'Repair the Defect'- Emerging Topical Fluoridated Remineralizing Agents: A Review.

Abstract:
A universal public health issue that affects 60% to 90% of people worldwide is dental caries, especially in younglings. Dental caries is an incessant affair with phases of demineralization and remineralization rather than being a continuous and unidirectional process of hard tissue demineralization. Cavitation results from an overbalance in the demineralization process. While remineralization is the process of increasing ion deposition into crystal gaps in demineralized enamel to achieve net mineral gain, it is defined as the supply of calcium and phosphate ions from a source external to the tooth surface. Despite the fact that many other therapies for early enamel carious lesions have been tried in recent years, fluorides have emerged as the most popular remineralizing agent due to their superior cariostatic efficacy and affordability. Alternative preparations with additional benefits would be appealing because currently available topical fluorides necessitate patient participation and multiple treatments over the course of a year.

Key-words: Dental caries, Demineralization, Remineralization, Fluoride.

Introduction:

A global public health issue that affects 60% to 90% of people around the world is dental caries, especially in younglings. Dental caries gradually causes more damage, thus it's critical to manage the condition starting at a young age. The effects of this disease, especially in young children, can include pain, infection, and face swelling, which may necessitate visits to the emergency room.[1] Dental caries is an incessant affair with phases of demineralization and remineralization rather than being a continuous and unidirectional process of hard tissue demineralization. Cavitation results from an overbalance in the demineralization process.[2] While remineralization is the process of increasing ion deposition into crystal gaps in demineralized enamel to achieve net mineral gain, it is defined as the supply of calcium and phosphate ions from a source external to the tooth surface. [3]

Early enamel carious lesions have been managed with a variety of therapeutic methods in recent years. Due to its excellent cariostatic efficiency, topical fluoride became the most widely used remineralizing agent in the middle of the 20th century. Despite their effectiveness and affordability, topical fluorides require patient participation and multiple administrations over the course of a year; as a result, alternative preparations that offer additional advantages might be of interest. [4]

Rationale for De / Remineralization:

The pH of the environment and the presence of contaminants are the two main factors that affect how soluble

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hydroxyapatite is. The initial catalyst for hydroxyapatite's dissolution and precipitation is pH. [4] In comparison to apatite, calcium (Ca^{2+}) and phosphate (PO^{4-}) ions are more saturated at low pH than at high pH. Saliva and plaque fluid are extremely saturated with hydroxyapatite at neutral pH. Therefore, if a proper precipitation nucleus is present, a mineral will precipitate. Consuming fermentable sugars causes the plaque to create acid, which lowers pH and raises the calcium and phosphate concentrations required for saturation. Additionally, the fermentation (acid production) by oral bacteria is slowed down by a falling pH. [4]

The pH of the oral environment, namely the calcium and phosphate levels, determines whether minerals will precipitate or dissolve in enamel and dentin. When the crucial pH for the dissociation of hydroxyapatite is reached, which is somewhere between 5.5 and 5.2, the acid ions mostly react with the phosphates in saliva and plaque. As pH is further lowered, acid ions gradually interact with the phosphate groups of hydroxyapatite, partially or completely dissolving the surface crystallites.

The process releases accumulated fluoride, which interacts with Ca2+ and hydrogen phosphate (HPO2) ions to generate fluorapatite, or apatite that is 4 fluoride enriched. Even fluorapatite will dissolve if the pH falls even lower than the crucial pH of 4.5. Remineralization takes place if acid ions are neutralised while the HPO2- and Ca2+ ions are kept in solution. The type of plaque fluid determines how the apatites are composed after that. The chemical makeup of the enamel's outer layers is gradually altered as a result of this episodic pH cycling, becoming gradually less soluble over time. The post-eruptive enamel maturation is the term used to describe this process. [4]

The majority of recent studies have concentrated on various calcium phosphate-based techniques to support and improve fluoride's capacity to rebuild tooth mineral. [5] Numerous fluoride remineralizing agents have been studied up to this point and several of them are currently being utilised in clinics with very promising outcomes.

Fluoridated remineralizing agents:

1. Silver Diamine fluoride (SDF):

SDF, a clear liquid that combines the remineralizing and antibacterial properties of fluoride and silver, is a promising therapeutic agent for treating carious lesions in infants and others who require special care. Fluoride is now recognised to prevent demineralization of tooth structure, but SDF may also prevent demineralization of dental tissue by interfering with the biofilm due to its antibacterial action. As a result, SDF is now one of the methods available to stop caries by altering how bacteria interact with tissue and promoting remineralization. [6]

Crystal and Niederman (2019) substantiate SDF's effectiveness to arrest and prevent caries in primary teeth and that it fulfils the US institute of Medicine's six quality targets based on many systemic reviews.

1. Safe: No significant adverse effects have been reported in any clinical trials that have been carried out and published internationally.
2. efficient—it stops about 80% of lesions that have been treated;
3. Effective—can be used in a matter of minutes by medical experts in a variety of community and healthcare settings;
4. Timely: Because of its simplicity of use, it can be used as an intervention tool as soon as the issue is identified;
5. Patient-centered-meets a child's or adult's immediate needs in a single therapy session while being minimally invasive and pleasant; and
6. Equitable - its use is equally efficient and affordable, making it a therapeutic option for lower income groups. [6,7]

Mechanism of Action of SDF:

Three key mechanisms are as follows:

The promotion of remineralization and a barrier to demineralization of enamel and dentine;

The antibacterial activity on cariogenic bacteria;

Inhibitionof collagenase -induced loss of dentine collagen matrix.

Silver phosphate and calcium fluoride are produced when SDF reacts with hydroxyapatite, creating a reservoir of fluoride and phosphate ions that aid in remineralization. The silver ions enter the lesions and remain there to have an effect (25–30 microns into the enamel, 200–300 microns into the dentin, and up to 2 mm into a deep carious lesion). The resulting silver compounds, including silver oxide and silver phosphate, are what give the carious lesions their dark colour.

The black staining in the arrested lesions that are shown following SDF application is the only disadvantage of SDF. In order to prevent the development of a sclerotic black surface on the tooth and the hardening of the soft diseased dentin, parents and children should be made aware of any black or dark brown stains that may result from the administration of SDF. Other than black staining, side effects of SDF application at any dose include metallic taste, pulpal and oral soft tissue irritation, tiny, reversible white lesions in the oral mucosa, and gingivitis.

According to Knight et al., adding potassium iodide (KI) before applying the SDF could lessen tooth discolouration. In particular on enamel and to a lesser extent on dentin, Sayed et al. revealed that the glutathione biomolecule also influences lowering tooth discolouration following application of SDF. However, KI is not advised for use by expecting mothers or nursing women for the first six months due to concerns regarding the thyroid development of the unborn child as a result of iodide overdose. [7,8]

2. Nano silver fluoride (NSF):

Due to the scientific and commercial possibilities of nanotechnology, it is quickly becoming prevalent in dentistry. Consequently, Silver Nanoparticles (AgNPs) have drawn interest because of their large specific surface area and high surface atom fraction. AgNPs are well-known antibacterial agents globally.

- Particles size: (3.2–1.2 nm)
- Shape: spherical

AgNPs, chitosan, and fluoride are all components of the novel experimental substance known as nano silver fluoride (NSF). With additional preventative and antibacterial qualities, it is comparable to SDF. It has been created as a powerful anti-infectious agent with aesthetic consideration to stop the negative effects of discolouration.

Chitosan, AgNPs, and the fluoride formulation work together in synergy to stop caries, demonstrating the effectiveness of NSF. When AgNPs are used, the surface area that is accessible to the microbe is much enlarged compared to when silver is typically used to provide antimicrobial properties in nitrate form.

AgNPs' conceivable mode of action stems from their extraordinarily wide surface area of interaction with bacteria. Once connected, the nanoparticles pierce the bacterial membrane. Sulfur-containing proteins and AgNPs like Ag+, as well as phosphorus-containing substances like DNA, can interact with them in the cell membrane and, possibly, impede function. AgNPs have the ability to kill bacteria by attacking their respiratory systems. [9] According to Danilcauk and Kim [10], AgNPs have a propensity for a continuous release of Ag+ inside the bacterial cells, which can produce free radicals and cause oxidative stress, further boosting their bactericidal activity. DNA replications would be hampered by these contacts in the cell membrane, which would cause bacterial mortality.

Although silver nanoparticles' antibacterial effectiveness is well established, Scarpelli et al. (2017)[11] discovered that AgNPs had a remineralizing effect on deciduous dental enamel and exhibited bactericidal activity against S. mutans, E. faecalis, and E. coli.

Nano Silver Fluoride (NSF) was discovered to be easier and more efficient than traditional fluorides in treating incipient caries lesions because of its remineralizing capacity, according to E silva et al. (2018)[12]. Additionally, they discovered stronger Streptococcus mutans adhesion interference and greater S. mutans acidogenicity inhibition than NaF.

The literature currently lacks significant information on the depths to which AgNPs penetrate enamel, as well as the impact of their sizes and shapes on enamel remineralization.

Advantages:

- Non-invasive process with considerably lower risk of cross-infection; uncomplicated, less technique-sensitive, and not requiring any dental equipment or a clinical setting. As of yet, no negative effects have been documented.

- The tooth structure does not get immediately darkly stained while using Nano Silver Fluoride (NSF). Because nano silver can not create oxides and their particle size alters their chemical reactivity, the colloid cannot turn teeth black.
- As an adjuvant, chitosan can have a favourable impact on in vitro enamel demineralization by reducing the loss of ions, particularly from hydroxyapatite. This avoids enamel mineral loss during pH cycling. [9] Additionally, Silver nanoparticles (AgNPs) do not encourage colour change in tooth enamel, which is a cosmetic advantage over conventional silver products, according to Freire et al. [13].
- Additionally, 5% NSF is eight times more cost-effective than 38% SDF (Tirupathi et al. 2019) [14]. Its application at the community level is therefore inexpensive and trustworthy.

As a result, NSF is regarded since a useful alternative to Silver Diamine Fluoride (SDF) when administered directly to caries lesions, as its cosmetic benefit outweighs the disadvantages of discolouration. Additionally, NSF application is noninvasive, harmless, and economical, and it can be used on both adults and children without creating obstacles to receiving dental healthcare. To determine the long-term usefulness of its qualities with a large sample size, however, further research is required. [9]

3. Titanium tetra-fluoride (TiF_4):

Over the past 40 years, interest in titanium tetra-fluoride (TiF4), a potentially intriguing agent for remineralizing tooth structure, has grown. Since titanium is naturally non-toxic, there have been no side effects associated with TiF4 reported to far. TiF4 has been administered in a variety of experiments as solutions with concentrations ranging from 1% to 4%, but gels or varnishes have also been employed as a carrier. [15] The creation of an acid-resistant surface coating, an increased and rapid uptake of fluorides, greater penetration and longer retention of fluoride, and no unintended demineralization are all factors that contribute to TiF4's defensive capacity. [16]The acid-resistant coating might be made of TiO2, which is created when titanium reacts with oxygen groups obtained from water or oxygen that is bonded to phosphate (Tveit et al., 1988)

It is also mentioned that this glaze-like layer, which is fluoride and titanium-rich, may serve as a reservoir for fluoride ions, which could subsequently slow acid dissolution or speed up remineralization of the underlying tooth hard tissue.

Additionally, because the TiF4 solution is highly acidic on its own, it may cause demineralization of the enamel surface and the production of HF. This may increase the fluoride ions' depth of penetration into the apatite lattice. The effectiveness of TiF4 may possibly be attributed to its capacity to replace calcium in the apatite lattice or to the synthesis of a titanium phosphate compound, both of which increase the hard tissues of the teeth's enamel's acid resistance (Leadley et al., 1997; Ribeiro et al., 2006). Although it was anticipated that demineralized lesions with a higher porosity would have a deeper penetration of titanium, the penetration depth was actually found to be higher in sound than in demineralized enamel (Chevitarese et al., 2004). [15]

Although numerous research have demonstrated the impacts and advantageous qualities of TiF4, its performance is still in doubt and the chemistry is not well known

S. No.	Materials	Author	Study	Result
1	**SDF**	Shah *et al.* (2017)[17]	Compared the efficacy of SDF, fluoride varnish, and APF gel as topical fluoride agents in vivo.	SDF can be used efficiently as a topical fluoride agent since it significantly enhances the fluoride content of enamel when applied in vivo to enamel when compared to Fluoride Varnish and APF Gel.
		Farhadian *et al.* (2020)[18]	Examined the impact of SDF versus NaF varnish on the demineralized enamel's microhardness.	Both NaF and SDF have the ability to remineralize early enamel defects, although SDF has the greater potential.
2	**NSF**	Nozari *et al.* (2017)[19]	compared the ability of NSF, Nano hydroxyapatite (n - HAP), and NaF varnish to remineralize primary anterior teeth's enamel.	In terms of remineralizing early caries, NSF might have the most efficacy, whereas NaF varnish and n-HAP serum performed similarly.
		Akyildiz *et al.* (2019)[20]	compared the remineralization impact of an experimental NSF formulation to SDF and NaF varnish already used in clinical settings utilising an in vitro model.	On artificial enamel caries lesions, it was discovered that NSF was not as effective as NaF varnish and SDF. It was advised to conduct more research on NSF.
3	**TiF_4**	Buyukyilmaz *et al.* (1994)[21]	Quantitative microradiography was used to examine the cariostatic potential of TiF4 solution administered topically around braces.	TiF4 may work very well as a cariostatic agent for orthodontic applications.
		Exterkate *et al.* (2007)[22]	In bovine enamel lesions, daily treatments with varying concentrations of TiF4 (100, 250, and 500 ppm) were compared with analogous NaF treatments administered at the same pH.	TiF4 is a potential cariostatic agent, particularly when used to stop caries from developing.
		Alaxandria *et al.* (2017)[23]	studied the remineralizing ability of 4% titanium tetrafluoride (TiF4) and contrasted it with varnish containing sodium fluoride.	A 4% TiF4 varnish is a potential substance that can react with enamel to protect it against surface and subsurface demineralization. TiF4 and NaF varnishes have demonstrated a protective effect against mineral loss on the enamel subsurface.

Conclusion:

Remineralization can take place to repair the lost tooth structure by using such agents, which accelerate the remineralization process rather than demineralization, as the focus of restorative dentistry has evolved in recent years to a conservative approach. Newer in vivo studies in this area will undoubtedly produce the better clinically applicable medicines with satisfactory outcomes.

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