Pediatric Dental Medicine

A New Look at Silver Compounds-Based Medications Used in the Caries Management

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Нов поглед към препаратите на основата на сребърни съединения при управление на кариеса

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Summary

Caries is the most common chronic disease in the world. As knowledge of its etiology progresses, therapy is aimed at preventing the appearance of carious lesions and a minimally invasive approach in the treatment of emerging lesions.

Silver has been used in medicine and dental medicine since ancient times, due to its proven antibacterial properties. In dental medicine silver is used as part of various chemical compounds – silver nitrate ($AgNO_3$), SDF (silver diamine fluoride), silver fluoride (AgF) and others.

Indications for the use of silver compounds are: carious lesions, disinfection of root canals in endodontic treatment, treatment of ulcers in the oral cavity, pain relief in aphthous stomatitis.

Silver and fluorine are used in dentistry for centuries. In order to ensure their interaction, a combined preparation is created – silver diamine fluoride. The action of silver compounds on carious lesions is associated with the stationing of the lesion in the dentin by affecting the microorganisms. In combination with fluorine, remineralization of demineralized tissues is also observed. Silver-based medications are mainly used for primary teeth and treatment of young children with early childhood caries (ECC).

Key words: *silver nitrate, silver diamine fluoride, antibacterial properties, dentin carious lesions, primary dentition*

Резюме

Кариесът е най-разпространеното хронично заболяване в света. С напредване на знанията за етиологията му, терапията се насочва към превенция на появата на кариозните лезии и минимално инвазивен подход в лечението на появили се лезии.

Среброто се използва от векове в медицината и денталната медицина. То е известно с антибактериалните си свойства. В денталната медицина среброто се използва под формата на различни съединения – сребърен нитрат, сребърен диамин флуорид, сребърен флуорид.

Показания за употребата на сребърните съединения са: кариозни лезии, дезинфекция на коренови канали при ендодонтско лечение, лечение на улцери в устната кухина, повлияване на болката при афтозен стоматит.

Доказаните ползи на среброто и флуора водят до създаването на комбиниран препарат сребърен диамин флуорид (SDF), който осигурява комплексното им действие. Ефектът на сребърния диамин флуорид е свързан със стациониране на кариозната лезия в дентина, намалява чувствителността на зъбите, намалява необходимостта от обша и местна анестезия при дентално лечение, намалява страха при деца от предстояща стоматологична манипулация. Препаратите на сребърна основа се използват предимно при временни зъби и лечение на малки деца с кариес на ранното детство (КРД).

Ключови думи: *сребърен нитрат, сребърен диамин флуорид, антибактериални свойства, дентинови кариозни лезии, временно съзъбие*

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Worldwide, dental caries continues to be the most common chronic disease in childhood [1, 2, 3]. Despite the application of various preventive measures, in the last years there is an increase in the frequency of early childhood caries [4, 5, 6]. Left without treatment, the early childhood caries affects the quality of life of the child and its family, it affects the physical, mental and emotional development [7]. The disease is defined as an important predictor of caries development later in permanent dentition [8, 9, 1].

Recent researches in cariesology prove that the development of caries can be prevented, and in cases of already manifested caries lesion, its progression can be stopped [11]. With regard to caries prevention, it has been found that when a cariogenic biofilm is present or the protective properties of saliva are limited, natural remineralization as well as that aided by the use of fluoride-containing products is insufficient to prevent or limit the carious process [12]. This outlines the need to find opportunities for favorable modification of the dental biofilm and improvement of the remineralization process in order to prevent and limit carious disease [13]. These options include more effective, available (including financially) and reliable treatment approaches that are easy to apply (under standard conditions), do not require special equipment and are accessible to the most vulnerable groups of the population [14].

Modern strategies for caries management and its consequences are realized through the use of cariostatic agents to stop the progression of the disease, as part of the treatment, instead of applying the old and limited to surgical treatment approach focused on preparation and obturation of the carious lesion [15]. Agents with a high cariostatic effect in the dentin are those based on solutions of silver compounds, especially those that were developed later and contain fluorides in their composition [16].

Silver has been used in medicine and dental medicine since ancient times, due to its proven antibacterial, dehydrating and sclerosing properties. Silver nitrate is one of the most widespread silver salts. Its antibacterial action is based on the extracellular and intracellular binding properties of the silver. Positive silver ions can electrostatically bind to the bacterial membrane and cell wall, which contain negatively charged peptidoglycans [17]. Silver can be included in the transport systems of microorganisms and as a result, silver ions can bind to various cellular structures – proteins, bacterial DNA, etc. By binding to DNA, it blocks its replication and stops cell division of the microorganisms. By binding to sulfhydryl groups of various enzymes, silver ions inactivate them, which inhibits bacterial metabolism [18].

The silver nitrate solution is colorless and odorless. Before the discovery of penicillin and other antibiotics it has been used in medicine in the treatment of wounds, in the treatment of sexually transmitted diseases, even in the form of eye drops in newborns, in order to prevent gonorrhea infection from the mother during birth [18].

In dental medicine silver is used as part of various chemical compounds – silver nitrate (AgNO3), SDF (silver diamine fluoride), silver fluoride (AgF) and others. In the form of sticks, silver has been used in the treatment of ulcers in the oral cavity, to reduce the pain of aphthous stomatitis [19]. Ammoniacal silver nitrate (Howe's solution) has been used for disinfection of root canals [20], for disinfection of infected dentin, in the treatment of deep carious lesions and indirect pulp capping, as the solution can penetrate the affected dentin and fill the demineralized dentin with silver particles [21].

The use of silver nitrate solution in the treatment of dentin carious lesions begins in the early 20th century. The idea for this was based on the infectious nature of the carious disease, relying on the disinfecting properties of the compound. In the period 1940-1970 there were scientific studies that examined the effectiveness of the solution to prevent the development of carious lesions on smooth and occlusal surfaces. Their results show that there is no significant reduction in the frequency of caries in cases where it was used, compared to those in

which it was not [22, 23]. Other studies are focused on the effect of silver nitrate solution on stationing the carious lesions. The results show that the effect is visible in both primary and permanent teeth [18].

Studies have evaluated the penetration characteristics of silver nitrate, indicating that it penetrates not only infected but also healthy dentin. Variations in the level of penetration have been found in different groups of teeth, as well as between different areas of the same tooth. Penetration has been shown to be equal in teeth with healthy, infected and missing pulp [24]. According to some authors, three zones of silver nitrate penetration are observed [25, 26]. They are divided into: outer zone of strong penetration, intermediate zone of lower penetration and inner zone of strong penetration [25] or superficial zone (up to 1 mm) of black coloring, intermediate zone of brown colored destructured material and deep zone with rough silver particles (the deeper localized, the larger) [24]. When applying silver nitrate (ammonia or ordinary) and followed by application of eugenol, 4 zones were identified:

1. A very thin, superficial layer of free silver precipitated on the dentin surface by eugenol.

2. A layer of dark brown carious dentin. The layer of carious dentin turns dark brown from silver nitrate.

3. Silver free zone. Between the carious dentin and the black precipitate of silver, deep in the dentinal tubules, an uncolored area is found, almost free of silver particles.

4. Area of black, precipitated silver particles [26].

Despite the known caustic action of silver nitrate, most studies show small or no damage to the pulp when applied to healthy or carious dentin, even in moderately deep carious lesions [26]. Examination of extracted human teeth revealed the following histological changes in the pulp.

Inflammatory changes in the underlying pulp were found when applying ammonia solution of silver nitrate on deep carious lesions. Histological observation shows that after its application many of the degenerate odontoblasts contain silver particles. In areas where the accumulation of silver particles is high, hemorrhages and swelling may be found in the pulp. Similar changes are absent in carious teeth that have not been treated with an ammonia solution of silver nitrate. The changes in the pulp are only superficial and are not observed in depth. There is no history of pain in patients with indirect pulp capping with this solution. [25, 26].

The effect of the combination of ammonia solution of silver nitrate (Howe's solution) with following application of eugenol for 5 min on exposed dental pulp, due to deep carious process, was studied [24, 26]. The following changes are observed in the area of pulp disclosure:

1. Large, superficial hemorrhage just below the disclosure. The surface of the coagulum contains a high percentage of silver globules, similar to those in the dentinal tubules. No precipitated silver is found in the deeper areas of the coagulum.

2. A wide strip of inflamed pulp just below the coagulum. This zone of inflammation is also observed in untreated exposed pulps, covered with zinc oxide and eugenol for an equivalent period of time. However, it is wider in teeth treated with silver nitrate.

3. The pulp near the inflamed is normal [26].

According to modern perception for the carious disease and the minimally invasive approach in dentistry, the goal of the treatment of carious lesions is to remineralize demineralized dental structures, not their radical removal. Combined with fluorine agents are widely used for stimulating the remineralization process in the enamel and the most widespread used fluoride compound is sodium fluoride [27]. Sodium fluoride in the form of a varnish contains 2, 26% (22 600 ppm) fluoride and is effective in preventing caries. It is used for this purpose for decades. ADA recommends applications of fluorine varnish in patients at high risk of developing caries at intervals of 3-6 months [28].

Based on the strong antibacterial action of silver and the proven high remineralizing properties of sodium fluoride, in 1969 their combined use in the form of silver diamine fluoride was introduced

for the treatment of carious lesions affecting the dentin [30].

Silver diamine fluoride (SDF) is a colorless solution for topical use containing fluorine ions. Its pH is alkaline (values 8-9). The solution contains ammonia and silver fluoride. Ammonium ions combine with silver to form a complex ion called a diamine-silver ion, $[Ag(NH_3)_2]+$. This complex ion is very stable and the reaction of its formation is reversible [31, 32]. SDF (Ag (NH3)2 F) reacts with calcium hydroxyapatite ($Ca_{10}(PO4)_6(OH)_2$), releasing CaF_2 and Ag_3PO_4, which are responsible for the prophylactic effect and the stationing of the carious lesions. The reaction proceeds as follows: $Ca_{10}(PO4)_6(OH)_2 + Ag(NH_3)2F -> CaF_2 + Ag_3PO_4 + NH_3(H_2O)$. The resulting calcium fluoride is a reservoir for fluoride ions, which are involved in the formation of calcium fluorapatite which is more resistant to acid attacks then the hydroxyapatite [32, 33].

There are several advantages of using SDF in the treatment of carious lesions. It kills cariogenic microorganisms, precipitates in the carious dentin and causes an immediate stop in the development of the carious lesion. Silver nitrate and calcium precipitates seal the dentinal tubules [34]. Its use does not require anesthesia, removal of the carious dentin or other actions causing discomfort and fear in young patients [32].

Its use is indicated in very young children when conventional methods of treating carious lesions are inapplicable. In children with early childhood caries, SDF can be used to slow or stop the progression of lesions. Its use can be a cost-effective way for the treatment of disadvantaged children or in areas where there is a great lack of dentists [29]. The use of silver diamine fluoride as a therapeutic agent was put in for the first time in Japan. Currently, treatment of carious lesions with SDF is applied in a number of countries – China, Australia, Mexico, Brazil, Spain, USA and others [32, 34].

SDF is used in the treatment of dentin hypersensitivity and in teeth with molar incisor hypomineralization (MIH) [35]. It presents with various degrees of pain on exposed dentinal surfaces. The pain can be provoked by chemical, thermal, osmotic and other stimuli. The treatment protocols are similar to those in the use of SDF for the treatment of carious lesions [33, 34].

SDF is also used in the treatment of root canals. The elimination of microorganisms in them during endodontic treatment is essential for its success. In a study, various antibacterial agents were used to disinfect root canals, but high resistance to Entercoccus faecalis has been reported. A laboratory study showed that 3.8% SDF (38% solution diluted 1:10) showed a 100% reduction of E. faecalis after 60 minutes exposure. Saforide 3.8% is a commercial product containing SDF. The manufacturer's recommendation is three applications within 24 hours [33].

The use of SDF requires some considerations. The treated dentin changes color to dark brown or black. This proves the effectiveness of the agent and determines the stationing of the lesion. If SDF touches the skin, the skin changes its color. The coloring is reversible with a duration of 2-3 weeks. To reduce the change in the color of the tooth surface, iodine solution is applied after application. Reapplication may be required for stationing the lesion [33].

A way for managing the problem of tooth discoloration caused by SDF is to use it together with potassium iodide (KI), which reacts with the free silver ions to form a creamy-white silver iodide. An in vitro study showed that the application of SDF/KI didn't lead to significant differences in the level of bacterial inhibition compared to cases where only SDF was used. Another way to prevent black coloration is to replace the silver from AgF with silicon ion, using ammonium hexafluorosilicate, $(NH4)_2SiF_6$, or SiF_6 for short, but the acid resistance of the SiF-treated teeth is less than that of treated with SDF [32]. Up to now there are no clinical trials for either SDF/KI or SiF published in English. More research is needed to substantiate the promising results of these in vitro studies before they become widely available in clinical practice [32].

The use of SDF in combination with the atraumatic technique (ART) is sometimes known as sil-

ver modified ART (SMART) recovery or with the Hall technique as SMART Hall [34]. The application is done either immediately before the placement of the obturation or the crown using Hall's technique, for primary molars (after selective removal of irreversibly damaged tissue) [34].

Treatment protocol:

1) Protective equipment is worn by the clinician. Protective equipment for the patient is used – bib, glasses.

2) One drop of SDF is placed in a deep plastic container (in a different plastic container with a deep bottom is placed a saturated solution of potassium iodide);

3) The tooth surfaces should be dried;

4) Isolation of the tongue and cheeks with gauze or cotton rolls;

5) If the affected surface is close to the gingiva, Vaseline or a gingival barrier should be placed to protect it;

6) Dry the affected surface with air or a cotton pellet;

7) An applicator which is irrigated with SDF is used, and the excess is removed in the walls of the container;

8) Apply directly on the affected surface using the applicator;

9) Leave for 1 minute on the tooth surface, if necessary, remove the excess with a cotton pellet or gauze sponge. Another applicator is used to apply a saturated solution of potassium iodide. The procedure is repeated 1-3 times until the disappearance of white precipitates. It takes 5-10 seconds between applications.

10) Rinse with water.

11) Remove the isolation [33].

Sometimes reapplication is needed after 6-12 months [33].

Indications for the application of SDF:

1) Patients at high risk of caries/patients with early childhood caries;

2) Non-cooperative patients, whose behavior is not affected by the respective techniques;

3) Patients with carious lesions that require multiple visits to the dental office;

4) Patients without access to dental care [32, 33].

5) Deep asymptomatic dentinal lesions;

6) Irrecoverable dentinal lesions;

7) Lesions, the treatment of which cannot be completed in one visit;

8) Carious lesions of the root (in primary and permanent teeth);

9) Cervical non-carious lesion causing hypersensitivity;

10) Molar incisor hypomineralization causing hypersensitivity [32].

Contraindications for the application of SDF:

1) Patients with poor oral hygiene;

2) The use of potassium iodide is contraindicated in pregnant, lactating women, patients with diseases of the thyroid gland, patients with allergies;

3) Patients with ulcerations, mucositis, stomatitis;

4) Patients with allergies to silver, fluorine, ammonia;

5) Presence of symptoms of irreversible pulpitis;

6) Abscess with dental origin;

7) Presence of fistula;

8) X-ray finding for affected pulp or periodontium of the tooth [32].

The main disadvantage is related to the black staining, which remains permanently on the tooth surfaces after treatment with silver agents. Studies show that parents perceive it better when it is in the area of the distal teeth, but in many cases, they prefer the unaesthetic vision even of the front teeth to an alternative of treatment under general anesthesia [18]. Healthy dental structures do not change their color. At a later age and achieving cooperative behavior in the child, the color of the tooth can be restored by making a filling or placing a crown [24]. Studies have shown that silver nitrate does not change the bond strength between the dentin and the composite material using an appropriate adhesive system [34]. The results obtained in the analysis of the relationship between hard dental tissues and GIC after its application are contradictory [34, 35, 36].

The work with medications, containing silver nitrate, should be careful. Once on the skin, it causes a temporary black coloration, which disappears after about 2 weeks, as the silver does not penetrate in the dermis. However, contact with the eyes may cause blindness due to corneal burns. Therefore, the use of goggles is recommended by both the doctor and the patient during the procedure [18].

The cases of allergies from silver are rare. The toxicity of silver nitrate depends on its dose. Ingestion of 2 or more grams of silver nitrate causes death. Silver easily binds to chlorine ions in the body, forming insoluble salts, which lead to electrolyte imbalance in the body. The doses used to treat carious lesions are significantly lower. One milliliter of 25% silver nitrate solution contains 0.25 g of silver nitrate and is equal to 20 drops of the solution. One drop of the solution contains 13 mg of silver nitrate and is equivalent to 0.33% of the lethal dose. One drop of solution can be used for approximately 20 applications on tooth surfaces using a micro-brush [18, 24].

In case of accidental ingestion of a large amount of SDF, it is necessary to seek medical help. Vomiting may be induced to avoid absorption by the body; when 10% calcium gluconate solution (10 ml) is administered, calcium ions will react with fluorine ions to form insoluble calcium fluoride (CaF2), which cannot be absorbed in the gastrointestinal tract [32].

Over the years, there were conducted various studies to evaluate the effect on the progression of carious lesions, both in the use of silver nitrate solutions, followed by the use of fluoride preparations [33, 37] and in the use of combined agents (containing silver and fluorine components) [29, 33, 37].

The results of a larger study with more than 5,000 participants in the United States recommended the use of 25% silver nitrate solution, followed by the application of 5% sodium fluoride varnish as a method for non-invasive treatment of carious lesions in children. As a result of applying the method, the authors found the stationing of almost all carious lesions, their radiographic examination showed the formation of a compacted visible layer (protective barrier), which suggests the formation of tertiary dentin. Follow-up of carious lesions in 106 of these children over a period of 4 years showed that 98% of carious lesions remained stationed [31].

A comparative study of results obtained in the treatment of carious lesions with a solution of silver nitrate and following application of fluoride varnish, and treatment with silver diamine fluoride (SDF). After 1 year, are found insignificant differences between the results of the two treatment protocols. A mutual disadvantage in both studied groups is the black coloration of the teeth, but no other negative effects have been established [31].

In Western Australia in the second half of the 20th century for the treatment of caries of primary teeth is introduced the usage of AgF. The procedure for its application is two-phase - it requires reduction of silver fluoride with tin fluoride (SnF2). Although AgF is much more soluble in water than other silver compounds with halogen elements (1820 g/L at 15 C), it forms colorless cubic crystals. The AgF solution is strongly alkaline – pH 11. Its stability is lower compared to SDF [32].

Nowadays, silver fluoride is less widely used in dentistry than SDF, which is widely produced as a 38% solution by various brands [30]. The commercial products FAgamin -Tedequim, Advantage Arrest SDF 38%, Saforide 38%, Riva Star, Dengen Caries Arrest, e-SDF 38% Silver Diamine Fluoride, SDF Pro and others are available on the market.

Silver-based agents, although associated with some disadvantages, mainly aesthetic, are defined as sufficiently reliable and effective alternative means of managing carious lesions in primary dentition, especially in very young and non-cooperative children.

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