial role in collagen breakdown in dentin caries lesions.[26] Mei M *et al.* conducted a study to find the effect of silver diamine fluoride on matrix metalloproteinases and concluded that 38% silver diamine fluoride could effectively block MMP-2,MMP-8, and MMP-9 which may be another reason for the anti-caries effect of silver diamine fluoride.[27]

Tersariol *et al.* reported that cathepsin activities were associated with MMPs activities in dentine.[28]Scaffa*et al.* suggested that cathepsins may also be responsible for the collagen degradation in caries lesions.[29]Cathepsins are proteolytic enzymes that can be identified in dentine caries and human pulp. They are members of the C1 family of papain-like enzymes, which are the largest and the best-characterised family of cysteine peptidases. Cathepsins can extracellularly degrade type I collagen and proteoglycans, which are the main components of the dentine organic structure. Cathepsins are active and stable in acidic environments and mostly unstable at neutral acidity. [30]Cathepsins vary in their structure, catalytic mechanishm and the proteins on which they act upon. Cathepsin B is found in carious dentin and saliva but its activity varies depending on the depth and age of the carious lesion while remaining stable in saliva.[31] Cathepsin B cleaves the non helical telopeptidase extensions of collagen.[32] Cathepsin K can catabolize collagen and break down dentine. It cleaves the collagen at the triple helical region.[30]Cathepsins are activated by active MMPs in the carious lesion and vice versa. Cathepsin K is a unique protease that is both a telopeptidase and a collagenase.[33]It is also the only cysteine cathepsin capable of cleaving collagen at the triple helical region. Cathepsin K is involved in mineralised tissue resorption under normal and pathological conditions. The

cathepsin activity in carious dentine significantly increases with increasing depth, indicating that odontoblast- or pulp derived cathepsins may be important in actively progressing carious lesion.[31]The ability of the Silver diamine fluoride solution to maintain the alkaline environment may be responsible for inactivation of the cathepsins. The antibacterial effect of silver diamine fluoride originates from the inhibition of enzyme actions and dextran‐induced agglutination of *Streptococcus mutans* cariogenic strains. Silver diamine fluoride can inhibit cariogenic strains of *S. mutans* at a concentration of 0.12 micromole/ml or more. It can inhibit dextran‐induced agglutination of S. mutans at 0.59 micromole/ml. Silver ion present within silver diamine fluoride is responsible for these anti S. mutans effect.[35]

Benefecial Effects of Silver DiammineFuoride: Arrest of Caries: It has been reported by several authors that the caries arrest effect of silver diamine fluoride increase significantly if it is reapplied within one year.[36] When SDF is applied its ability to arrest caries depends on the lesion size and location with effectiveness varying between 47% and 90% which decreases overtime.[37] Anterior teeth have higher rates of caries lesion arrest than posterior teeth.[38] It has been found that after single application of silver diamine fluoride, 50% of the arrested carious lesion at 6 months revert back to active lesions at 24 months.[39]

Prevention of Caries: Silver diamine fluoride when applied to carious lesions has the ability to exert its beneficial effect on the other tooth surfaces.[40,41] Annual application of silver diamine fluoride prevents many more carious lesions than four times per year fluoride varnish in both children and elders.[42]Because of this caries arrest and prevention effect SDF can be effectively used for treating early childhood caries.

Desensitising Agent: When Silver diamine fluoride is applied on the tooth surface it forms a squamous layer and the silver phosphate formed blocks the dentinal tubules. It can therefore be applied on hypersensitive dentin.[43]

Root canal Irrigant: 3.8% silver diammine fluoride shows potent antimicrobial effect and can be used as a root canal irrigant.[44] It has been found that silver diamine fluoride can effectively reduce the bacterial load from the canal walls and circumpulpal dentin.[45]

Subjects with behavioural or medical issues: Since SDF application is easy and painless, many patients who are unable to undergo traditional restorative dentistry can benefit from this treatment. This includes patients undergoing chemotherapy, immunocompromised patients ,those suffering from chronic diseases or subjects with special needs like Downs syndrome, autism etc.SDF treatment helps in building trust and a positive dental experience for such patients.[46]

Application of Silver Diammine Fluoride: During clinical application of silver diamine fluoride, excavation of the carious lesion is not always necessary because the excavation only helps to reduce the extent of blackish discoloration after caries has been arrested. The application time varies between 10seconds to 3 minutes with an average application time of one minute. In case it is applied for a shorter period, reapplication should always be considered. No eating or drinking after application of silver diamine fluoride for 30 minutes to one hour is recommended.[37] Steps to be considered for silver diamine fluoride application:[37]

- Gross debridement of carious lesion, so that silver diaminevfluoride can come into contact with denatured dentin
- An application time of 1 min is usually recommended and before application affected tooth surface should be dried with either by cotton roll, gauze piece, or by compressed air
- Gentle flow of compressed air should be used to dry the silver diamine fluoride liquid
- Contact of silver diamine fluoride liquid with surrounding gingival tissue and mucosa should be avoided using rubber dam or cotton rolls, otherwise irritation of these tissues will be a common finding
- Any excess silver diamine fluoride liquid should be removed with a cotton pellet and isolation of operating site should be continued for 3 min after application
- A plastic dappen dish should always be used for silver diamine fluoride as it corrodes metal and glass.

Safety measures during SDF application: There is no reported deaths or systemic adverse effects in published clinical trials using topical silver diamine fluoride as per the manufacturer's recommendation. However, the maximum limit is recommended as one drop per 10 kg of body weight per treatment visit at weekly intervals.[47]On application of silver diamine fluoride pulpal damage is unlikely; however, it should not be placed on exposed pulp, lesion close to pulp should be monitored periodically after application of silver diamine fluoride.[37]

Overcoming the blackish discoloration Of Silver diamine fluoride:

The chemical reaction for silver diamine fluoride can be stated as-

$$Ag(NH3)_2F(aq) \rightarrow Ag(s)+2NH3(g)+F\text{-}(aq)$$

The fluoride ion is responisible for remineralization and the excess silver ions cause the blackish discoloration. If potassium iodide is added silver iodide is formed.

$$Ag(NH3)2F(aq)+KI(aq) \rightarrow AgI(s)+2NH3(g)+F\text{-}(aq)$$

Silver iodide is yellow, and insoluble in water. But the AgI precipitate is easily rinsed away. The SDF delivers the antimicrobial silver ions, but excess remain that can be precipitated as Ag_2S because the KI solution is applied after the SDF, the excess silver ions are removed. [48]

Conclusion

From the various literatures that are available, it can be concluded that 38% silver diamine fluoride is a very effective agent for preventing the caries and halting progression. No harmful effect of silver diamine fluoride on the pulp has been noted. It is very useful for the management of caries in young children. More clinical trials are needed to prove the beneficial effects of silver diamine fluoride at large.

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