

Silver Compounds Used in Pediatric Dentistry for Caries Arrest: a Review of Current Materials and New Technologies

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Abstract

Silver compounds have been used in medicine and dentistry for centuries. Their use in pediatric dentistry has long been restricted because of some drawbacks, chief among them being the discoloration of teeth with black stains. However, recent advances in technology have resulted in the development of new silver agents that do not have the limitations of previously used ones. This led to the reintroduction of silver compounds in pediatric dentistry. The aim of the present review was to examine the evidence supporting the therapeutic use of silver compounds in pediatric dentistry for caries arrest, as well as the mode of action and biocompatibility, characteristics, advantages, and disadvantages of different silver-containing agents.

Keywords

nanosilver fluoride, nanotechnology, non-operative treatment, silver diamine fluoride

INTRODUCTION

Dental caries, which affects millions of children globally, is the most common chronic disease in children. The multifactorial etiology of this disease has been recognized as a result of the continuous efforts over the years to better understand the carious process. Although each person has a unique combination of primary and secondary etiological factors, it is generally agreed that childhood is a very dangerous time for the rapid onset and progression of carious lesions, which presents a significant problem for dental professionals.

The concepts regarding the treatment of dental caries have changed several times as pediatric dentistry has evolved, beginning with extraction as a method of treating dental caries and progressing to the principles of non-operative and minimally invasive operative treatment in childhood, which are the main focus of modern pediatric dentistry.

There is increasing interest in caries-arresting agents

that can be applied directly to the carious lesion without the need for prior mechanical treatment.

AIM

Silver compounds have been used for centuries in medicine, and for over a century in dentistry. The aim of the present review was to analyze the evidence supporting the usage of silver compounds in pediatric dentistry to arrest carious lesions, as well as the biocompatibility, principle of action, characteristics, advantages and disadvantages of various silver-containing materials.

History of the medical use of silver

Silver (Ag⁺) has a significant antibacterial action. It has been used in medicine for ages and has provided numerous

benefits to this field.^[1] When used in concentrations less than 50 ppm, silver can kill pathogenic bacteria. Currently, it is used for acute burn coverings, catheter linings, water purification systems, hospital gowns and in dentistry for caries prevention.

Caries lesions were prevented from progressing by using a mixture of amalgam scraps and nitric acid as early as 1891. Howe PR was responsible for popularizing this silver nitrate solution, which is why it was dubbed “Howe’s solution.” It was first used in Boston, USA, to arrest caries among disadvantaged children.^[2]

Since the early 1900s, there have been reports on the use of silver nitrate (AgNO₃) to stop the progression of dental caries. Through the years, there has been fluctuations in the popularity of its use and conflicting reports on how effectively it stops dental cavities. Although references to its use date back to 1981, it is currently regarded as outdated.^[3]

Duffin proposed the use of 25% AgNO₃ solution followed by 5% NaF varnish to arrest carious lesions in dentine.^[4] This protocol shows promising laboratory results, but still needs further confirmation of its safety and efficacy.^[2]

Silver diamine fluoride (SDF)

Silver diamine fluoride is a liquid solution which has multiple scientific verifications of its powerful effect against cariogenic bacteria. Numerous in vitro studies confirm the antimicrobial effect of silver ions and the remineralizing effect of fluoride ions SDF contains. SDF can be used for caries management in young children, especially those with special care needs.^[5]

SDF was first invented by Drs Yamaga and Nishino in Japan. They combined the actions of silver, ammonia, and fluoride producing the first silver diamine fluoride product named Saforide (Bee Brand Medico Dental Co, Ltd, Osaka, Japan).^[6] Since 1990, its popularity has been in the decrease with the development of operative dentistry and its restorative materials and techniques. Nevertheless, SDF products have recently become a topic of interest again and their properties and action have been an object of new studies.^[7]

Organizations like the American Academy of Pediatric Dentistry (AAPD) and the World Health Organization (WHO) support the SDF application for caries management in primary dentition.^[8] In most European countries, SDF application is very limited - it is mainly used as a dentine hypersensitivity remedy and its caries arresting use is off label. In countries such as France, Germany, Greece, Ireland, Italy, Netherlands, Portugal, and Spain, only one commercial SDF product is used - “Riva star” but only in unit dose capsules that increase the expenses for the treatment. SDF is not included in any formal national programs for caries management. Its use is taught only didactically. The European Academy of Pediatric Dentistry, the Organization for Caries Research and the European Federation of Conservative Dentistry have published clinical guidance and recommendation for caries management in which SDF treatment is included. However, currently, most national

dental societies don’t have any issued SDF-specific guidelines and protocols.^[7]

In 2021, the WHO included SDF in the WHO Model List of Essential Medicines for both adults and children.^[9]

SDF characteristics

Chemically, SDF is composed of diamine silver ion complex [Ag(NH₃)₂]⁺ and fluoride ion (F⁻). Metal amine complexes are less oxidizing and more stable than the silver ion.^[10] SDF has a metallic taste and is an alkaline, colorless solution with a pH of about 9 to 10. On the market, it is found in various concentrations - 10%, 12%, 30%, and 38%.^[11] The most commonly used concentration is 38%. A solution of 38% SDF contains approximately 25% silver (253,900 ppm), 8% ammonia, 5% fluoride (44,800 ppm), and 62% water. SDF is produced in several countries.^[9] Marketed brands of SDF are presented in **Table 1**.

Table 1. Commercially available SDF products

Product name	Manufacturer	Country
Riva Star	SDI Dental Limited	Australia
Topamine	Pharmadesign Co., Ltd.	Australia
Advantage Arrest	Elevate Oral Care	USA
Saforide	Toyo Seiyaku Kasei Co. Ltd.	Japan
Ancarie	Maquira, Maringa, PR	Brazil
Cariostatic	Inodon Laboratorio	Brazil
Cariestop	BiodinamicaQuimica e Farmaceutica Ltda	Brazil
Bioride	DensplyIndustria e Comercio Ltda	Brazil
Fluoroplat	NAF Laboratorios	Argentina
Fagamin	Tedequim SRL	Argentina
E-SDF	Kids-e-Dental	India

The caries-arresting mechanism of SDF is not entirely clear, but there are certain suggestions:

- A solution of 38% SDF contains 44,800 ppm fluoride. The enamel of the teeth contains hydroxyapatite crystals. Fluoride ions can displace hydroxyl ions to form fluorohydroxyapatite, which is more resistant to cariogenic environment.
- The effect of silver diamine fluoride on the organic composition of dentine is through inhibition of matrix metalloproteinases and cysteine cathepsins that cause the breakdown of demineralized collagen.
- The silver ions have an antimicrobial effect, which is expressed in cellular wall penetration, disruption of cellular respiration, and interruption of the replication of cells. It has been demonstrated that dentine caries lesions treated with SDF have less bacterial number in comparison to lesions treated without SDF.

- When using SDF as a teeth hypersensitivity treatment, the opened dentinal tubules are sealed by silver precipitates and calcium fluoride which reduces the sensitivity.^[12]
- SDF is light-sensitive. Therefore, light might have a role in the caries arrest.^[13] When light curing after the SDF application, silver precipitation is increased, which results in improving the caries arresting effect.^[14] Also, caries arrest is higher in anterior teeth, because they are more exposed to light compared to posterior teeth and are easier to clean.^[15]

SDF is considered to be a material that is efficient, cost-effective, and non-invasive and may be applied for deciduous and permanent dentition.

Indications for treatment with SDF

- High caries risk (xerostomia or early childhood caries).
- Behavioral problems or medical conditions challenging the treatment.
- Patients with carious lesions that may not all be treated in one visit.
- Difficult-to-treat dental carious lesions.
- Patients with limited dental care access.^[16]
- Non-carious cervical lesions giving sensitivity.
- Root surface carious lesions (deciduous and permanent dentition).
- Molar incisor hypomineralization to reduce sensitivity.

Contraindications for treatment with SDF

- Irreversible pulpitis, or a dental abscess/fistula.
- Radiographic signs of pulpal involvement, or periradicular pathology.
- Not able or willing to brush and unlikely to. Patients (or parents) unable or unwilling to take responsibility.
- Patients with ulceration, mucositis, stomatitis.
- Patients with allergy to silver, fluoride and ammonia.^[17]

Disadvantages of SDF

A significant disadvantage of SDF use is the black staining of teeth, which has limited its use.^[18] Carious tissue changes its color to black after SDF application as a result of metallic silver formation. The discoloration appears in a 2-to-3-week period after the treatment. Exposure to light increases the brown-black appearance of carious lesions. Both parents and patients may have serious aesthetic concerns about the black stains.^[19]

SDF + KI

To manage discoloration, application of potassium iodide (KI) over the SDF is suggested. This leads to white precipitate formation of silver iodide and the spare silver ions are removed. The potassium iodide is applied until the solution turns clear, then is rinsed and dried.^[20] However, it has been observed recently that the improvement of the color after KI application was only temporary, because after some time, the discoloration of the treated teeth appears again. Also, when SDF and KI are used in combination, the concentration of free silver ions decreases, which can lead to limitation of the positive SDF effects.^[14] KI is also contraindicated to pregnant or breastfeeding females.^[20]

SDF + glutathione

Another alternative for decreasing the staining from SDF is applying glutathione after the SDF. Glutathione (GSH 20%) is a tri-peptide biomolecule that contains a thiol group which adsorbs onto metal surfaces. This makes the glutathione an ideal means to control the release of Ag⁺ by coating the silver particles and limiting their aggregation and therefore decreasing the color changes in teeth. Color changes in enamel lesions treated by SDF and glutathione are less than those observed in dentine lesions. This is probably because the formation of metallic silver is much less on the enamel than dentine. To minimize the discoloration in dentine lesions, it may be necessary to use higher percentage of GSH.^[14]

The antibacterial and remineralizing effects of 38% SDF and its role as caries-arresting tool are certain. However, the major concern leading to its limited use is the unaesthetic appearance after its application. Efforts were made to find a solution for this problem. Research in the field of nanotechnology demonstrated that if the size of the bulk silver is reduced, the surface area increases considerably. In this way, bioactive molecules can be attached to improve the antimicrobial effects and prevent black staining in teeth.^[21]

Nanotechnology

Nanotechnology is a relatively new multidisciplinary field that brings together researchers from various scientific fields, including biology, chemistry, material science, and physics, to create advanced functional nano-sized materials.^[22] The prefix 'nano' is derived from the old Latin word 'nanus,' which means 'dwarf,' implying that nanotechnology deals with exceedingly small objects with dimensions ranging from 10⁻⁹ to 10⁻⁷ m.^[23]

The American physicist and Nobel Prize laureate Richard Feynman is considered the father of nanotechnology. His idea about nano-sized materials was conceived in 1959 and since then it has been implicated in different fields, including medicine.^[24]

Some of the most popular objects of research in this field are the silver nanoparticles (AgNPs).^[25] They are known for their excellent electrical conductivity, chemical stability, strong antifungal and antimicrobial action.

These properties allow them to be used in many different fields such as medicine, textile industry, electronics, etc.^[22] Silver nanoparticles have been demonstrated to be potential antibacterial agents for dental decay prevention in children.^[26] Their virulence is 25 times greater than that of other agents such as chlorhexidine. Also, they have the ability to invade and disrupt biofilm matrix. Hence, they can be used for prophylaxis and treatment of some of the most common diseases such as early childhood caries (ECC) and rampant caries.^[19]

Methods of preparation of nanomaterials

There is an array of physical, chemical and biological methods that are available to synthesize nanomaterials.^[27] Physical methods prepare nanoparticles by evaporation - condensation using a tube furnace at atmospheric pressure. These methods are fast, they don't involve hazardous chemicals, and use radiation as reducing agents. However, they have high levels of energy consumption, solvent contamination, and absence of even distribution. When silver nanoparticles are prepared with chemical methods, water and organic solvents are used. Silver salts reduction has two stages - nucleation and subsequent growth. Generally, silver nanomaterials are synthesized using two methods - the top-down and bottom-up approaches. In the top-down method nanoparticles are ground mechanically from bulk metals and then stabilized using colloidal protective agents. The bottom-up methods involve chemical reduction, electrochemical techniques, and sono-decomposition. Compared to the physical methods, the chemical ones have high yield which is their biggest advantage. However, both methods are very expensive and some of the materials used in the process such as 2-mercaptoethanol, borohydride, and citrate thio-glycerol are considered toxic.

AgNPs can overcome the resistance of bacteria against antibiotics thanks to their crystallographic surface structure and large surface-to-volume ratios, which can make them alternative antimicrobial agents.^[28]

A number of mechanisms related to the AgNPs antimicrobial activity have been proposed, but the exact modes of action aren't fully understood.^[29] The antimicrobial action of AgNPs is linked with four well-defined mechanisms: (1) AgNPs interact directly with the cell membranes of bacteria and alter their permeability, causing cellular damage. The adhesion to the cellular wall is done by binding to biomolecules that contain sulfur, nitrogen, oxygen or phosphorus and this changes the membrane permeability and causes a leak of cellular contents; (2) when exposed to oxygen-rich environment, silver ions are released into the cytoplasm, which causes microbial death^[30] by reducing the intracellular levels of adenosine triphosphate (ATP), inhibition of mitochondrial activity, and denaturation of proteins^[31]; (3) the interaction between AgNPs and different cellular components leads to cellular toxicity through the oxidation of lipids, proteins, and nucleic acids - this affects the function of these biomolecules and ultimately disturbs the biochemical pathways; and (4) AgNPs dephosphorylate the tyrosine phosphorylated proteins which are in charge of DNA replication and recombination in Gram-negative bacteria.^[32] Eventually, the combined effects of the silver nanoparticles cause release of cellular components, cell lysis, and death (Fig. 1).

The development of nanoscience resulted in the start of its use in the field of dentistry and the creation of nano silver fluoride (NSF) as a new agent for caries arrest. Targino et al.^[19] first made NSF as a colloidal solution - silver nitrate was chemically reduced using chitosan as a carrier and fluoride as a stabilizer. The solution contained silver nanoparticles (376.5 µg/ml), chitosan (28,585 µg/ml), and sodium fluoride (5,028.3 µg/ml). Haghgoo et al.^[33] mixed nano silver and sodium fluoride creating varnish. These types of NSF are the most studied ones. They have been demonstrated to be safe and have significant antimicrobial efficacy against the primary caries causing bacteria - *Mutans streptococci* and *Lactobacilli*.^[34]

The NSF treatment is a non-invasive option for caries management. It can be applied for caries lesions affecting

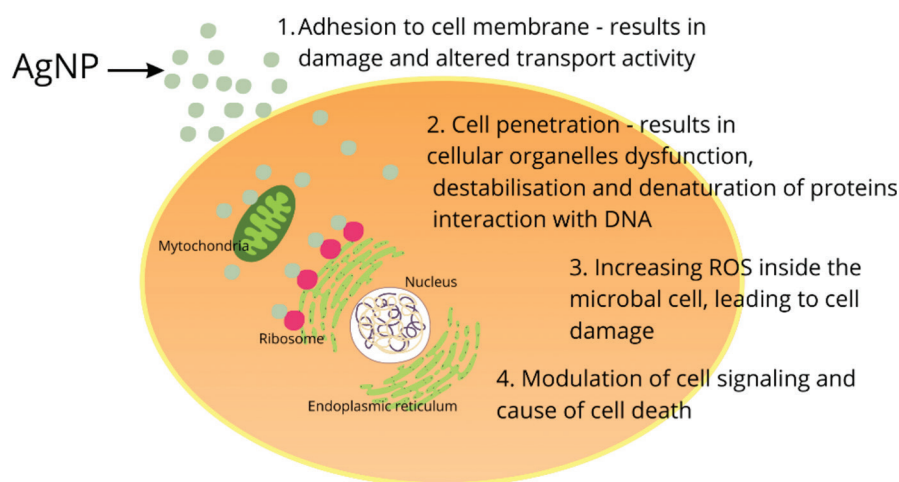


Figure 1. Schematic representation of the AgNPs antimicrobial action.

enamel and dentine with a simple technique without any risk. It is considered as effective as silver diamine fluoride for caries prevention and caries arrest, but it doesn't stain the teeth. Compared to conventional caries treatment it can be less expensive and not so time-consuming, making it economic and ergonomic. Hence, most communities can afford such treatment.^[35]

Cytotoxicity of chitosan

Chitosan [poly (1,4- β -d-glucopyranosamine)] is a natural polysaccharide that is prepared by N-deacetylation of chitin. It has a great potential as a biomaterial for the creation of nanosized drug carriers and gene transfer vectors. Some of its advantages are good stability and simple preparation protocol.^[36] Furthermore, chitosan nanoparticles ease the delivery of the drug across cellular barriers by temporarily opening the tight junctions between the epithelial cells.^[37] This means that chitosan nanoparticles may enter the systemic circulation through the gastrointestinal tract, nasal cavity, or alveolar sacs and cause toxicity to the human body.^[38] Moreover, it has been found that human cells could internalize chitosan nanoparticles, which reduces their viability and proliferation and damages the integrity of their cell membranes. In addition, chitosan nanoparticles show different levels of cytotoxicity depending on the main material used for the nanoparticles synthesis and the kind of the interacting cells.^[39]

Green synthesized nanoparticles

The conventional methods that produce NPs are expensive, toxic, and not eco-friendly. To eliminate these problems, researchers found out natural sources and products that could be used for the NPs synthesis.^[40] Green synthesized AgNPs have many advantages over the chemically produced AgNPs such as simple, rapid, eco-friendly, cost-effective production and biocompatibility, therefore, they may be used as a reliable alternative to them.^[21] The synthesis is accomplished using diversity of sources like different bacteria, fungi, algae, and plants, resulting in large-scale production with less contamination.^[41]

Green synthesis using plant extracts

Of all green sources for the production of silver nanoparticles, the most frequently used ones are plants, because plant phytochemicals show greater reduction and stabilization.^[42]

The preparation process includes collection of different plant parts from various sources, followed by washing them from debris and other unwanted materials using first ordinary water and then distilled water. Then, an extract is prepared by putting dried parts of the plant in deionized water or alcohol for a couple of hours at a temperature lower than 60°C. The plant extract is combined with solutions with different concentration of Ag salt as metal precursor, followed by heating, which leads to AgNPs synthesis. The

plant extract acts as a reducing and stabilizing agent and the use of chemical stabilizers is avoided.^[43]

Tea is one of the most commonly consumed beverages worldwide. It is the second most popular beverage in the world and is consumed for its flavor and stimulant effect. Tea made from the leaves of 'Camellia sinensis' (Green tea), is one of the most favored beverages worldwide.^[44] Green tea is mainly composed of epigallocatechin, epigallocatechin-3-gallate (EGCG), epicatechin and epicatechin-3-gallate, which act as reducing and capping agents.^[45] Green tea polyphenols have demonstrated significant antioxidant, anticarcinogenic, anti-inflammatory, thermogenic, probiotic, and antimicrobial properties in numerous human, animal, and in vitro studies.^[46] The use of a green tea extract has recently become quite popular due to its favorable protocol, which is a fast, simple, eco-friendly, safe, and economically feasible green technique. Thus, green synthesized NSF using green tea extract can be considered as an option to treat carious deciduous teeth in underprivileged communities.^[47]

CONCLUSION

Silver compounds have been used in dentistry for over a century. Although SDF is not new to the dental market, it has recently made a comeback in the research field due to its positive effect on caries arrest, combined with its simple application. However, the incorporation of this product into dental practice is still limited due to its low accessibility, a lack of specific protocols for use provided by Pediatric Dentistry Associations, limited training in most universities, and the black staining effect that limits patients' and parents' acceptance of treatment. To explore the wider usage of silver compounds, an effort to mask the discoloration should be made. In this context, silver nanoparticles should be further investigated as a new opportunity for caries arrest.

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Competing Interests

The authors have declared that no competing interests exist.

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Соединения серебра, используемые в детской стоматологии для остановки кариеса: обзор современных материалов и новых технологий

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Резюме

Соединения серебра веками использовались в медицине и стоматологии. Их использование в детской стоматологии долгое время было ограничено из-за некоторых недостатков, главным из которых является изменение цвета зубов с образованием чёрных пятен. Однако недавние достижения в области технологий привели к разработке новых серебряных агентов, которые не имеют ограничений, присущих ранее использовавшимся. Это привело к повторному внедрению соединений серебра в детскую стоматологию. Целью настоящего обзора было изучение доказательств, подтверждающих терапевтическое использование соединений серебра в детской стоматологии для остановки кариеса, а также механизма действия и биосовместимости, характеристик, преимуществ и недостатков различных серебросодержащих препаратов.

Ключевые слова

фторид наносеребра, нанотехнологии, консервативное лечение, диаминфторид серебра