Silver Diamine Fluoride (SDF) 38% has been receiving a great deal of attention by U.S. dental professionals since it was cleared for use by the Food and Drug Administration in August 2014 under the provisions of the Federal Food, Drug and Cosmetics Act. The Cleared Indication For Use is, “Treatment of dentinal hypersensitivity. For use in adults over the age of 21.” In addition, in October of 2016 the U.S. Food and Drug Administration (FDA) granted “Breakthrough Therapy Designation” to Advantage Arrest™ Silver Diamine Fluoride 38% for the arrest of tooth decay in children and adults.

In the age of the internet, access to credible information about the history, safety and efficacy of SDF is important. In addition, a significant number of national and local television news programs and social media postings have communicated information about the use of SDF for the treatment of carious lesions in all populations.

SDF has been used by dental professionals outside the U.S. for both the treatment of dentinal hypersensitivity and as a caries therapy for more than 50 years. This review is intended to provide U.S oral health professionals with an understanding of the history of SDF around the world, including the most current information regarding use in the U.S.

Under federal law, the use of a drug or medical device by a licensed medical professional for an indication not Approved or Cleared by the FDA is allowable and not uncommon. This is termed “off-label” use.

As the organization permitted to market the only FDA Cleared SDF product in the United States, (Advantage Arrest™ Silver Diamine Fluoride 38%,) it is our intention to provide a review of all scientific literature available to us in order to help insure that oral health professionals, and through them their patients, are well informed about this therapy.

This document is not assumed to contain all published information regarding SDF, as that would be virtually impossible, since SDF has been in use in many countries for decades. It is however meant to provide a fair and balanced view of the benefits and risks of the use of SDF. If, after reading this document you have any questions please send an email to the address below and we will get back to you promptly.

Please address any questions to:

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Frequently Asked Questions

Since the launch of Advantage Arrest Silver Diamine Fluoride 38% in April, 2015 we have fielded questions from oral health professionals on a range of subjects including Clinical Application, Safety, Precautions, Restorative Aspects, Insurance Coding and Reimbursement.

Clinical Application

1. Since the FDA cleared Advantage Arrest Silver Diamine Fluoride 38% (SDF) for the treatment of hypersensitivity, with fluoride varnish as the comparative device, is this clinical application the same as fluoride varnish?

For the site-specific control of hypersensitivity, the technique to apply Advantage Arrest is similar to that of fluoride varnish. SDF is not for generalized or full mouth applications. Read the package insert for full application and precaution instructions.

2. I currently use fluoride varnish off-label as an in-office fluoride treatment for caries prevention or to attempt caries arrest. Can I use Advantage Arrest in this same way?

Yes. However, Advantage Arrest is only applied site-specifically on carious lesions or high-risk sites such as non-sealed occlusal surfaces or interproximal areas where incipient lesions are suspected. Care should be taken to isolate each cleaned application site with cotton rolls. The high pH, metallic taste and propensity to temporarily stain soft tissue/skin and permanently stain demineralization make the application of silver diamine fluoride different than the generalized full-mouth application associated with fluoride varnishes.

Many clinicians apply SDF site specifically and then apply a fluoride varnish generally. In some cases, this can help keep SDF in contact with the treatment site in patients that cannot sit for the recommended 1 minute soaking period.

The chemical action of the SDF occurs almost immediately in the outer layers of the softened enamel and/or dentin and can be confirmed by changes in the hardness and density of the treated surface, similar to caries that arrests naturally because of positive changes in oral hygiene, diet, or daily application of fluoride in custom trays. The darkening of the lesion occurs over 24 hours and may increase over a week. Reexamination of the lesion and reapplication of SDF may be warranted to ensure caries arrest. Reapply SDF at regular recalls until the tooth is restored or exfoliates.

3. Does Advantage Arrest prevent caries only at the point of application and adjacent sites?

No. When applied to a carious lesion or at-risk site, Advantage Arrest has demonstrated the ability in studies summarized in this packet to act as a reservoir for silver and fluoride. The silver is bactericidal against cariogenic biofilm not only at the site, but has a halo effect as saliva flows throughout the oral cavity. The same is true for the fluoride, helping to promote remineralization and prevent demineralization on all dentition.
4. **Is there a recommended frequency of application of SDF for caries control?**

Caries arrest studies were conducted with SDF applications of once and twice annually, with twice annual applications demonstrating the best benefit. Arrested lesions were retreated every 6 months. Clinicians have reported that they will recall their first cohort of SDF patients within 3-6 weeks to evaluate the application and action of the treatment. Once they have a feel for the predictability of the material with their application technique, they will set recall appointments based on the risk level and caries activity of the patient with higher risk patients at 3 month intervals. Moderate to high-risk patients, where it appears that home care and diet counseling has had positive impact, are recalled at 6 months.

5. **Does the application of SDF to a lesion cause discoloration?**

Darkening of decayed and demineralized sites occurs as the lesion arrests. Non-lesioned tooth structure does not stain with the application of silver diamine fluoride. This process is similar to what is seen when caries arrests due to changes in diet or increased use of other fluorides. A recent study showed that patients see the discoloration as a clear indication that the treatment is working. Similar to the treatment of eroded and hypersensitive dentin, the treated area can be restored using glass ionomer or with a sandwich restoration of both glass ionomer and composite.

Silver diamine fluoride 38% should not be diluted in an attempt to reduce discoloration. Studies have shown that diluted solutions may not be effective for caries arrest. Ionic silver adsorbs onto almost any protein surface and is especially tenaciously bound to denatured proteins. This accounts for the specificity to carious collagen over normal collagen, but both will stain. The differentiator between these stains is that with SDF use intrinsic pigmentation of a carious lesion occurs and surface protein staining occurs primarily on healthy tissue. These oxides are bound to the tissue and don’t wash or polish away. This is why the blackened lesion retains its dark color, and is most likely the reason the antimicrobial effect is long-lasting.

The functional indicator of effectiveness is when the silver oxide is bound to the diseased collagen. If the surface doesn’t turn grey/black, the silver didn’t bind and the antimicrobial effect will only be short-lived.

6. **Are there any studies, reports or articles on parent/patient reaction to lesion staining caused by application of SDF?**

Yes, through August of 2017 there have been two published studies/surveys and one poster presented on this topic, with all three showing similar results.

*Parental Perceptions and Acceptance of Silver Diamine Fluoride Staining, YO Crystal, MN Janal, DS Hamilton and R Niederman, J Am Dent Assoc., Jul 2017*

The aim of the study was to assess parental perception of SDF staining and to determine whether parents’ level of acceptability of SDF would change with the location in the mouth, the child’s behavior and demographic factors. A diverse group of 120 parents (98 mothers and 22 fathers) were surveyed. 67.5% of those surveyed judged SDF staining to be esthetically tolerable on posterior
teeth, with only 27.9% making this same assessment if the stain was located in the anterior region. In the absence of behavioral barriers to conventional restorative treatments 53.6% of parents were likely to choose SDF on posterior teeth, while only 26.9% would choose SDF for anterior areas. The level of acceptance increased as children’s behavioral barriers increased. At the extreme, when provided the option of general anesthesia, acceptance of SDF application increased to 68.5% in the posterior and to 60.3% on anterior teeth. Socioeconomic status did impact acceptance of treatment.

Four major findings were presented:

• Acceptance of SDF staining was greater in posterior than the anterior teeth
• Acceptance levels increased as the child required more advanced methods of behavior guidance
• The effects of location and cooperation changed with socioeconomic status
• Only approximately one-third of parents found SDF to be unacceptable under any circumstances

Discussion emphasized the need for parental/patient informed consent forms for the application of SDF.

Effect and Acceptance of Silver Diamine Fluoride Treatment on Dental Caries in Primary Teeth, J Clemens, J Gold, J Chaffin, J Pub Hlth Dent, July 2017

This study enrolled 32 pre-cooperative children aged 2-5 years with 118 active caries lesions in primary teeth. Teeth were treated with SDF and children were recalled at two weeks (assess color, hardness, pain and a parent survey was conducted on ease, taste, discoloration and painlessness) and at 3 months (assess color, hardness and pain). Survey results showed:

• 90.0% strongly agreed or agreed with the statement “SDF application is an easy process.”
• 86.6% strongly agreed or agreed with the statement “I am comfortable with discoloration of cavities after SDF.”
• 93.3% strongly agreed or agreed with the statement “SDF application was pain free.”
• 86.6% strongly agreed or agreed with the statement “The taste of SDF was acceptable.”

Parental Acceptance of Silver Diamine Fluoride, J Tesoriero, A Lee, Albert Einstein College of Medicine/Montefiore Medical Center, AAPD 2017 Scientific Poster Sessions, Washington DC, May 2017

This pediatric residency pair attempted to determine if parents will accept the use of SDF as a cariostatic agent to treat their child’s dental caries.

33 questionnaires were completed on one of two clinical options on primary molars, A. composite restoration treatment and B. SDSF treatment. 73% of parents preferred the SDF treatment.

7. Will Advantage Arrest stain composites or crowns?

Surface layer staining is possible if silver diamine fluoride flows past the area of contact onto restorations. The stain can be prevented with careful application...
and by wiping adjacent restorations following application to lesions or high-risk sites. If staining of restorations occur they can be removed with **standard pumice or** office cleaning devices.

Be aware that existing restorations can present with marginal leakage and associated demineralization. If silver diamine fluoride reaches these compromised margins, it is possible for caries arrest and discoloration to occur.

**8. Can I cover a treated and discolored site or excavate on recall appointments?**

Yes, if Advantage Arrest is used during a diagnostic appointment to arrest active disease, during the restorative visit the treated site can be evaluated for caries arrest providing you and the patient several options. You could choose to 1) reapply SDF, 2) simply leave the site as is, 3) cover the site without anesthetic or excavation or finally 4) excavate the site and place a restoration.

**9. How can I apply Advantage Arrest to interproximal sites where I suspect carious or incipient lesions?**

Practitioners have shared success treating interproximal lesions using tufted or sponged floss soaked with silver diamine fluoride, then pulled into the contact point and left for 60 seconds.

**10. If a tooth surface does not stain from the application of Advantage Arrest is there no preventative effect of the application?**

Studies have shown that there is a protective effect to the site of the application of silver diamine fluoride and a halo effect for the entire mouth.

**11. Are there any post appointment instructions for the patient or the caregivers/guardians?**

There are no postoperative limitations. Patients may eat or drink immediately. Patients may brush their teeth with fluoridated toothpaste on their regular schedule.

**12. What does an arrested lesion treated with SDF look like on radiographs?**

Arrested lesions look like a lesion (scar) on radiographs. You will observe only slight increases in radio-opacity as the mineralization of the previously softened dentin increases. Ultimately the best test of arrest is still the color change and tactile hardness of the dentin surface.

It is advised that you educate your referring dentist about your use of Advantage Arrest since the appearance of a treated lesion might be new and confusing for many practitioners.

**13. Can SDF be used as a cavity liner?**

SDF is cleared in the same FDA category as cavity liners. Although there are no head to head clinical trials comparing SDF as a cavity liner, it has been used successfully in this way.

SDF will not discolor intact enamel or dentin. SDF can discolor demineralized tooth structure brown/black. Some of this discoloration may shadow a restoration and can create less than optimal esthetic restorations.
14. How far into enamel and dentin does SDF penetrate?

Silver and fluoride penetrate about 25 microns into healthy enamel and 200-300 microns into healthy dentin without discoloration. The fluoride creates calcium fluoride and fluorapatite while silver binds with phosphates and protein structures in the tooth. Clinical experience is showing that SDF will initially penetrate and arrest about 2 millimeters of carious tooth structure and seal off deeper active caries from needed nutrients. These deeper portions can arrest by natural means in time and additional SDF applications may speed this process.

15. Who is allowed to apply SDF in clinical practice in my state?

Each State dental practice act is different. Since SDF is a fluoride-containing product indicated for the control of dentinal hypersensitivity, it should fit into the same rules as fluoride varnishes. Please confirm that within your own state's dental practice acts.

16. How do SDF treated sites appear on various systems sold for the detection and/or visualization of caries?

We know of no research from any current detection devices on the impact of SDF treated sites on device detection abilities/anomalies. If you have one of these devices, we encourage you to ask them what you can expect from the use of SDF in your practice.

Our Experience in this field leads us to the following thoughts;
CariVu® is a trans-illumination device. It shines light through the tooth and looks for shadows (which can be active/inactive decay, cracks or anything that blocks light). We would anticipate the Carivu would see SDF treated sites similar to images of decay.

DiagnoDent® detects porphyrins (byproducts from bacteria) trapped in the tooth. DiagnoDent does not see the tooth itself. We would anticipate Diagno-Dent to show lower readings as SDF lowers bacteria levels within lesions.

Spectra® is a blue light, yellow filter caries detector. This uses the tooth’s auto-fluorescence to detect decay and anomalies in the tooth. Spectra is also capable of seeing porphyrins. We would anticipate where good images can be acquired, especially near marginal edges, you would notice a lower reading of red fluorescence from the device, indicating a lowering of bacterial activity.

17. Should SDF be light cured?

It is not recommended to light cure after an application of SDF. Light curing the SDF causes the silver to oxidize before allowing it to fully penetrate the tooth. If you are placing a restoration on top of the SDF treated surface at the same appointment, wait at least 60 seconds to allow the SDF to penetrate the lesion, then light cure the SDF treated area prior to restorative procedures. This may prevent or reduce the graying of the restoration and allow you the opportunity to further prepare margins to minimize staining.
Safety

1. **What have been the reported adverse events with the use of silver diamine fluoride worldwide?**

   Where silver diamine fluoride has been used in other countries there are no reports of adverse effects, outside of patients with an allergy to silver.

2. **Is SDF safe for use in children?**

   One drop of SDF (20 uL) contains as much fluoride as a liter of bottled water at 1 ppm F. Regarding the margin of safety for dosing, a study was conducted for FDA review for market clearance in rats and mice to determine the lethal dose by oral and subcutaneous administration. The worst-case scenario is subcutaneous administration and that lethal dose was found to be 380 mg/kg. One drop (25uL) of 38% silver diamine fluoride (SDF) contains 9.5 mg silver diamine fluoride. Thus, one drop of 38% SDF applied to 10 kg (22 lb.) child would equal 0.95 mg/kg, equal to a four-hundred fold safety margin.

   In setting up protocols for undergraduate application of 38% SDF, the University of California San Francisco set a recommended limit of one drop per 10 kg (22 lb.) per treatment visit, with weekly intervals at most.

3. **What are the safety implications for application of SDF for a patient that has more than six sites to be treated?**

   The Margin of Safety for the volume of product needed to treat six sites is within 130 times the NOAEL (no-observed-adverse-effect-level). Treating more sites in one visit will likely have little practical impact on patient safety. Like protocols for fluoride varnish application, the suspension for several days of fluoride supplements is advised.

4. **Is SDF application safe for use with pregnant patients?**

   The FDA cleared silver diamine fluoride for marketing as a medical device, not a drug, and it has not been studied in pregnant woman. Based on known toxicological and pharmacological information, SDF is not expected to have adverse effects on pregnant patients. This is equivalent to pregnancy category C for drugs.

5. **Is it safe for children for the provider to place SDF on a site(s) for arresting caries, and fluoride varnish on all teeth for prevention, on the same visit?**

   Yes, since one drop of SDF, enough to treat multiple sites, contains 1/10th the milligrams of fluorine of a 0.5 mL unit-dose package of 5% sodium fluoride (NaF) varnish.
   - One drop of SDF (0.025 mL) plus one package (0.5 mL) of 5% NaF Varnish will deliver 12.5 mg F to the patient.
   - One drop of SDF (0.025 mL) plus one package (0.3 mL) of 2.5% NaF Varnish will deliver 4.51 mg F to the patient
   - One drop of SDF (0.025 mL) makes up only 1.12 mg F of the amounts above.
Precautions

1. Patient exclusions and inclusions?
   Do not use silver diamine fluoride on patients:
   - With an allergy to silver
   - With ulcerative gingivitis or stomatitis
   - Without an informed consent
   - With a low caries risk, CDT code D 0601
   - Near any open wound including exposed pulp (direct pulp caps)

   Do use silver diamine fluoride for patients:
   - With any non-symptomatic active caries
   - With deep caries as an indirect pulp cap
   - With any incipient watch spot
   - With newly erupted molars
   - With any at-risk sites such as: unsealed deep pits and fissures, enamel defects, exposed root surfaces, furcations, food traps and old restoration margins

2. Does SDF discolor skin or oral tissue?
   Contact to skin is not harmful but is likely to cause temporary tattooing. The effect is not immediate, rather it will be noticed within hours. The speed of discoloration is accelerated with light contact. The staining will be limited to direct areas of contact and will fade over a period of 24-72 hours. Patients should be protected with bibs and safety glasses as in any clinical procedure. If you believe you have touched the applicator to the skin of a patient, it is good to advise them of possible temporary tattooing.

   Contact to oral soft tissue is less likely to cause temporary tattooing, but is still possible. Take care to protect soft tissue with petroleum jelly or cocoa butter when an application is adjacent to gingival tissue (root caries, treatment of restoration margins). Light blanching is also possible from prolonged direct contact, but has been reported to be minor and resolves within 1-2 days.

3. Are there any contraindications for the use of SDF for the control of caries?
   SDF should not be placed on exposed pulps. Studies have shown that 38% silver diamine fluoride conveys more effective protection against decay in other teeth than fluoride varnish with reduced overall fluoride exposure.

4. Does SDF stain countertops, instruments, clothing etc.?
   Yes. When dispensing SDF it is a good idea to use an absorbent material that has a coated bottom like a patient bib under the dappen dish and applicator to avoid contact with metal trays and office countertops. If SDF comes in contact with instruments or countertops wash immediately with water, soap, ammonia or iodine tincture and then rinse thoroughly with water. Sodium hypochlorite (household bleach) can also be used for difficult stains once they set into the surface.
SDF treated sites tend to discolor more rapidly with light curing. Care should be taken when bonding translucent restorative materials in anterior teeth. The use of opaquers is recommended when covering extensive anterior treated sites. Self-cured materials may diminish anterior discoloration issues associated with light curing. Stains to clothing are permanent. Use an applicator that does not drip the SDF as it passes over the patient to the site of treatment.

**Restorative Aspects**

1. **Can SDF be used on a prepared tooth just prior to restoration cementation?**

   Yes. Desensitizing agents have been shown to be protective of the pulp when placed on crown preparations to reduce dentin permeability. Advantage Arrest, a desensitizer, has been shown safe to the pulp when placed on exposed dentin. In addition, studies have shown desensitization and efficacy in treating softened dentin before placing direct restorations. Usually the tooth is first treated with silver diamine fluoride 38%. This provides the benefit of sealing tubules plus the antimicrobial benefits of both silver and fluoride. When SDF is applied at the same appointment as the restoration, graying of the restoration is possible. Graying of the restoration has not been reported when done at separate appointments.

2. **Does an SDF treated site compromise the bond strength of glass ionomer (GI), resin-modified glass ionomer (RMGI) or resin composite restorations?**

   A recent in vitro study investigated the micro-tensile bonding strength of resin composite to the dentin of primary molars and found that pretreating does not affect the bonding strength. The study concluded: “In the SDF group, the fracture occurred most often within the adhesive layer, suggesting that bonding strength might be stronger between the adhesive and the dentin pretreated with SDF.” (Pediatric Dentistry, V 38, N 2, Mar/Apr 2016, pgs. 148-153)

   SDF treated sites tend to discolor more rapidly with light curing. Care should be taken when bonding translucent restorative materials in anterior teeth. The use of opaquers is recommended when covering extensive anterior treated sites. Self-cured materials may diminish anterior discoloration issues associated with light curing.

**Insurance Coding and Reimbursement**

1. **How can Advantage Arrest be coded using CDT?**

   SDF is cleared for dentinal hypersensitivity treatment. That code is:
   
   D9910 – application of desensitizing medicament
   
   Includes in-office treatment for root sensitivity. Typically reported on a “per visit” basis for application of topical fluoride. This code is not used for bases, liners or adhesives under restorations.
On January 1, 2016 a new CDT code became effective for the use of SDF or 25% silver nitrate and has had one revision effective January 1, 2018. The code that will be effective on January 1, 2018 has the addition of “……per tooth” and reads as follows:

**D1354 – interim caries arresting medicament application – per tooth**

Conservative treatment of an active, non-symptomatic carious lesion by topical application of a caries arresting or inhibiting medicament and without removal of sound tooth structure.

The ADA has provided a guide to report D1354, linked here:


2. **Can I use code D1208 – topical application of fluoride- excluding varnish for the application of SDF?**

   Yes. Since Advantage Arrest contains fluoride and studies/articles in this packet demonstrate the ability of SDF to prevent caries, D1208 is an appropriate code when the product is used as a topical application of fluoride in primary prevention. Clinical notes should reflect the reason for the application. It is also helpful to identify caries risk to justify the reimbursement with a recognized caries risk assessment tool. Codes D0602 – caries risk assessment and documentation, with a finding of moderate risk and D0603 - caries risk assessment and documentation, with a finding of high risk are especially important to justify patient use.

   D1999 – unspecified preventive procedure by report (and including a report) can also be used to record your patient encounter.

3. **Are third party payers reimbursing for D1354?**

   Yes. Many carriers have already included reimbursement for D1354 within many of their plans. It is common for insurance providers to not reimburse for new codes as they develop usual and customary payment data. However, it is important the new D1354 code is used so providers can see the volume and associated fees to determine future coverage.

4. **Do any state Medicaid plans currently pay for D1354?**

   Yes. The American Academy of Pediatric Dentistry indicated in a 2016 publication (“Are Your Kids Covered?”) that 19 states were covering D1354. Based on direct feedback from various state agencies we anticipate an additional 8-10 states will begin coverage for D1354 January 1, 2018.
Advantage Arrest Package Insert

**Advantage Arrest.**  
Silver Diamine Fluoride 38%

Professional Tooth Desensitizer  
Rx Only

**Desensitizing Ingredient:** Aqueous Silver Diamine Fluoride, 38.3% to 43.2% w/v

**Inactive Ingredients:** Purified water

**Clinical Pharmacology:** Product forms insoluble precipitates with calcium or phosphate in the dentinal tubules to block nerve impulses.

**Indication and Usage:** Treatment of dentinal hypersensitivity. For use in adults over the age of 21.

**Contraindications:** This product is contraindicated in patients with ulcerative gingivitis or stomatitis, or known sensitivity to silver or other heavy-metal ions. Patients with more than six affected sites, patients having had full mouth gingivectomies and patients showing abnormal skin sensitization in daily circumstances are recommended for exclusion.

**Warnings:** This product is intended for local application only. Not for ingestion. Protect the patient’s eyes. Use caution to avoid contact with skin or clothing. In the event of exposure to eyes or skin, flush the area copiously with water and immediately seek medical consultation. This product yielded positive cytotoxicity in standard testing.

**Precautions for Use:**

1. Advantage Arrest does not normally stain enamel or burnished dentin. Advise patients that soft dentin or margins of composite restorations may be stained. Staining may be reversed by gentle polishing with tincture of iodine (weak iodine solution).

2. Advise patients that air-drying and product application can cause momentary transient pain to hypersensitive areas. Advantage Arrest has not been shown to cause pulpal necrosis even when soft dentin is treated.

3. Minimize product contact with gingiva and mucous membrane by using recommended amounts and careful application. Advantage Arrest may cause reversible short-term irritation. When applying Advantage Arrest to areas near the gingiva, apply petroleum jelly or cocoa butter and use cotton rolls to protect the gingival tissues. Alternatively, a rubber dam can be used to isolate the area.

4. If accidental contact occurs, thoroughly wash the area with water, saline solution or ~3% hydrogen peroxide. This includes contact with skin, clothes, floors and cabinets. Because Advantage Arrest is clear and thus may be difficult to see, use caution to avoid transferring the material from gloved hands to other surfaces.

**Precautions for Handling:**

1. **Storage Precautions**
   1) Store in original packaging in a cool, dark place.
   2) Replace cap immediately after use.
   3) Use as soon as dispensed.

2. Advantage Arrest will stain skin, clothes, counter tops, floors and instruments brown or black. Refer to the following for stain removal:
   1) Skin; wash immediately with water, soap, ammonia or iodine tincture and then rinse thoroughly with water. Do not use excessive methods in an attempt to remove difficult stains from skin as the stains will eventually fade.
   2) Clothing/Countertops/Floors/Instruments; use the same procedures as with stained skin. Difficult stains may be treated with sodium hypochlorite.

3. If Advantage Arrest is dispensed into a separate container, be sure to wash or thoroughly wipe the container clean immediately after use.

**Adverse Reactions:** Transient irritation of the gingiva has rarely been reported.

**Dosage and Administration:**

1. Isolate the affected area of the tooth with cotton rolls or protect the gingival tissue of the affected tooth with petroleum jelly. Alternatively, a rubber dam can be used to isolate the area.

2. Clean and dry the affected tooth surface.

3. For up to 5 treated sites per patient, dispense 1-2 drops of solution into a disposable dappen dish. Transfer material directly to the tooth surface with an applicator.


If needed, one or two reapplications may be administered at intervals of one week.

**How Supplied:** Single 10 mL dropper-bottle containing 8 mL of product. Not sterile.

**Storage:** Do not freeze or expose to extreme heat. Keep in an air-tight container in a dark place.

**Caution:** Federal law restricts this device to sale by or on the order of a dentist or physician.

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Use of Silver Diamine Fluoride for Dental Caries Management in Children and Adolescents, Including Those with Special Health Care Needs

Developed by
American Academy of Pediatric Dentistry

Issued
2017

Abstract

**Background:** This manuscript presents evidence-based guidance on the use of 38 percent silver diamine fluoride (SDF) for dental caries management in children and adolescents, including those with special health care needs. A guideline workgroup formed by the American Academy of Pediatric Dentistry developed guidance and an evidence-based recommendation regarding the application of 38 percent SDF to arrest cavitated caries lesions in primary teeth.

**Types of studies reviewed:** The basis of the guideline’s recommendation is evidence from an existing systematic review “Clinical trials of silver diamine fluoride in arresting caries among children: A systematic review.” (JDR Clin Transl Res 2016;1[3]:201-10). A systematic search was conducted in PubMed®/MEDLINE, Embase®, Cochrane Central Register of Controlled Trials, and gray literature databases to identify randomized controlled trials and systematic reviews reporting on the effect of silver diamine fluoride and address peripheral issues such as adverse effects and cost. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of the evidence and the evidence-to-decision framework was employed to formulate a recommendation.

**Results:** The panel made a conditional recommendation regarding the use of 38 percent SDF for the arrest of cavitated caries lesions in primary teeth as part of a comprehensive caries management program. After taking into consideration the low cost of the treatment and the disease burden of caries, panel members were confident that the benefits of SDF application in the target populations outweigh its possible undesirable effects. Per GRADE, this is a conditional recommendation based on low-quality evidence.

**Conclusions and practical implications:** The guideline intends to inform the clinical practices involving the application of 38 percent SDF to enhance dental caries management outcomes in children and adolescents, including those with special health care needs. These recommended practices are based upon the best available evidence to-date. A 38 percent SDF protocol is included in Appendix II.

**KEYWORDS:** SILVER DIAMINE FLUORIDE, CLINICAL RECOMMENDATIONS, GUIDELINE, ANTI-INFECTIVE AGENTS, CARIOSTATIC AGENTS, SILVER COMPOUNDS, CARIES, TOPICAL FLUORIDES

Scope and purpose

The guideline intends to inform the clinical practices involving the application of silver diamine fluoride (SDF) to enhance dental caries management outcomes in children and adolescents, including those with special health care needs. Silver diamine fluoride in this guideline’s recommendation refers to 38 percent SDF, the only formula available in the United States. These recommended practices are based upon the best available evidence to-date. However, the ultimate decisions regarding disease management and specific treatment modalities are to be made by the dental professional and the patient or his/her representative, acknowledging individuals’ differences in disease propensity, lifestyle, and environment.

The guideline provides practitioners with easy to understand evidence-based recommendations. The American Academy of Pediatric Dentistry’s (AAPD) evidence-based guidelines are being produced in accordance with standards created by the National Academy of Medicine (formerly known as the Institute of Medicine) and mandated by the National Guideline Clearinghouse™ (NGC), a database of evidence-based clinical practice guidelines and related documents maintained as a public resource by the Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services (USDHHS).

**Health intents and expected benefits or outcomes.**

The guideline is based on analysis of data included in a recent systematic review and meta-analysis¹ and summarizes evidence of the benefits and safety of SDF application in the context of dental caries management, mainly its effectiveness in arresting cavitated caries.

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**ABBREVIATIONS**


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Review provided courtesy of Elevate Oral Care • West Palm Beach, FL • ELE615 - 1217 13
caries lesions† in the primary dentition. Its intent is to provide the best available information for practitioners and patients or their representatives to determine the risks, benefits, and alternatives of SDF application as part of a caries management program. Prevention of new caries lesion development and outcomes in permanent teeth, such as root caries lesion arrest, were not the focus of this guideline; however, because they are of interest and relevant to caries management within the scope of pediatric dentistry, they are mentioned and will be included in future iterations of the guideline as the supporting evidence base increases.

Clinical questions addressed. The panel members used the Population, Intervention, Control, and Outcome (PICO) formulation to develop the clinical questions that will aid practitioners in the use of SDF in primary teeth with caries lesions. Does the application of SDF arrest cavitated caries lesions as effectively as other treatment modalities in primary teeth?2

Methods
This guideline adheres to the National Academy of Medicine’s guideline standards3 and the recommendations of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument.4 The guidance presented is based on an evaluation of the evidence presented in a 2016 systematic review published by Gao and colleagues.1

Search strategy. Literature searches were used to identify systematic reviews that would serve as the basis of the guideline. Secondly, the results of the searches served as sources of evidence or information on issues related to, but outside the context of, the PICO, such as cost, adverse effects, and patient preferences.

Literature searches were conducted in PubMed®/MEDLINE, Embase®, Cochrane Central Register of Controlled Trials, gray literature, and trial databases to identify systematic reviews and randomized controlled trials of SDF. Search results were reviewed in duplicate at both the title and abstract and the full-text level when warranted. Disagreements were resolved by consensus; if agreement could not be reached, the AAPD Evidence-Based Dentistry Committee (EBDC) overseeing the workgroup was consulted to settle the question. A detailed description of the search strategies is presented in Appendix I.

Inclusion and exclusion criteria. The criteria used to identify publications for use in the guideline were determined by the clinical PICO question. See Appendix I for search strategies. Publications which addressed the use of SDF to arrest caries lesions in primary teeth, regardless of language, merited full-text review; in vitro studies and studies of the use of SDF outside of the guideline’s stated outcomes were excluded. No new randomized controlled trials were identified that warranted updating the meta-analysis found in the systematic review1 selected as the basis for this guideline.

Assessment of the evidence. The main strength of this guideline is that it is based on a systematic review of prospective randomized and controlled trials of SDF1. Evidence was assessed via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach6, a widely adopted and peer reviewed system of evaluating study quality (Table 1). The guideline recommendation is based on the meta-analysis of four controlled trials (three randomized), extracted in duplicate, from a systematic review of SDF1. Randomized (RCTs) and controlled clinical trials (CCTs) offer the highest level of clinical evidence; therefore, a recommendation based on a systematic review and meta-analysis of graded RCTs/CCTs provides more reliable and accurate conclusions that can be applied towards patient care.

This guideline is limited by the small number of RCTs evaluating SDF, the heterogeneity of the included trials, and selection bias that may have been introduced by possibly poor sequence generation7,8 and selective reporting by one study7. Weaknesses of this guideline are inherent to the limitations found in the systematic review1 upon which this guideline is based. Major limitations of the supporting literature include lack of calibration and/or evidence of agreement for examiners assessing clinical outcomes and unclear definitions or inconsistent criteria for caries lesion activity.9,10 Arguably, without a valid and reliable method to determine lesion activity at baseline and follow-up, misclassification bias is possible, especially because clinicians cannot be blinded with regard to SDF application (due to the dark staining).9,10 The absence of rigorous caries detection and activity measurement criteria in the reviewed literature can decrease the validity of the reported results.9,10 Other

<table>
<thead>
<tr>
<th>Table 1. QUALITY OF EVIDENCE GRADES†</th>
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<tbody>
<tr>
<td>Grade</td>
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<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
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<tr>
<td>Low</td>
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<tr>
<td>Very Low</td>
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</table>

† A caries lesion is a detectable change in the tooth structure that results from the biofilm-tooth interactions occurring due to the disease caries. It is the clinical manifestation (sign) of the caries process.

† Quality of evidence is a continuum; any discrete categorization involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations.

Formulation of the recommendations. The panel formulated this guideline collectively via surveys, teleconferences, and electronic communications from January 2017–August 2017. The panel used the evidence-to-decision framework in an iterative manner to formulate the recommendations. Specifically, the main methods used were discussion, debate, and consensus seeking. To reach consensus, the panel voted anonymously on all contentious issues and on the final recommendation. GRADE was used to determine the strength of the evidence.

Understanding the recommendations. GRADE rates the strength of a recommendation as either strong or conditional. A strong recommendation “is one for which guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention).” A strong recommendation implies most patients would benefit from the suggested course of action (i.e., either for or against the intervention). A conditional recommendation “is one for which the desirable effects probably outweigh the undesirable effects (conditional recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (conditional recommendation against an intervention), but appreciable uncertainty exists.” A conditional recommendation implies that not all patients would benefit from the intervention. The individual patient’s circumstances, preferences, and values need to be assessed more than usual. Practitioners need to allocate more time for consultation along with explanation of the potential benefits and harms to the patients and their caregivers when recommendations are rated as conditional. Practitioners’ expertise and judgment as well as patients’ and their caregivers’ needs and preferences establish the suitability of the recommendation to individual patients. The strength of a recommendation presents different implications for patients, clinicians, and policy makers (Table 2).

Table 2. IMPLICATIONS OF STRONG AND CONDITIONAL RECOMMENDATIONS FOR DIFFERENT USERS OF GUIDELINES

<table>
<thead>
<tr>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients</td>
<td>The majority of individuals in this situation would want the suggested course of action, and only a small proportion would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.</td>
</tr>
<tr>
<td>For policy makers</td>
<td>Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.</td>
</tr>
</tbody>
</table>


Recommendations

The SDF panel supports the use of 38 percent SDF for the arrest of cavitated caries lesions in primary teeth as part of a comprehensive caries management program. (Conditional recommendation, low-quality evidence)

Summary of findings

The recommendation is based on data from a meta-analysis of data extracted from RCTs and CCTs of SDF efficacy with various follow-up times and controls (Table 3). Based on the pooled estimates of SDF group, approximately 68 percent (95 percent confidence interval [95% CI]=9.7 to 97.7) of cavitated caries lesions in primary teeth would be expected to be arrested two years after SDF application (with once or twice a year application). Using data with longest follow-up time (at least 30 months follow-up; N=2,567 surfaces from one RCT and one CCT), SDF had 48 percent higher (95% CI=32 to 66) success rate in caries lesion arrest compared to the controls (76 percent versus 51 percent arrested lesions, in absolute terms). In other words, 248 more cavitated caries lesions would be expected to arrest by treatment with SDF compared to control treatments, per 1000 surfaces after at least 30 months follow-up. Considering the stratum with most data (N=3,313 surfaces from three RCTs and one CCT, with follow-up of 24 months or more), similar estimates of relative and absolute efficacy were produced (i.e., RR 1.42 [95% CI=1.17 to 1.72]) and 72 percent versus 50 percent arrested lesions, in absolute terms. Other follow-up and application frequency strata are listed in the summary of findings (Table 3). The range of estimates of SDF efficacy between the included trials was categorically wide. Rates of arrest on untreated groups may seem unusually high, and this may be due to background fluoride exposure. In one of the trials, all participants (i.e., both the SDF-treated and control children) received 0.2 percent sodium fluoride (NaF) rinse every other week in school, while in other trials, children were either given fluoride toothpaste or reported use of fluoride toothpaste. The panel determined the overall quality of the
The panel made a conditional recommendation regarding the use of SDF for the arrest of cavitated caries lesions in primary teeth as part of a comprehensive caries management program. After taking into consideration the low cost of the treatment and the disease burden of caries, panel members were confident that the benefits of SDF application in the target populations outweigh its possible undesirable effects. Specifically:

1. Untreated decay in young children remains a challenge, from clinical and public health standpoints, in the U.S. and worldwide. It confers significant health and quality of life impacts to children and their families, and it is marked by pronounced disparities.

2. Surgical-restorative work in young children and those with special management considerations (e.g., individuals with special health care needs) often requires advanced pharmacologic behavior guidance modalities (e.g., sedation, general anesthesia). These pathways of care have additional health risks and limitations (e.g., possible effects on brain development in young children, mortality risks), and often are not accessible, at all or in a timely manner.

The U.S. Food and Drug Administration has issued a warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than three may affect the development of children’s brains.

3. The cost of managing severe early childhood caries is disproportionately high, especially when hospitalization is necessary. The need to treat children in a hospital setting with general anesthesia is a common scenario in the U.S. and other countries. Studies report that children from the less-affluent regions have higher dental surgery rates than those from more-affluent communities (25.7 vs. 6.9 per 1,000), which results in an economic burden for communities already impacted by the effects of poverty-related health problems.

Table 3. SUMMARY OF FINDINGS: EVIDENCE FOR THE RELATIVE AND ABSOLUTE EFFICACY OF SDF APPLICATION COMPARED TO NO SDF FOR THE ARREST OF CAVITATED CARIES LESIONS ON PRIMARY TEETH

<table>
<thead>
<tr>
<th>Patient or population: Children and adolescents with cavitated caries lesions on primary teeth</th>
<th>Intervention: SDF (various periodicities)</th>
<th>Comparison: No SDF (various controls, including active agents and treatment)</th>
<th>Outcome: Caries arrest in primary teeth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time; N surfaces (studies)</td>
<td>Relative efficacy, RR (95% CI)</td>
<td>Absolute estimates, % arrested lesions (95% CI)</td>
<td>Quality assessment</td>
</tr>
<tr>
<td>24 months; 746 surfaces (2 RCTs: Yee et al., 2009 &amp; Zhi et al., 2012) v</td>
<td>RR 1.45 (0.79 to 2.66)</td>
<td>47.9% (3.8 to 95.6) A</td>
<td>SDF (0.79 to 2.66) 68.0% (9.7 to 97.7)</td>
</tr>
<tr>
<td>≥ 24 months; 3313 surfaces (3 RCTs: Llodra et al., 2005, Yee et al., 2009 &amp; Zhi et al., 2012, 1 CCT: Chu et al., 2002) 5</td>
<td>RR 1.42 (1.17 to 1.72)</td>
<td>49.6% (28.8 to 70.5) C</td>
<td>SDF (48.0 to 88.1)</td>
</tr>
<tr>
<td>≥ 30 months; 2567 surfaces (1 CCT: Chu et al., 2002 &amp; 1 RCT: Llodra et al., 2005) 5</td>
<td>RR 1.48 (1.32 to 1.66)</td>
<td>50.8% (32.5 to 69.0) b</td>
<td>SDF (52.1 to 90.6)</td>
</tr>
<tr>
<td>Semi-annual application ≥ 24 months; 1784 surfaces (2 RCTs: Llodra et al., 2005 &amp; Zhi et al., 2012)</td>
<td>RR 1.25 (0.99 to 1.58)</td>
<td>72.4% (47.2 to 88.5) A</td>
<td>SDF (80.9 to 92.4)</td>
</tr>
</tbody>
</table>

CCT= Controlled clinical trials; CI= Confidence interval; RCTs= Randomized control trials; RR= Relative risks.

* Rates of arrest on untreated groups may seem unusually high, and this may be due to background fluoride exposure. In one of the trials, all participants (i.e., both the SDF-treated and control children) received 0.2 percent NaF rinse every other week in school, while in other trials, children were either given fluoride toothpaste or reported use of fluoride toothpaste.

v Yee is once a year application of SDF, and Zhi is once a year vs. twice a year.

5 Chu is once a year application of SDF, Llodra is twice a year, Yee is once a year, and Zhi is once a year vs. twice a year.

Ω The pooled effect estimates and confidence intervals for the relative risk and absolute percentages were derived from random effect modeling.

a At least one domain had ‘unclear’ risk of bias assessment.

b High heterogeneity.

c Wide confidence interval of the relative risk.

d Very high heterogeneity.

e Wide confidence interval.
4. With caries lesion arrest rates upwards of 70 percent (i.e., higher than other comparable interventions), SDF presents as an advantageous modality. Besides its efficacy, SDF is favored by its less invasive (clinically and in terms of behavior guidance requirements) nature and its inexpensiveness.

5. The undesirable effects of SDF (mainly esthetic concerns due to dark discoloration of carious SDF-treated dentin) are outweighed by its desirable properties in most cases, while no toxicity or adverse events associated with its use have been reported.

In sum, the panel felt confident that a conditional recommendation was merited because, although a majority of patients would benefit from the intervention, individual circumstances, preferences, and values need to be assessed by the practitioner after explanation and consultation with the caregiver.

Research considerations. Research is needed on the use of SDF to arrest caries lesions in both primary and permanent teeth. The panel urges researchers to conduct well-designed randomized clinical trials comparing the outcomes of SDF to other treatments for the arrest of caries lesions in primary and permanent teeth.

Potential adverse effects. Silver diamine fluoride contains approximately 24-28 percent (weight/volume) silver and 5-6 percent fluoride (weight/volume). Exposure to one drop of SDF orally would result in less fluoride ion content than is present in a 0.25 mL topical treatment of fluoride varnish. The exact amount of silver and fluoride present in one drop of SDF is determined by the specific gravity of the liquid and the dropper used. More studies are required to determine that amount, given the stability of the product manufactured and packaged in the U.S.

In published clinical trials encompassing over 4,000 young children worldwide, exposure to manufacturer’s recommended amounts of SDF has not resulted in any reported deaths or systemic adverse effects.

Oral absorption can include absorption in mucous membranes in the mouth and the nasal cavity. The short-term health effects in humans as a result of exposure to water or food containing specific levels of silver are unknown. The Environmental Protection Agency (EPA) suggests levels of silver in drinking water not to exceed 1.142 mg/L (1.42 ppm). Silver diamine fluoride should not be used in patients with an allergy to silver compounds.

The main disadvantage of SDF is its esthetic result (i.e., permanently blackens enamel and dentinal caries lesions and creates a temporary henna-appearing tattoo if allowed to come in contact with skin). Skin pigmentation is temporary since the silver does not penetrate the dermis. Desquamation of the skin with pigmentation occurs when keratinocytes are shed over a period of 14 days. Silver diamine fluoride also permanently stains most surfaces (e.g., counters, clothing) with which it comes into contact.

Guideline implementation. This guideline will be published in the AAPD’s Reference Manual and the journal, Pediatric Dentistry. Social media, news items, and presentations will be used to notify AAPD members about the new guideline.

This guideline will be available as an open access publication on the AAPD’s website. Patient education materials are being developed and will be offered in the AAPD’s online bookstore. See Appendix II for practical SDF guidance and the Resource Section of the AAPD Reference Manual for a SDF chairside guide.

Cost considerations. Silver diamine fluoride is an effective and inexpensive means of arresting cavitated caries lesions in primary teeth. It is inexpensive due to the low cost of materials and supplies and relatively short chair time required for application. Nevertheless, an empirical cost analysis discussion for SDF would need to address the several additional considerations and parameters. First, given the wide array of surgical and non-surgical management approaches for cavitated caries lesions in the primary dentition, agreement on consensus endpoints and, therefore, total cost is challenging and controversial. Second, cost should include patient/family and practitioner time, health care services utilized, and cost of non-health impacts, if any. Third, SDF economic analyses are likely best approached via a cost-utility framework, wherein expenditures are juxtaposed to quality-adjusted or disease-free years. To illustrate the importance of defining a consensus treatment endpoint, in this scenario disease-free years can be interpreted as caries inactive, no surgical intervention needed, or pain-free years. Finally, the economic benefits of SDF application must be considered in the context of pathways of clinical care (i.e., disease management) and account, among other factors, for the risks and costs associated with advanced behavior management techniques (e.g., indicated surgical-vestorative work may require sedation or general anesthesia in some cases), families’ preferences, and opportunity costs (e.g., time investment beyond the direct costs).

Recommendation adherence criteria

Guidelines are used by insurers, patients, and health care practitioners to determine quality of care. In principle, following best practices and guidelines is believed to improve outcomes and reduce inappropriate care. Therefore, measuring adherence to oral health-related guidelines is key and can serve as manifestation of the dental community’s role as a “responsible steward of oral health.” Though measurement of oral health outcomes is in its early days at both system and practice levels, system-level performance measures for some oral health areas have been developed by the Dental Quality Alliance of the American Dental Association in partnership with the AAPD and other dental organizations. The goals of professional accountability, transparency, and oral health care quality can be furthered through these measures.

Workgroup. In December 2016, the AAPD’s Board of Trustees approved a panel nominated by the EBDC to develop a new evidence-based clinical practice guideline on SDF. The panel consisted of general and pediatric dentists in public and
private practice involved in research and education; the stakeholders consisted of representatives from general dentistry, dental hygiene, governmental and non-governmental agencies, and international and specialty dental organizations.

**Stakeholders and external review.** This guideline was reviewed by external and internal stakeholders continuously from the beginning of the process until the formulation of the guideline. Stakeholders were invited to take part in anonymous surveys to determine the scope and outcomes of the guideline, bringing in points of view from different geographical regions, dental specialties, and patient advocates. Comments also were sought on the draft of the guideline. All stakeholder comments were taken into consideration, addressed, and acted upon as appropriate per group deliberation. Additional feedback from stakeholders is expected after publication and dissemination of the guideline.

**Intended users.** The target audience for this guideline is general dentists, pediatric dentists, pediatricians, and family practice physicians. Public and private payors will benefit from reviewing the evidence for coverage decisions regarding SDF use, and patients and patient advocates may find it useful as a reference for current available treatments for caries management. The target populations include children and adolescents, including those with special health care needs.

**Guideline updating process.** The AAPD's EBDC will monitor the biomedical literature to identify new evidence that may impact the current recommendations. These recommendations will be updated five years from the time the last systematic search, unless the EBDC determines that an earlier revision or update is warranted.

References appear after Appendices.

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**Appendices**

**Appendix I—Search strategies**

**PubMed** (MEDLINE)-- no date limit

**Search #1. 145 results**
cariestop OR "silver diamine fluoride" [Supplementary Concept] OR "silver diamine" OR "silver diammine" OR "diamine fluoride" OR "diammine fluoride" OR saforide OR "Riva star"

**Search #2. 6589771 results**

**Search #3. 14 results**
#1 and #2

**Search #4. 410530 results**

**Search #5. 14 results**
#1 and #4*

**Search #6. 890576 results**

**Search #7. 8 results**
#1 AND #6

* Search results vetted in duplicate using an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses checklist.
Appendix II—Practical guidance *

* Silver diamine fluoride in this guideline’s recommendation refers to 38 percent SDF, the only formula available in the United States.

Setting
Practitioners must first consider the current standard of care of the setting where SDF therapy is intended for use. Silver diamine fluoride is optimally utilized in the context of a chronic disease management protocol, one that allows for the monitoring of the clinical effectiveness of SDF treatment, disease control, and risk assessment.

Practical recommendation: Know the setting where SDF is to be used to be consistent with goals of patient-centered care.

Indications and usage
The following scenarios may be well-suited for the use SDF:

• High caries-risk patients with anterior or posterior active cavitated lesions.
• Cavitated caries lesions in individuals presenting with behavioral or medical management challenges.
• Patients with multiple cavitated caries lesions that may not all be treated in one visit.
• Difficult to treat cavitated dental caries lesions.
• Patients without access to or with difficulty accessing dental care.
• Active cavitated caries lesions with no clinical signs of pulp involvement.

Practical recommendation: SDF is a valuable caries lesion–arresting tool that can be used in the context of caries management. Evaluate carefully which patients/teeth will benefit from SDF application.

Preparation of patients and practitioners
Informed consent, particularly highlighting expected staining of treated lesions, potential staining of skin and clothes, and need for reapplication for disease control, is recommended.

The following practices are presented to support patient safety and effectively use SDF:

• Universal precautions.
• No operative intervention (e.g., affected or infected dentin removal) is necessary to achieve caries arrest.8
• Protect patient with plastic-lined bib and glasses.
• Cotton roll or other isolation as appropriate.
• Use a plastic dappen dish as SDF corrodes glass and metal.
• Carefully dispose of gloves, cotton rolls, and micro brush into plastic waste bag.

Application
Cavious dentin excavation prior to SDF application is not necessary.8 Caries dentin excavation may reduce proportion of arrested caries lesions that become black, and may be considered for esthetic purposes.30 Functional indicator of effectiveness (i.e., caries arrest) is when staining on dentinal carious surfaces is visible.

The following steps may vary depending on differing practices, settings, and patients:

• Remove gross debris from cavitation to allow better SDF contact with denatured dentin.
• Minimize contact with gingiva and mucous membranes to avoid potential pigmentation or irritation; consider applying cocoa butter or use cotton rolls to protect surrounding gingival tissues, with care to not inadvertently coat the surfaces of the carious lesion.
• Dry with a gentle flow of compressed air (or use cotton rolls/gauze to dry) affected tooth surfaces.
• Bend micro sponge brush, dip and dab on the side of the dappen dish to remove excess liquid before application;24 apply SDF directly to only the affected tooth surface.
• Dry with a gentle flow of compressed air for at least one minute.
• Remove excess SDF with gauze, cotton roll, or cotton pellet to minimize systemic absorption.4 Continue to isolate site for up to three minutes when possible.

Practical recommendation: No need for surgical intervention (e.g., dentin excavation). SDF application is minimally invasive and easy for the patient and the practitioner. It may be desirable for the caries lesion to be free of gross debris for SDF to have maximum contact with the affected dentin surface.

Application time
An application time of one minute, drying with a gentle flow of compressed air, is recommended. Clinical studies that report application times range from 10 seconds to three minutes. A current review states that application time in clinical studies does not correlate to outcome.24 More studies are needed to confirm an ideal protocol.

Practical recommendation: Ideal time of application should be one minute, using a gentle flow of compressed air until liquid is dry. When using shorter application periods, monitor carefully at post-op and re-care to evaluate arrest and consider re-application.

Post-operative instructions
No postoperative limitations are listed by the manufacturer. Eating and drinking immediately following application is acceptable. Patients may brush with fluoridated toothpaste as per regular routine following SDF application.

Several SDF clinical trials recommended no eating or drinking for 30 minutes – one hour.13,31,32 As patients are used to these recommendations for in-office topical fluoride applications, the recommendation may not be unreasonable to patients, and it may allow for better arrest results. More clinical studies are needed to establish best practices.
Application frequency
The effectiveness of one-time SDF application in arresting dental caries lesions ranges from 47 percent to 90 percent, depending on the lesion size and the location of the tooth and the lesion. One study showed that anterior teeth had higher rates of caries lesion arrest than posterior teeth.33 The effectiveness of caries lesion arrest, however, decreases over time. After a single application of 38 percent SDF, 50 percent of the arrested surfaces at six months had reverted to active lesions at 24 months.13

Reapplication may be necessary to sustain arrest.8,31-33 Annual application of SDF is more effective in arresting caries lesions than application of five percent sodium fluoride varnish four times per year.30 Increasing frequency of application can increase caries arrest rate. Biannual application of SDF increased the rate of caries lesion arrest compared to annual application.33 Studies that had three times per year applications showed higher arrest rates.7,31,33,34 Frequency of application after baseline has been suggested at three month follow up, and then semiannual recall visits over two years.24 One option is to place SDF on active lesions in conjunction with fluoride varnish (FV) on the rest of the dentition, or alternate SDF on caries lesions and FV on the rest of the dentition at three months interval to achieve arrest and prevention in high risk individuals.35 Another study recommends one month post operative evaluation of treated lesions with optional reapplication as required to achieve arrest of all targeted lesions.35 Individuals with high plaque index and lesions with plaque present display lower rates of arrest. Addressing other risk factors like presence of plaque may increase the rate of successful treatment outcomes.33

Practical recommendation: If the setting allows, monitor caries lesion arrest after 2-4 week period and consider reapplication as necessary to achieve arrest of all targeted lesions. Provide re-care monitoring based on patient’s disease activity and caries risk level (every three, four, or six months). Careful monitoring and behavioral intervention to reduce individual risk factors should be part of a comprehensive caries management program that aims not only to sustain arrest of existing caries lesions, but also to prevent new caries lesion development.

Adverse reactions
No severe pulpal damage or reaction to SDF has been reported.7,36-38 However, SDF should not be placed on exposed pulps. Teeth with deep caries lesions should be closely monitored clinically and radiographically.

Serum concentration of fluoride following SDF application per manufacturer recommendations posed little toxicity risk and was below EPA oral reference dose in adults.39

The following adverse effects have been noted in the literature:
• Metallic/bitter taste.24
• Temporary staining to skin which resolves in 2-14 days.24
• Mucosal irritation/lesions resulting from inadvertent contact with SDF, resolved within 48 hours.7

Esthetics
The hallmark of SDF is a visible dark staining that is a sign of caries arrest on treated dentin lesions. This dark discoloration is permanent unless restored. A recent study that assessed parental perceptions and acceptance of SDF based on the staining found that staining on posterior teeth was more acceptable than on anterior teeth.50 Although staining on anterior teeth was perceived as undesirable, most parents preferred this option to avoid the use of advanced behavioral guidance techniques such as sedation or general anesthesia to deliver traditional restorative care. It was also found that about one-third of parents found SDF treatment unacceptable under any circumstance due to esthetic concerns. To identify those patients, a thorough informed consent, preferably with photographs that show typical staining, is imperative.40 To improve esthetics, once the disease is controlled and patient’s circumstances allow, treated and now-arrested cavitated caries lesions can be restored.35

Other considerations
• Coding – D1354; Reimbursement for this procedure varies among states and carriers. Third-party payors’ coverage is not consistent on the use of this code per tooth or per visit. Practitioners are cautioned to check insurance coverage for this code as it is transitioning in most areas.
• Caries arrest is more likely on the maxillary anterior teeth8,31 and buccal/lingual smooth surfaces31.
• Pretreatment of dentin with SDF does not adversely affect bond strength of resin composite to dentin.41,42

References on next page.
**References**


The Short-term Effects of Diammine Silver Fluoride on Tooth Sensitivity: a Randomized Controlled Trial

INTRODUCTION

Tooth sensitivity to various stimuli, including cold air, has been explained by hydrodynamic changes within the dentinal tubules that activate intradental nerves (Markowitz and Pashley, 2008). Incidence is thought to be increasing. The etiology can be tooth wear, aggressive oral hygiene, and diet. Successful treatments physically block dentinal tubules (Arends et al., 1997).

Sodium fluoride varnish and fluoride solutions and gels have been shown to reduce sensitivity (Thrash et al., 1992; Ritter et al., 2006). However, there is continuing interest in finding effective treatments. Nevertheless, recent studies have designs that are weak or statistically underpowered (Erdemir et al., 2010; Jalali and Lindh, 2010).

The purpose of this study was to assess the clinical effectiveness and safety of topical diammine silver fluoride as a tooth desensitizer in adults.

METHODS

Design

This is a randomized clinical trial with two groups (Fig. 1). The study tested application of diammine silver fluoride in a single visit, because previous unpublished work had shown that a single application forms insoluble precipitates with calcium and phosphate that physically block dentinal tubules. The International Clinical Trials Registry number is NCT01063530.

Study Sites

The study was conducted in two sites, Lima and Cusco, Peru.

Participants

To be included, a participant must have at least one vital cuspid or premolar with a buccal cervical defect and clinical hypersensitivity in response to compressed air with a score ≥ 15 on a visual analogue scale (VAS) for pain. The individual will have had generally healthy gum tissue surrounding this tooth and no ulceration and no leukoplakia in this gingival tissue. Candidates were excluded if they were using any type of tooth desensitizer, had received a fluoride varnish treatment within the preceding month, or were taking prescription medications, aspirin, or non-steroidal anti-inflammatory drugs; women who were pregnant were also excluded. Individuals using smokeless tobacco or chewing coca leaves were excluded. Individuals with known sensitivity to silver or other heavy-metal ions were excluded.
Participants were recruited from the patient populations of Cayetano University School of Dentistry and the private dental practices of the investigators in Lima and Cusco between January and June, 2010, and were offered a small financial incentive for participation.

The Institutional Review Board of Universidad Peruana Cayetano Heredia approved the protocol, and the informed consent of all participants was obtained.

Treatment Conditions

Diammine silver fluoride [Ag(NH₃)₂F, CAS RN 33040–28–7, Saforide, Toyo Seiyaku Kasei Co. Ltd. Osaka, Japan] was used. It is clear and colorless, with a weak odor of ammonia. According to the manufacturer, the solution includes not less than 24.4 w/v% and not more than 26.8 w/v% of silver (Ag), not less than 5.0 w/v% and not more than 5.9 w/v% of fluorine (F). Diammine silver fluoride is also referred to as silver diammine fluoride, silver diamine fluoride, or silver fluoride.

Assignment to Conditions

Participants were randomly assigned to treatment with diammine silver fluoride or sterile water. The randomization was stratified on study site and baseline tooth sensitivity score (< 37 and ≥ 37) to a five-second blast of pressurized air at 2 cm distance from the tooth, and blocking was used to ensure that the two groups would be balanced across the study period and within each stratum. The stratification at 37 was chosen from the literature (Ritter et al., 2006). A pre-test of the VAS with 10 individuals confirmed the mean response in this range. Block sizes were equal to 2 or 4, and were chosen randomly with 2/3 and 1/3 probability, respectively. The assignments were generated by the project statistician, using the “sample” function of R statistical software (Version 2.7.1, The R Foundation for Statistical Computing, 2008). The assignments were recorded on slips of paper numbered consecutively within each stratum and then placed inside sealed envelopes sequentially numbered by stratum. The statistician retained the master list until all the data were analyzed. The clinician would open the envelope and apply the agent. The agents (active or control) were packaged in identical dark glass bottles labeled as A or B. The packaging was done at Cayetano University.

Clinical Procedure

The clinical procedure was that a disposable microbrush was dipped into a drop of the diammine silver fluoride or the control and then applied to the surface for 1 sec. Then the surface was gently air-dried and the procedure repeated.

Measures

Primary Outcome-Clinical

Reduction of pain (tooth sensitivity)—The teeth were isolated with gauze, and participants were asked to report tooth pain on a 100-mm visual analogue scale (VAS; Ritter et al., 2006) before treatment and after treatment with a five-second blast of pressurized air at 2 cm distance from the tooth. The VAS was anchored with “no pain” and “intolerable pain”. The follow-up test was repeated at 24 hrs and 7 days later. A single person in each site conducted the assessment in Spanish. The scale was pre-tested to ensure that the descriptors were translated properly.

Safety

Damage to gingiva—Tissues were photographed before treatment to establish the normal baseline condition. A single examiner examined gingival tissues surrounding each treated tooth immediately after treatment, and at 24 hrs and 7 days later. The primary safety measure is erythema. It was assessed visually.
with the use of a standard dental light. Erythema (red changes) was rated on a 1 to 3 scale, where 1 is no redness, 2 is redness with bleeding on probing, and 3 is a severe change. The Gingival Index (Löe, 1967) was used to measure gingival inflammation in the mouth overall. White changes, ulceration, and staining were secondary measures. Changes were rated as present or absent. Examiners were trained to criteria using photographs and clinical cases. Intra- and inter-examiner reliability was established in 15 cases, and intraclass correlation was used to assess reliability. All intraclass correlations exceeded 0.8.

Data Analysis Plan

The data from the two sites were analyzed separately. To confirm reduction in pain, we calculated average difference scores between pre- and post-treatment VAS scores for each individual for each time-point (24 hrs and 7 days after treatment), and $t$ tests were used to compare changes. The primary end point was at 7 days. Generalized estimating equations (GEE) linear regression was used in a secondary analysis to compare the reduction in pain across the 3 time-points, where the outcome is pain at the 3 time-points, the baseline pain is a covariate, and robust standard errors are used to account for multiple observations per participant and heteroscedasticity (Hardin and Hilbe, 2002). In addition, separate analyses of covariance were done at each time-point to compare the reduction in pain due to the active treatment between the two study sites, where the outcome is the pain at a particular time-point, baseline pain was entered as a covariate, and treatment and site, as well as a treatment-group-by-site interaction, were entered as factors.

We used Fisher’s Exact Test to assess whether there were more participants with erythema score $>1$ in the silver fluoride group vs. the control group at 24 hrs and 7 days post-treatment. The primary end-point was assessed at 24 hrs. A $t$ test assessed any differences in Gingival Index. Any white changes, ulceration, and staining (argyria) were reported.

Power Analysis

The data from the two sites were analyzed separately, and power is described below for the separate site analyses.

Reduction in tooth sensitivity—The primary end-point was assessed at 7 days post-treatment. In a similar desensitization study comparing fluoride varnishes (Ritter et al., 2006), pain in response to air dropped from 36.9 (SD = 26.2) at baseline to 20.8 (SD = 4.3) at 2 wks post-treatment. We expected a similar or larger drop after 7 days with diammine silver fluoride, based on unpublished work from the University of Hong Kong, and little or no drop from the water. Thus, having 31 individuals in a group will allow for detection of effect size from 0.64 upwards, with an alpha of 0.05 and power of 0.8.

RESULTS

Participants

One hundred twenty-six adults (71 in Lima and 55 in Cusco) participated. About 378 candidates were screened between January and June 2010. The main reason (95%) for exclusion was lack of tooth sensitivity. The remainder were excluded because of the use of medications. No individuals were excluded because of tobacco use or coca. All of those eligible agreed to participate, but 10 were excluded because they failed to appear for the first visit. The proportion of women enrolled was 86% in Lima and 80% in Cusco. The average age of participants was 44 yrs and 43 yrs, respectively. There were no dropouts.

Participants and clinicians were blind to treatment assignment. Odor was not a threat to blinding, because the smell is not detectable clinically when such small quantities are used. Taste was not a threat in this study, because only minute amounts of material were applied and the tooth was air-dried after application.

Table 1. Tooth Sensitivity by Study Site and Condition

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Time</th>
<th>Condition</th>
<th>Mean VAS (SD) [Range]</th>
<th>Mean VAS (SD) [Range]</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima</td>
<td>Baseline</td>
<td>Silver Fluoride (N = 37)</td>
<td>57.3 (26.7) [17, 99]</td>
<td>49.3 (19.3) [15, 84]</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>Silver Fluoride (N = 37)</td>
<td>28.2 (22.1) [2, 75]</td>
<td>52.1 (22.8) [16, 89]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>Silver Fluoride (N = 37)</td>
<td>-29.1 (27.5) [94, 10]</td>
<td>2.6 (15.3) [44, 32]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Silver Fluoride (N = 37)</td>
<td>21.5 (23.0) [1, 78]</td>
<td>49.9 (21.2) [9, 85]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>Silver Fluoride (N = 37)</td>
<td>-35.8 (27.7) [97, 12]</td>
<td>0.4 (16.2) [38, 33]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cusco</td>
<td>Baseline</td>
<td>Silver Fluoride (N = 26)</td>
<td>51.7 (20.5) [22, 92]</td>
<td>51.6 (22.4) [16, 99]</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>Silver Fluoride (N = 26)</td>
<td>45.2 (24.1) [11, 87]</td>
<td>50.6 (22.0) [15, 95]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>Silver Fluoride (N = 26)</td>
<td>-6.5 (13.1) [34, 22]</td>
<td>-1.0 (11.7) [37, 20]</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Silver Fluoride (N = 26)</td>
<td>28.3 (21.8) [2, 94]</td>
<td>46.1 (24.4) [3, 92]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>Silver Fluoride (N = 26)</td>
<td>-23.4 (21.0) [56, 24]</td>
<td>-5.5 (18.1) [77, 18]</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

*Two-sample t test (unequal variances).
Clinical Effectiveness

The average pain scores before and after treatment, by site, are given in Table 1. At the Lima site, the silver fluoride group had slightly higher baseline scores (average = 57.3) than the control (average = 49.3; \( P = 0.16 \)). At the Cusco site, the baseline scores were similar between the silver fluoride group (average = 51.7) and control (average = 51.6; \( P = 0.98 \)). The primary study endpoint was the change from baseline to 7 days. In Lima, the average change in pain score between baseline and day 7 for the silver fluoride group was -35.8 (SD = 27.7) mm vs. 0.4 (SD = 16.2) for the controls (\( P < 0.0001 \)). In Cusco, the average change in pain score between baseline and day 7 for the silver fluoride group was -23.4 (SD = 21.0) mm vs. -5.5 (SD = 18.1) mm (\( P = 0.0015 \)) for water.

Comparison of tooth sensitivity at 24 hrs and 7 days between study groups by analysis covariance, adjusted for the baseline sensitivity level, gave similar results. There was no significant three-way interaction among study site, time, and study group (GEE linear regression; \( P = 0.20 \)), but all two-way interactions were significant: study site by time (\( P = 0.043 \)), study site by study group (\( P = 0.0006 \)), and study group by time (\( P = 0.0076 \)). Hence, an analysis of time effect was done separately by study site. In Lima, there was no significant time-by-study-group interaction (\( P = 0.21 \)). The overall study group difference in tooth sensitivity (over both timepoints), adjusted for baseline sensitivity, was 29.9 (\( P < 0.001 \)). The overall difference in sensitivity between 24 hrs and 7 days was 4.5 (\( P = 0.014 \)). In Cusco, there was a significant study-group-by-time interaction (\( P = 0.015 \)), so the overall study group difference is not reported. The differences in sensitivity between 24 hrs and 7 days were 16.9 (\( P = 0.005 \)) for silver fluoride and 4.5 (\( P = 0.097 \)) in the control group, respectively.

Safety

The number and percent of participants with a erythema score of 2 for the gingival tissue of the tooth treated for each treatment condition by site and time are given in Table 2. Scores were low; no individual had score 3, severe erythema, either before or after the application of silver fluoride. There was no difference in the proportion of participants with erythema score >1 between the silver fluoride group and the placebo (Fisher’s Exact Test, \( P = 1.0 \)) at any time-point in the Lima population. There was a small but significant increase in the proportion of participants at the Cusco site who experienced an erythema score >1 at 24 hrs (\( P = 0.0076 \)). There was no difference in the proportion of participants with an erythema score >1 between the groups in Cusco after 7 days (\( P = 1.0 \)). No white or dark changes were noted in gingiva in any participant at any time in any condition at either site. An independent examiner, who was blind to treatment condition and time, examined the photographs and confirmed this lack of change.

The Gingival Index scores for each treatment condition and site are listed in Table 3. The mean (SD) Gingival Index scores for the mouth for treatment and control groups at baseline were: (Lima) silver fluoride, 0.29 (0.24), control 0.33 (0.35) (\( P = 0.59 \)); and (Cusco) silver fluoride, 0.47 (0.24), control 0.38 (0.27) (\( P = 0.19 \)). At 7 days, the mean (SD) changes in GI scores were: (Lima) silver fluoride, -0.02 (0.09), control 0.03 (0.13) (\( P = 0.076 \)); and (Cusco) silver fluoride, -0.16 (0.27), control -0.03 (0.09) (\( P = 0.023 \)). Similar results were observed after 24 hrs.

Photographs of the teeth suggest that the silver fluoride did not stain most exposed root surfaces (see Fig. 2 for an example). This result was found only when surfaces had untreated decay.

Table 2. Numbers and Percentages of Participants with Erythema Score of 2 by Study Site and Condition

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Time</th>
<th>Condition</th>
<th>n (%)</th>
<th>n (%)</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima</td>
<td>Baseline</td>
<td>Silver Fluoride (N = 37)</td>
<td>3 (8.1)</td>
<td>2 (5.9)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>Silver Fluoride (N = 37)</td>
<td>3 (8.1)</td>
<td>2 (5.9)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Silver Fluoride (N = 37)</td>
<td>3 (8.1)</td>
<td>1 (2.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cusco</td>
<td>Baseline</td>
<td>Silver Fluoride (N = 26)</td>
<td>6 (23.1)</td>
<td>7 (24.1)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>Silver Fluoride (N = 26)</td>
<td>10 (38.5)</td>
<td>2 (6.9)</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Silver Fluoride (N = 26)</td>
<td>3 (11.5)</td>
<td>3 (10.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sites combined</td>
<td>Baseline</td>
<td>Silver Fluoride (N = 63)</td>
<td>9 (14.3)</td>
<td>9 (14.3)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
<td>Silver Fluoride (N = 63)</td>
<td>13 (20.6)</td>
<td>4 (6.3)</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Silver Fluoride (N = 63)</td>
<td>6 (9.5)</td>
<td>4 (6.3)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Fisher’s exact test
DISCUSSION

In a population with teeth sensitive to air, this trial demonstrated that a topical solution of diammine silver fluoride was more effective than a placebo in reducing tooth pain. Reductions grew larger between 24 hrs and 7 days post-treatment. The study was conducted in two sites by different investigators to increase generalizability and had sufficient statistical power to detect clinically meaningful differences in pain. The study involved many more individuals than the typical study (Ritter et al., 2006).

The results, however, are consistent with those from similar studies of other desensitizers, such as self-administered 0.717% fluoride solution (Thrash et al., 1992) or fluoride varnish (Ritter et al., 2006). In the fluoride solution study, the authors concluded that two one-minute applications reduced sensitivity to cold. Participants in the varnish study experienced a pain reduction in response to ice, but not to air, at 2 wks. The current study reported significant pain reductions in response to air in 24 hrs that were maintained at 7 days. The magnitude of reduction was considerably greater than in the other studies. The current study did not use ice as a stimulus.

There were no unintended effects on the gingiva, and any inflammation resulting from the treatment was minor and transient. No staining of the gingival tissues was observed.

Staining of teeth was found only when surfaces had untreated decay. The staining of carious dentin can be minimized by the application of potassium iodide solution after treatment without reducing the effect (Knight et al., 2009). Staining of teeth was found only when surfaces had untreated decay. The staining of carious dentin can be minimized by the application of potassium iodide solution after treatment without reducing the effect (Knight et al., 2009).

Diammine silver fluoride has been shown to arrest caries in animal models (Tanzer et al., 2010) and to be more effective than sodium fluoride varnish in human trials (Chu et al., 2002; Llodra et al., 2005; Rosenblatt et al., 2009; Tan et al., 2010). It did not cause abscesses in teeth with open cavities that were treated. The mechanism of action for caries arrest may be antimicrobial (Knight et al., 2009). Studies have also shown that diammine silver fluoride is free of adverse effects (Chu et al., 2002; Llodra et al., 2005; Tan et al., 2010). This suggests that diammine fluoride may be particularly effective in individuals in whom sensitivity is associated with demineralization and caries.

**Figure 2.** Root caries at baseline (left panel), 24 hrs after treatment (middle panel), and 7 days after treatment with diammine silver fluoride (right panel).

### Table 3. Overall Gingival Index Score by Study Site and Condition

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Time</th>
<th>Condition</th>
<th>Mean (SD) [Range]</th>
<th>Mean (SD) [Range]</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima Silver Fluoride (N = 37)</td>
<td>Control (N = 34)</td>
<td>Baseline</td>
<td>0.29 (0.24) [0.0, 1.2]</td>
<td>0.33 (0.35) [0.0, 1.5]</td>
<td>0.59</td>
</tr>
<tr>
<td>Lima Silver Fluoride (N = 37)</td>
<td>Control (N = 34)</td>
<td>24 hrs</td>
<td>0.28 (0.24) [0.0, 1.2]</td>
<td>0.35 (0.36) [0.0, 1.7]</td>
<td></td>
</tr>
<tr>
<td>Lima Silver Fluoride (N = 37)</td>
<td>Control (N = 34)</td>
<td>Change from baseline</td>
<td>-0.01 (0.05) [0.2, 0.1]</td>
<td>0.02 (0.07) [0.2, 0.2]</td>
<td>0.076</td>
</tr>
<tr>
<td>Lima Silver Fluoride (N = 37)</td>
<td>Control (N = 34)</td>
<td>7 days</td>
<td>0.27 (0.23) [0.0, 1.2]</td>
<td>0.36 (0.39) [0.1, 1.8]</td>
<td></td>
</tr>
<tr>
<td>Lima Silver Fluoride (N = 37)</td>
<td>Control (N = 34)</td>
<td>Change from baseline</td>
<td>-0.02 (0.09) [0.2, 0.0]</td>
<td>0.03 (0.13) [0.5, 0.3]</td>
<td>0.076</td>
</tr>
<tr>
<td>Cusco Silver Fluoride (N = 26)</td>
<td>Control (N = 29)</td>
<td>Baseline</td>
<td>0.47 (0.24) [0.1, 0.9]</td>
<td>0.38 (0.27) [0.0, 1.2]</td>
<td>0.19</td>
</tr>
<tr>
<td>Cusco Silver Fluoride (N = 26)</td>
<td>Control (N = 29)</td>
<td>24 hrs</td>
<td>0.36 (0.21) [0.1, 0.8]</td>
<td>0.36 (0.24) [0.0, 1.2]</td>
<td></td>
</tr>
<tr>
<td>Cusco Silver Fluoride (N = 26)</td>
<td>Control (N = 29)</td>
<td>Change from baseline</td>
<td>-0.11 (0.16) [0.6, 0.1]</td>
<td>-0.02 (0.12) [-0.3, 0.3]</td>
<td>0.020</td>
</tr>
<tr>
<td>Cusco Silver Fluoride (N = 26)</td>
<td>Control (N = 29)</td>
<td>7 days</td>
<td>0.31 (0.19) [0.0, 0.8]</td>
<td>0.35 (0.26) [0.1, 1.2]</td>
<td></td>
</tr>
<tr>
<td>Cusco Silver Fluoride (N = 26)</td>
<td>Control (N = 29)</td>
<td>Change from baseline</td>
<td>-0.16 (0.27) [0.8, 0.7]</td>
<td>-0.03 (0.09) [-0.3, 0.2]</td>
<td>0.023</td>
</tr>
<tr>
<td>Sites Combined Silver Fluoride (N = 63)</td>
<td>Control (N = 63)</td>
<td>Baseline</td>
<td>0.36 (0.26) [0.0, 1.2]</td>
<td>0.35 (0.32) [0.0, 1.5]</td>
<td>0.72</td>
</tr>
<tr>
<td>Sites Combined Silver Fluoride (N = 63)</td>
<td>Control (N = 63)</td>
<td>24 hrs</td>
<td>0.31 (0.23) [0.0, 1.2]</td>
<td>0.35 (0.31) [0.0, 1.7]</td>
<td></td>
</tr>
<tr>
<td>Sites Combined Silver Fluoride (N = 63)</td>
<td>Control (N = 63)</td>
<td>Change from baseline</td>
<td>-0.05 (0.12) [0.6, 0.1]</td>
<td>0.00 (0.10) [-0.3, 0.3]</td>
<td>0.0023</td>
</tr>
<tr>
<td>Sites Combined Silver Fluoride (N = 63)</td>
<td>Control (N = 63)</td>
<td>7 days</td>
<td>0.28 (0.22) [0.0, 1.2]</td>
<td>0.35 (0.33) [0.1, 1.8]</td>
<td></td>
</tr>
<tr>
<td>Sites Combined Silver Fluoride (N = 63)</td>
<td>Control (N = 63)</td>
<td>Change from baseline</td>
<td>-0.08 (0.20) [0.8, 0.7]</td>
<td>0.00 (0.12) [-0.5, 0.3]</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

*Two-sample test (unequal variances).

**Analysis of covariance, adjusted for study site, with heteroscedasticity-consistent standard errors.
Diammine silver fluoride has been demonstrated to be a clinically effective and safe tooth desensitizer after 24 hrs and 7 days. Clinical trials are warranted to examine effectiveness over a longer period of time and in comparison with other agents.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of Silvia Navarro in recruitment of participants. ADP Silver Dental Arrest, LLC, Redmond, OR, USA, was the study sponsor.

REFERENCES


Since its approval in Japan more than 80 years ago, more than 2 million containers have been sold. The silver acts as an antimicrobial, the fluoride promotes remineralization and the ammonia stabilizes high concentrations in solution. Because silver diamine fluoride is new to American dentistry and dental education, there is a need for a standardized guideline, protocol and consent. The University of California, San Francisco, School of Dentistry paradigm shift committee assembled a subcommittee with the following goals:

- Use available evidence to develop a list of clinical indications.
- Define a protocol that maximized safety and efficacy and minimized inadvertent staining of clinical facilities.

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For more information, visit https://www.elevateoralcare.com.

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Build an informed consent document at the eighth-grade reading level.

We conducted a systematic review, inquired of authors of published clinical and in vitro studies about details and considerations in their protocols and consulted experts in cariology and materials chemistry where evidence was lacking. The work of this committee resulted in the adoption of silver diamine fluoride use in the UCSF student clinics.

**Methods**

A literature review was designed by a medical librarian to search PubMed and the International Association of Dental Research abstract archive with the following search terms: “33040-28-7” OR “1Z00ZK3E66” OR “silver diamine fluoride” OR “silver fluoride” OR “silver diamine fluoride” OR “diammine silver fluoride” OR “ammonical silver fluoride” OR “ammoniacal silver fluoride”. Differences in nomenclature have led to confusion around this material. Another review was completed with the terms “dental” OR “caries” AND “silver nitrate” AND “clinical.”

**Material**

Silver diamine fluoride (38% w/v Ag(NH$_3$)$_2$F, 30% w/w) is a colorless topical agent comprised of 24.4-28.8% (w/v) silver and 5.0-5.9% fluoride at pH 10, and marketed as Advantage Arrest by Elevate Oral Care LLC (West Palm Beach, Fla.). Other companies may market silver diamine fluoride in the future following determination of substantial equivalence and FDA clearance.

**Mechanisms**

Silver diamine fluoride is used for caries arrest and treatment of dentin hypersensitivity. In the treatment of exposed sensitive dentin surfaces, topical application results in the development of a squamous layer on the exposed dentin, partially plugging the dentinal tubules. High concentration aqueous silver has been long known to form this protective layer. Decreased sensitivity in treated patients is consistent with the hydrodynamic theory of dentin hypersensitivity.

Dental caries is a complex progression involving dietary sugars, bacterial metabolism, demineralization and organic degradation. The collagenous organic matrix is exposed once a dentin surface is demineralized and destroyed by native and bacterial proteases to enable a lesion to enlarge. Upon application of silver diamine fluoride to a decayed surface, the squamous layer of silver protein conjugates forms, increasing resistance to acid dissolution and enzymatic digestion. Hydroxyapatite and fluorapatite form on the exposed organic matrix, along with the presence of silver chloride and metallic silver. The treated lesion increases in mineral density and hardness while the lesion depth decreases. Meanwhile, silver diamine fluoride specifically inhibits the proteins that break down the exposed dentin organic matrix: matrix metalloproteinases, cathepsins and bacterial collagenases. Silver ions act directly against bacteria in lesions by breaking membranes, denaturing proteins and inhibiting DNA replication. Ionic silver deactivates nearly any macromolecule. Silver diamine fluoride outperforms other anticaries medicaments in killing cariogenic bacteria in dentinal tubules.

Silver and fluoride ions penetrate ~25 microns into enamel and 50-200 microns into dentin. Fluoride promotes remineralization, and silver is available for antimicrobial action upon release by re-acidification. Silver diamine fluoride arrested lesions are 150 microns thick.

Artificial lesions treated with silver diamine fluoride are resistant to biofilm formation and further cavity formation, presumably due to remnant ionic silver. More silver and fluoride is deposited in demineralized than nondemineralized dentin. Correspondingly, treated demineralized dentin is more resistant to caries bacteria than treated sound dentin. When bacteria killed by silver ions are added to living bacteria, the silver is re-activated so that effectively the dead bacteria kill the living bacteria in a “zombie effect.” This reservoir effect helps explain why silver deposited on bacteria and dentin proteins within a cavity has sustained antimicrobial effects.

**Clinical Evidence**

**Silver Nitrate Plus Fluoride Varnish**

Before the FDA cleared silver diamine fluoride, some U.S. dentists sequentially applied silver nitrate then fluoride varnish to dentinal decay as the only available noninvasive option for caries treatment. Duffin rediscovered silver nitrate from the early literature, which had been lost...
to modern cariology. Surprisingly, there is no mention of silver nitrate in either of the American Dental Association Council on Scientific Affairs reports on Nonfluoride Caries-Preventive Agents or Managing Xerostomia and Salivary Gland Hypofunction, and it is not part of standard dental school curricula. Case series of carious lesions arrested by silver nitrate date to the 1800s. For example, in 1891, 87 of 142 treated lesions were arrested. Percy Howe, DDS, then director of the Forsyth Institute in Boston, added ammonia to silver nitrate, making it more stable and effective as an antimicrobial for application to any infected tooth structure from early cavitated lesions to infected root canals. Duffin added the application of fluoride varnish following silver nitrate, simulating silver diamine fluoride. While his clinic doubled in patients, cases needing general anesthesia disappeared. His review of randomly selected charts showed only seven of 578 treated lesions progressed within two and a half years to the point that extractions were needed. Thus, with the exception of Duffin’s and one other report, attention to silver nitrate largely disappeared by the 1950s. The lore is that use and teaching of this intervention were lost with the introduction of effective local anesthetic to enable painless restorations and fluoride for caries prevention. Because no high-quality clinical trials have been performed, we did not include the silver nitrate plus fluoride varnish regimen in our recommendation.

Silver Diamine Fluoride

We found nine published randomized clinical trials evaluating silver diamine fluoride for caries arrest and/or prevention of at least one year in duration. These studies each involved hundreds of children aged 3 to 9 or adults aged 60 to 89 (FIGURES 1 and 2). Most participants had low (< 0.3 ppm) fluoride in the environmental water and reported using fluoride toothpaste (e.g., 73 percent). Silver diamine fluoride was applied with cotton isolation. Lesions were detected with mirror and explorer only. All studies were registered and met the Consolidated Standards of Reporting Trials requirements. Clinical cases and studies not meeting these criteria can be found elsewhere.

Caries arrest increased dramatically after reapplication from one year posttreatment to one and a half years, and increasingly to two to three years (FIGURE 1). Single application without repeat lost effect over time in the elderly. Twelve per year application resulted in more arrest than once per year. Twelve percent silver diamine fluoride was markedly less effective. Darkening of the entire lesion indicated success at follow-up and is suggested to facilitate diagnosis of caries arrest status by nondentists. A longitudinal study reported that color activation of silver diamine fluoride with 10% stannous fluoride resulted in less first molar caries. Tea extract was used in one group to activate color change for improved follow-up diagnosis; no differences in arrest were seen. Indeed, when stannous fluoride was used to activate color change, a break in the black color within a lesion at six months was highly sensitive and specific for active caries.

Silver diamine fluoride greatly outperformed fluoride varnish for caries arrest and was equivalent or better than glass ionomer cement (GIC) (FIGURE 1). The addition of semiannual intensive oral health education with the application of silver diamine fluoride in the elderly increased the arrest of root caries (FIGURE 1).

Caries Prevention

When silver diamine fluoride was applied only to carious lesions, impressive prevention was seen for other tooth surfaces. Fluoride-releasing GIC can have this effect but it is limited to surfaces adjacent to the treated surface and of short duration. Direct application to healthy surfaces in children also helps prevent caries (FIGURE 2). Two studies show great difference in the level of prevention in the elderly; the difference is hard to reconcile. As seen for arrest, prevention is less after one year without repeat application. Annual application of silver diamine fluoride prevented many more carious lesions than four-times-per-year fluoride varnish in both children and the elderly. Prevention was roughly equivalent to twice-per-year varnish in one study (FIGURE 2). The addition of semiannual intensive oral health education in a study of the elderly increased prevention. Although many fell out, GIC or resin sealants outperformed silver diamine fluoride in preventing caries in the first molars of children, though the cost was ~20 times more.
Ongoing Trials

Unpublished reports of clinical studies unanimously confirm better caries arrest and/or prevention by silver diamine fluoride over control or other materials. A one-year report of a study of the elderly demonstrated that the addition of a saturated solution of potassium iodide (SSKI) to decrease discoloration did not significantly alter caries arrest or prevention. This was confirmed in the two-year examinations (personal communication, Edward Lo). A one-year report of a study in children showed that the application once per week for three consecutive weeks, once per year, was more effective than that of single annual application. Other studies have recently begun to evaluate the ability of silver diamine fluoride to arrest interproximal carious lesions, to compare the relative efficacy of silver diamine fluoride to the combination of silver nitrate plus fluoride varnish and to compare the effects on populations with or without access to fluoridated water. Final reports from these studies will follow in the coming years.

Recommendations From the Literature on Clinical Efficacy

These studies show that 38% silver diamine fluoride is effective and efficient in arresting and preventing carious lesions. Application only to lesions appears to be similarly effective in preventing cavities in other teeth and surfaces as applying directly. Single application appears insufficient for sustained effects, while annual re-application results in remarkable success, and even greater effects with semi-annual application. From these data, we recommend twice-per-year application, only to carious lesions without excavation, for at least the first two years.

For any patient with active caries, we recommend considering replacement of fluoride varnish as the primary means to prevent new lesions, with application of silver diamine fluoride to the active lesions only. For patients without access to both sealants and monitoring, silver diamine fluoride is the agent of choice for prevention of caries in permanent molars — particularly as there is no margin to leak and thereby facilitate deep caries and it does not stain sound enamel.
Maximum Dose and Safety Margin

The margin of safety for dosing is of paramount concern. In gaining clearance from the FDA, female and male rat and mouse studies were conducted to determine the lethal dose (LD50) of silver diamine fluoride by oral and subcutaneous administration. Average LD50 by oral administration was 520 mg/kg and by subcutaneous administration was 380 mg/kg. The subcutaneous route is taken here as a worst-case scenario. One drop (25 μL) is ample material to treat five teeth and contains 9.5 mg silver diamine fluoride. Assuming the smallest child with caries would be in the range of 10 kg, the dose would be 0.95 mg/kg child. Thus, the relative safety margin of using an entire drop on a 10 kg child is 380 mg/kg LD50/0.95 mg/kg dose = four-hundredfold safety margin. The actual dose is likely to be much smaller, for example 2.37 mg total for three teeth was the largest dose measured in six patients.\(^4^6\) The most frequent application monitored in a clinical trial was weekly for three weeks, annually.\(^4^3\) Thus, we set our recommended limit as one drop (25 μL) per 10 kg per treatment visit, with weekly intervals at most. This dose is commensurate with the Environmental Protection Agency’s (EPA) allowable short-term exposure of 1.142 mg silver per liter of drinking water for one to 10 days (Agency for Toxic Substances and Disease Registry, ATSDR, 1990).

Cumulative exposure from lower-level acute or chronic silver intake has no real physiologic disease importance, but the bluing of skin in argyria should obviously be avoided. The EPA set the lifetime exposure conservatively at 1 gm to safely avoid argyria. The highest applied dose for three teeth measured in the pharmacokinetic study, 2.37 mg, would enable > 400 applications.\(^4^6\) Silver diamine fluoride is a safe and effective agent for the prevention and arrest of dental caries.

Longer studies are needed to determine whether caries arrest and prevention can be maintained with decreased application after two to three years, and whether more frequent use would enhance efficacy. Traditional or nontraditional restorative approaches, such as the atraumatic restorative technique (ART)\(^4^4\) and Hall crowns,\(^4^5\) should be performed as dictated by the response of the patient, disease progression and the nature of individual lesions.
nitr...tions. Meanwhile, gingival index improved slightly in silver diamine fluoride treated patients. Nonetheless, gingival contact should be minimized. In our experience, it has been adequate to coat the nearby gingiva with petroleum jelly, use the smallest available microspounge and dab the side of the dappen dish to remove excess liquid before application.

Concerns for fluoride safety are most relevant to chronic exposure, whereas this is an acute exposure. Chronically high systemic fluoride results in dental fluorosis. The ubiquitous use of fluoride-based gas in general anesthetics has shown that the first acute response is transient renal holding, and is rare. Concerns have been raised about poorly controlled silver diamine fluoride concentrations and fluorosis appearing in treated rats. However, silver and fluoride levels are closely monitored for the U.S. product, and the Health Department of Western Australia conducted a study that found no evidence of fluorosis resulting from long-term proper use of silver diamine fluoride. Therefore, we have concluded that the development of fluorosis after application of the U.S.-approved product is not a clinically significant risk.

Silver allergy is a contraindication. Relative contraindications include any significant desquamative gingivitis or mucositis that disrupts the protective barrier formed by stratified squamous epithelium. Increased absorption and pain would be expected with contact. Heightened caution and use of a protective gingival coating may suffice.

A saturated solution of potassium iodide (SSKI) is contraindicated in pregnant women and during the first six months of breastfeeding because of the concern of overloading the developing thyroid with iodide; thyroid specialists suggested a pregnancy test prior to use in women of childbearing age uncertain of their status.

Nonmedical Side Effects

Silver diamine fluoride darkens carious lesions. At least for children, many parents have seen the color changes as a positive indication that the treatment was effective. Application of an SSKI immediately following silver diamine fluoride treatment is thought to decrease staining (patent US6461161). This is an off-label use; potassium iodide is approved as an over-the-counter drug to facilitate mucus release to breathe more easily with chronic lung problems and to protect the thyroid from radioactive iodine in radiation emergencies. In our clinical experience, SSKI helps but does not dramatically effect stain; arrested lesions normally darken. Most stain remains at the dentin-enamel or cementum-enamel junction. However, SSKI maintains resistance to biofilm formation or activity in laboratory studies. Also, SSKI maintained caries arrest efficacy in the early results of an ongoing clinical trial. Meanwhile, silver diamine fluoride-treated lesions can also be covered with GIC or composite (see below for discussion on bonding).

Patients note a transient metallic or bitter taste. In our experience, with judicious use, the taste and texture.
response is more favorable than the response to fluoride varnish.

Even a small amount of silver diamine fluoride can cause a “temporary tattoo” to the skin (on the patient or provider), like a silver nitrate stain or henna tattoo, and does no harm. Stain on the skin resolves with the natural exfoliation of skin in two to 14 days. Universal precautions prevent most exposures. Long-term mucosal stain, local argyria akin to an amalgam tattoo, has been observed when applying silver nitrate to intraoral wounds; we anticipate similar stains with submucosal exposure to silver diamine fluoride.

Silver diamine fluoride stains clinic surfaces and clothes. The stain does not come out once it sets. Spills should be cleaned up immediately with copious water, ethanol or bleach. High pH solvents such as ammonia may be more successful. Secondary containers and plastic liners for surfaces are adequate preventives.

Effects on Bonding

Using a contemporary bonding system, silver diamine fluoride had no effect on composite bonding to noncarious dentin using either self-etch or full-etch systems. In one study, simply rinsing after silver diamine fluoride application avoided a 50 percent decrease in bond strength for GIC. In another study, increased dentin bond strength to GIC was observed. Silver diamine fluoride decreased dentin bonding strength of resin-based crown cement by approximately one-third. Thus, rinsing will suffice for direct restorations, while excavation of the silver diamine fluoride-treated superficial dentin is appropriate for cementing crowns.

Indications

Countless patients would benefit from conservative treatment of nonsymptomatic active carious lesions. We discuss the following indications.

First, extreme caries risk is defined as patients with salivary dysfunction, usually secondary to cancer treatment, Sjogren’s syndrome, polypharmacy, aging or methamphetamine abuse. For these patients, frequent prevention visits and traditional restorations fail to stop disease progression. Similar disease recurrence occurs in severe early childhood caries.

Second, some patients cannot tolerate standard treatment for medical or psychological reasons. These include the precooperative child, the frail elderly, those with severe cognitive or physical disabilities and those with dental phobias. Various forms of immunocompromise mean that these same patients have a much higher risk of systemic infection arising from untreated dental caries. Many only receive restorative care with general anesthesia or sedation and others are not good candidates for general anesthesia due to frailty or another medical complexity.

The Centers for Disease Control and Prevention (CDC) estimates 1.4 million people in the U.S. live in nursing homes and 1.2 million live in hospice. These individuals tend to have medical, behavioral, physical and financial limitations that beg a reasonable option. Third, some patients have more lesions than can be treated in one visit, such that new lesions arise or existing lesions become symptomatic while awaiting completion of treatment. This is particularly relevant to the dental school setting where treatment is slow. American dentistry has been desperately lacking an efficient instrument to be used at the diagnostic visit to provide a step toward controlling the disease.

Fourth, some lesions are just difficult to treat. Recurrent caries at a crown margin, root caries in a furcation or the occlusal of a partially erupted wisdom tooth pose a challenge to access, isolation and cleansability necessary for restorative success.

Following the above considerations, we developed four indications for treatment of dental caries with silver diamine fluoride:

1. Extreme caries risk (xerostomia or severe early childhood caries).
2. Treatment challenged by behavioral or medical management.
3. Patients with carious lesions that may not all be treated in one visit.
4. Difficult to treat dental carious lesions.

Finally, these indications are for our school clinics. They do not address access to care. The U.S. Department of Health and Human Services estimates 108 million Americans are without dental insurance, and there are 4,230 shortage areas with 49 million people without access to a dental health professional. Unlike fillings, failure of silver diamine fluoride treatment does not appear to create an environment that promotes caries, and thus needs to be monitored. Thus, a final important indication is:

5. Patients without access to dental care.

Clinical Application

We considered practical strategies to maximize safety and effectiveness in the design of a clinical protocol for the UCSF dental clinics (FIGURE 3).

The key factor is repeat application...
over multiple years. We believe that dryness of the lesion during application is also important. Isolation with gauze and/or cotton rolls is sufficient, while air drying prior to application is thought to improve effectiveness. Allowing one to three minutes for the silver diamine fluoride to soak into and react with a lesion is thought to effect success.

Allowing only a few seconds to soak in due to the cooperation limits of very young patients commonly results in arrest. Application time in clinical studies does not correlate to outcome. However, our committee decided to be cautious in our recommendations for initial use. Longer absorption time also decreases concerns about removing silver diamine fluoride with a posttreatment rinse. Removing any excess material with the same cotton used to isolate is routine to minimize systemic absorption.

Many clinicians place silver diamine fluoride at the diagnostic visit, then at one and/or three-month follow ups, then at semiannual recall visits (six, 12, 18, 24 months). Whether application needs

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**Silver Diamine Fluoride (SDF)**

**UCSF Protocol for Arresting Dental Carious Lesions or Treating Tooth Sensitivity**

**Material:** Advantage Silver Arrest (38% SDF, purified water) from Elevate Oral Care.

Shelf life: three years unopened. Do not refrigerate. Avoid freezing or extreme heat.

**Indications:**
1. Extreme caries risk (xerostomia or severe early childhood caries).
2. Treatment challenged by behavioral or medical management.
3. Patients with carious lesions that may not all be treated in one visit.
4. Difficult to treat dental carious lesions.
5. Patients without access to dental care.

**Maximum dose:** 25 μL (1 drop) / 10kg per treatment visit.

**SDF Contraindication:** Silver allergy.

**SDF Relative Contraindications:** Ulcerative gingivitis, stomatitis.

**SSKI Contraindications:** Pregnancy, breastfeeding.

**Considerations:**
- Decayed dentin will darken as the caries lesions arrest. Most will be dark brown or black.
- SDF can stain the skin, which will clear in two to three weeks without treatment.
- SDF can permanently stain operatory surfaces and clothes.
- A control restoration (e.g., GI via ART or other material) may be considered after SDF treatment.
- Saturated solution of potassium iodide (SSKI, Lugol’s Solution, various sources) can be used after SDF to decrease color changes.
- Re-application is usually recommended, biannually until the cavity is restored or arrested or the tooth exfoliates.

**Procedure:**
1. Plastic-lined cover for counter, plastic-lined bib for patient.
2. Standard personal protective equipment (PPE) for provider and patient.
3. One drop of SDF into the deep end of a plastic dappen dish (also obtain one drop of SSKI in a separate dappen dish if selected).
4. Remove bulk saliva with saliva ejector.
5. Isolate tongue and cheek from affected teeth with 2-inch by 2-inch gauze or cotton rolls.
6. If near the gingiva, consider applying petroleum jelly with a cotton applicator for safety.
7. Dry affected tooth surfaces with triple syringe or if not feasible dry with cotton.
8. Bend microsponge, immerse into SDF, remove excess on side of dappen dish.
9. Apply directly onto the affected tooth surface(s) with microspponge.
10. Allow SDF to absorb for up to one minute if reasonable, then remove excess with gauze or cotton roll.
    (If using SSKI, apply with a different microspponge. Repeat one to three times until no further white precipitates are observed. Wait five to 10 seconds between applications. Remove excess with cotton.)
11. Rinse with water.
12. Place gloves, cotton and microbrushes into plastic waste bags.

**FIGURE 3.** Clinical protocol for the UCSF dental clinics.
to continue after two or three years to maintain caries arrest is not known. Another approach is simply to substitute silver diamine fluoride for any application of fluoride varnish to a patient with untreated carious lesions. Increased frequency with higher disease burden follows the caries management by risk assessment (CAMBRA) principles. It is relevant to take photographs to track lesions over time.

Efforts to improve the penetration of silver diamine fluoride into affected dentin by chemical cavity preparation have not been studied but are being explored clinically. Pretreatment with ethylenediaminetetraacetic acid (EDTA) to remove superficial hydroxyapatite in affected dentin may open the dentinal tubules to further silver diamine fluoride penetration. Pretreatment with hypochlorite (bleach) may help breakdown bacteria and exposed dentin proteins, but this may be redundant to the action of the silver. Hypochlorite to decrease discoloration after silver diamine fluoride treatment is not recommended, as the color comes from silver that cannot be broken down like organic chromophores and might break down dentin proteins stabilized against the effects of bacteria and acid by interactions with silver.

Experience with the combination of silver nitrate plus fluoride varnish (see above) has many practitioners asking about a topical varnish after silver diamine fluoride placement to prevent silver diamine fluoride taste and keep the silver diamine fluoride in the lesion. We see no evidence that varnish would help achieve either goal. Varnish does not seal. Rather, allowing more time for residence and diffusion of silver diamine fluoride to react with and dry into the lesion is more likely to improve effectiveness. Also, in our experience, silver diamine fluoride results in less aversive taste and texture responses than to fluoride varnish.

In our experience, silver diamine fluoride results in less aversive taste and texture responses than to fluoride varnish.

Decreased darkening of lesions in the esthetic zone improves acceptance. SSKI is an option if the patient is not pregnant, though significant darkening should still be expected. SSKI and silver diamine fluoride are not to be combined prior to application — SSKI can be placed after drying the silver diamine fluoride-treated tooth. Silver diamine fluoride does not prevent restoration of a lesion, thus it does not prevent esthetic options. While silver diamine fluoride has been shown to be more effective than ART or interim restorative treatment (IRT), the two are compatible and can be combined across one or more visits.

The California Business and Professions Code permits dental hygienists and assistants to apply silver diamine fluoride for the control of caries because they are topical fluorides (Section 1910.(b)). Physicians, nurses and their assistants are permitted to apply fluorides in California and in many other states and federal programs. The recent decision of the Oregon Dental Board to allow dental hygienists and assistants to place silver diamine fluoride under existing rules for topical fluoride medicaments sets a precedent. Dental hygienists and assistants in Oregon were barred from providing silver nitrate in a previous decision. All providers need to be trained. Applications should be tracked if applied to the same patient by multiple clinics.

A new code, D1354, for “interim caries arresting medication application” was approved by the Code on Dental Procedures and Nomenclature (CDT) Code Maintenance Commission for 2016. The code definition is “Conservative treatment of an active, nonsymptomatic carious lesion by topical application of a caries arresting or inhibiting medicament and without mechanical removal of sound tooth structure.” The CDT Code is the U.S. HIPAA standard code set and is required for billing. The Commission includes representatives from the major insurers, Medicaid, ADA, AGD and specialty organizations. Insurers are in the process of evaluating coverage for this treatment.

Silver diamine fluoride is cleared by the FDA for marketing as a Class II medical device to treat tooth sensitivity. We are discussing off-label use as a drug to treat and prevent dental caries. This is a parallel situation to fluoride varnish, which has the same device clearance but is ubiquitously used off label by dentists and physicians as a drug to prevent caries. The same public health dentists who achieved the FDA device clearance are now applying for a dental caries indication. However, this is a more complicated process, normally only carried out by large pharmaceutical companies, and is likely to take longer.

Because silver diamine fluoride is new in the U.S., it is important to communicate effectively. In the UCSF clinics, we are using a special consent form (FIGURE 4) as a way to inform patients, parents and caregivers, and
to standardize procedures because we have so many inexperienced student clinicians. All practices have established procedures for consent and an extra form may not be needed in the community. The normal elements of informed consent apply. We sought to ensure awareness of the expected change in color of the dentin as the decay arrests, likelihood of reapplication and contraindications in the presence of silver allergy and stomatitis. Note the importance of distinguishing between allergy to nickel and other trace metals rather than silver allergy, which is rare. We used readability measurements to guide intelligibility and included a progressively discoloring lesion to show stain of a lesion but not healthy enamel.

UCSF Dental Center Informed Consent for Silver Diamine Fluoride

Facts for consideration:

- Silver diamine fluoride (SDF) is an antibiotic liquid. We use SDF on cavities to help stop tooth decay. We also use it to treat tooth sensitivity. SDF application every six to 12 months is necessary.
- The procedure: 1. Dry the affected area. 2. Place a small amount of SDF on the affected area. 3. Allow SDF to dry for one minute. 4. Rinse.
- Treatment with SDF does not eliminate the need for dental fillings or crowns to repair function or esthetics. Additional procedures will incur a separate fee.
- I should not be treated with SDF if: 1. I am allergic to silver. 2. There are painful sores or raw areas on my gums [i.e., ulcerative gingivitis] or anywhere in my mouth [i.e., stomatitis].

Benefits of receiving SDF:

- SDF can help stop tooth decay.
- SDF can help relieve sensitivity.

Risks related to SDF include, but are not limited to:

- The affected area will stain black permanently. Healthy tooth structure will not stain. Stained tooth structure can be replaced with a filling or a crown.
- Tooth-colored fillings and crowns may discolor if SDF is applied to them. Color changes on the surface can normally be polished off. The edge between a tooth and filling may keep the color.
- If accidentally applied to the skin or gums, a brown or white stain may appear that causes no harm, cannot be washed off and will disappear in one to three weeks.
- You may notice a metallic taste. This will go away rapidly.
- If tooth decay is not arrested, the decay will progress. In that case the tooth will require further treatment, such as repeat SDF, a filling or crown, root canal treatment or extraction.
- These side effects may not include all of the possible situations reported by the manufacturer. If you notice other effects, please contact your dental provider.
- Every reasonable effort will be made to ensure the success of SDF treatment. There is a risk that the procedure will not stop the decay and no guarantee of success is granted or implied.

Alternatives to SDF, not limited to the following:

- No treatment, which may lead to continued deterioration of tooth structures and cosmetic appearance. Symptoms may increase in severity.
- Depending on the location and extent of the tooth decay, other treatment may include placement of fluoride varnish, a filling or crown, extraction or referral for advanced treatment modalities.

I CERTIFY THAT I HAVE READ AND FULLY UNDERSTAND THIS DOCUMENT AND ALL MY QUESTIONS WERE ANSWERED:

________________________________________ (signature of patient) ________________ (date)

________________________________________ (signature of witness) ________________ (date)
Conclusion

Silver diamine fluoride is a safe, effective treatment for dental caries across the age spectrum. At UCSF, it is indicated for patients with extreme caries risk, those who cannot tolerate conventional care, patients who must be stabilized so they can be restored over time, patients who are medically compromised or too frail to be treated conventionally and those in disparity populations with little access to care.

Application twice per year outperforms all minimally invasive options including the atraumatic restorative technique — with which it is compatible but 20 times less expensive. It approaches the success of dental fillings after two or more years, and again, prevents future caries — while fillings do not. Silver diamine fluoride is more effective as a primary preventive than any other available material, with the exception of dental sealants, which are > 10 times more expensive and need to be monitored.

Saliva may play a role in caries arrest by silver diamine fluoride. Lower rates of arrest are seen in geriatric patients. The elderly tend to have less abundant and less functional saliva, which generally explains their higher caries rate. In pediatric patients, higher rates of arrest are noted for buccal or lingual smooth surfaces and anterior teeth. These surfaces bathe more directly in saliva than others. It is surprising that silver chloride is the main precipitant in treated dentin, as chloride is not a common component of dentin or silver diamine fluoride, so may come from the saliva.

Traditional approaches often provide only temporary benefit, given the highest rates of recurrent caries are in patients with the worst disease burden. The advent of a treatment for nonsymptomatic caries not requiring general anesthesia or sedation addresses long-standing concerns about the expense, danger and practical complexity of these services.

Experience suggests that dryness prior to application enhances effectiveness. Good patient management is still profoundly relevant to the very young and otherwise challenged patients, though this one-minute intervention is more tolerable than other options. Silver diamine fluoride can readily replace fluoride varnish for the prevention of caries in patients who have active caries. This is a powerful new tool in the fight against dental caries, particularly suited for those who suffer most from this disease.

Clinical evidence supports continued application one to two times per year until the tooth is restored or exfoliates, and otherwise perhaps indefinitely. Some treated lesions keep growing, particularly those in the inner third of the dentin. It is unclear what will happen if treatment is stopped after two to three years and research is needed.

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CLINICAL USE OF SILVER DIAMINE FLUORIDE IN DENTAL TREATMENT

FEBRUARY 2016
Decisions in Dentistry article on the use of Silver Diamine Fluoride in adult patients.
Dr. John Featherstone, Dean of the University of California San Francisco School of Dentistry and Dr Jeremy Horst, DDS, PhD.

KEY TAKEAWAYS
• Cleared by the U.S. Food and Drug Administration for treating dentinal hypersensitivity, in off-label use silver diamine fluoride can be used to prevent and arrest caries.
• The agent acts as an antimicrobial that remains active well after application. It also promotes remineralization and resistance to demineralization in enamel and dentin.
• In order to effectively implement treatment, clinicians should know the indications and contraindications, and gain informed consent for use.
• Dentists and (if allowed by state practice acts) dental auxiliaries who apply this agent must understand precautions for handling silver diamine fluoride.
• Repeat application completely stops many, but not all lesions. Research is needed to determine why some caries are not arrested.

Please use the link below to access the full article.

Limited evidence suggesting silver diamine fluoride may arrest dental caries in children


Linda L. Cheng, DDS, FAGD, ABGD

Systematic review conclusion. The authors of this systematic review (SR) suggest that silver diamine fluoride (SDF), commonly used at high concentrations (38%, 44,800 parts per million fluoride), may be effective in arresting active dental caries in the primary teeth of children; however, the appropriate dosing and application strategies for optimal caries control are still unknown.

Critical summary assessment. This SR of 19 prospective clinical studies of SDF treatment in children with or without control groups included trials with significant heterogeneity and various levels of risk of bias, with studies conducted after year 2000 generally having much lower risk. The meta-analysis consisted of 8 studies regarding 38% SDF applied to primary teeth, of which only 5 studies had control groups.

Evidence quality rating. Limited.

Clinical question. Does SDF arrest dental caries in children?

Review methods. The authors searched 7 databases in various languages including English, Chinese, Japanese, Portuguese, and Spanish with no time restrictions. The last search was conducted at the end of March 2016. They also manually searched the bibliographies of all potentially eligible studies to identify any other relevant articles. Two of the authors screened titles and abstracts and then retrieved the full texts. They included prospective clinical studies that investigated the caries-arresting effect of SDF treatment with or without control groups. They excluded literature reviews, case reports, laboratory studies, clinical trials that did not investigate caries arrest in children, and clinical treatment guidelines. Two of the authors independently reviewed and extracted the data. A third author resolved disagreements through discussions. The risk of bias for each included study was assessed according to 6 aspects: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The effect measure or outcome assessed was the percentage of dental caries that were arrested after treatment with SDF, which was either reported in the retrieved studies, or calculated from the number of teeth or tooth surfaces with active caries noted at baseline, compared with the number found to be arrested on follow-up if the data were available in the study. The authors conducted the SR and meta-analysis according to accepted guidelines.

Main results. The authors included a total of 19 clinical trials. Sixteen of the studies were regarding primary teeth; 3 were regarding permanent teeth. The authors noted that 14 studies used 38% SDF, 3 used 30% SDF, and 2 used 10% SDF. The authors included 8 studies on the application of 38% SDF in primary teeth in the meta-analysis, of which only 5 studies had control groups. Some of the other studies that reported 38% SDF as having a higher caries-arresting effect than no treatment did not provide specific data in the original reports and were thus not part of the meta-analysis. Their meta-analysis reported the caries-arresting rate to be 86% (95% confidence interval [CI], 47-98%; P = .06) at 6 months, 81% (95% CI, 59-93%; P = .01) at 12 months, 78% (95% CI, 70-85%; P < .001) at 18 months, 65% (95% CI, 35-86%; P = .32) at 24 months, and 71% (95% CI, 56-83%; P = .01) at or beyond 30 months. The overall proportion of primary teeth or tooth surfaces with active caries arrested after being treated with 38% SDF was calculated to be 81% (95% CI, 68-89%; P < .001).
Conclusions. Within the limitations of the available evidence and the limitations of the meta-analysis (as conducted on studies of which not all had a control group), the authors suggested that SDF, commonly used at high concentrations (38%, 44,800 ppm fluoride), may be effective in arresting caries in primary teeth among children. There was no consensus regarding the number and frequency of applications of SDF use to arrest caries.

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**COMMENTARY**

**Importance and context.** Early childhood caries (ECC) is defined as the presence of 1 or more decayed, missing due to caries, or filled tooth surfaces in a primary tooth in a child aged 71 months or younger. The prevalence of ECC is high, with studies reporting dental caries among 50% of children aged between 5 and 9 years in the United States and 47% of children aged between 25 and 30 months in Southeast Asia. Conventional restorative treatment for ECC may not always be affordable or available and relies on the cooperation of the child for successful treatment. SDF may be a potential cost-beneficial and cost-effective alternative to restorative treatment for managing ECC in children. It has also been reported to be painless and simple to use for young children or patients with special needs with low risk of experiencing cross infection. The caries does not have to be removed before its application. When SDF is applied on carious lesions, the fluoride enhances remineralization and the silver ions act as an antibacterial agent and inhibit the growth of cariogenic biofilms. SDF also preserves the dentin collagen from further degradation. SDF at 38% has been used mostly in Argentina, Australia, Brazil, China, and Japan. The authors of this SR evaluated the clinical effectiveness of SDF at arresting caries among children.

**Strengths and weaknesses of the SR.** The authors had a focused clinical question, clearly described inclusion and exclusion criteria, had descriptions of the included studies, and conducted the SR using accepted methods and standards. The authors included only prospective studies. The authors performed study selection and data extraction in duplicate; however, it was unclear if the study selection was done independently by the 2 authors or if the risk of bias in each study was assessed independently and by how many authors. The authors also did not assess the interrater reliability or agreement among the study authors, such as with k statistics. The authors did not define how active or arrested caries were each evaluated and how the evaluators differentiated between the 2 conditions. Without a valid method to differentiate between the 2 types of lesions to begin with, it was possible to have bias in studies in which the investigators were not blinded as to which lesions identified as active at baseline but arrested on follow-up were actually arrested at baseline from the beginning. The authors did conduct an extensive search in 7 databases in various languages along with supplementary searches in the references of included studies, but they did not search the gray literature or contact content experts. For the meta-analysis, the authors chose the random-effects model so that the sample size of each study would have less influence on the overall results compared with the fixed-effects model. Though a meta-analysis was conducted on subgroups with different follow-up periods ranging from 6 to more than 30 months, the frequency of application with 38% SDF on primary teeth also varied within the studies in each subgroup from 1-off to repeated applications every 3, 6, or 12 months. Only 5 of the 8 trials in the meta-analysis had control groups. Thus, the results of the meta-analysis and the overall percentage of active caries that became arrested—81% (95% CI, 68-89%; P < .001)—may have been calculated from before-and-after data in just the intervention group, but not in comparison with a similar group that received either an alternative treatment, placebo, or no treatment. The authors declared they had no potential conflicts of interest to the publication of the SR.

**Strengths and weaknesses of the evidence.** Except for the P value of heterogeneity (P = .667) given in the forest plot of studies using 38% SDF on primary teeth, the authors did not include any actual discussion about or possible sources of heterogeneity in the included studies. In the meta-analysis with the subgroups with different follow-ups that used 38% SDF, all the studies with high concentrations of SDF (38%) applied to primary teeth reported a statistically significant caries-arresting effect on children, but specific data were not provided in some of the studies. The effectiveness of low concentration SDF (12% and 10%) has yet to be confirmed because the number of studies available was small. Not all the studies had control groups or used the same controls (such as glass ionomer cement or fluoride varnish). Without a control group, study authors cannot demonstrate that the
lesion would have arrested on its own without any interventions applied. No meta-analysis was conducted strictly on the included studies that contained a control group, which would have provided information on the relative risk or probability of arresting the carious lesions by applying SDF versus leaving the lesions untreated. Not all the studies reported the sample size, random allocation, allocation concealment, and blinding. Selection bias, detection bias, and attrition bias were noted in some of the studies. The studies varied in sample size, outcome measures, and the number of teeth or tooth surfaces that served as the unit of analysis which could thus lead to clustered observations. Calculating the proportion of arrested caries based on teeth versus tooth surfaces (because each tooth has more than 1 surface) leads to different percentage results. Some of the studies, particularly the earlier ones, may have had low reliability as they were conducted before the establishment of evidence-based, minimum recommended reporting requirements for such studies as randomized clinical trials. Considering the risk of bias noted in some of the studies, the authors mentioned, but did not formally assess, the possibility of publication bias with a funnel plot. Besides staining the arrested caries of the treated tooth black, no significant complications, side effects, or adverse events were reported with the use of SDF even with the high fluoride concentration (38%, 44,800 ppm fluoride).

Implications for dental practice. The authors’ findings in this SR and meta-analysis did not provide the clinicians with high-quality evidence for using SDF in managing caries compared with no treatment or other caries management interventions. More well-designed and well-conducted clinical trials comparing the effectiveness of SDF with no treatment or other caries management approaches in populations with varying caries risk, lesion severities, and other fluoride exposures are needed.

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Effect of Silver Diamine Fluoride and Potassium Iodide Treatment on Secondary Caries Prevention and Tooth Discolouration in Cervical Glass Ionomer Cement Restoration

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Abstract: This study investigated the effect of silver diamine fluoride (SDF) and potassium iodide (KI) treatment on secondary caries prevention and tooth discolouration in glass ionomer cement (GIC) restoration. Cervical GIC restorations were done on 30 premolars with: Group 1, SDF + KI; Group 2, SDF (positive control); Group 3, no treatment (negative control). After cariogenic biofilm challenge, the demineralisation of dentine adjacent to the restoration was evaluated using micro-computed tomography (micro-CT) and Fourier transform infrared (FTIR) spectroscopy. The colour of dentine adjacent to the restoration was assessed using CIELAB system at different time points. Total colour change ($\Delta E$) was calculated and was visible if $\Delta E > 3.7$. Micro-CT showed the outer lesion depths for Groups 1, 2 and 3 were $91 \pm 7 \mu m$, $80 \pm 7 \mu m$ and $119 \pm 8 \mu m$, respectively ($p < 0.001$; Group 2 < Group 1 < Group 3). FTIR found that there was a significant difference in amide I-to-hydrogen phosphate ratio among the three groups ($p < 0.001$; Group 2 < Group 1 < Group 3). $\Delta E$ of Groups 1, 2 and 3 after biofilm challenge were $22.5 \pm 4.9$, $70.2 \pm 8.3$ and $2.9 \pm 0.9$, respectively ($p < 0.001$; Group 3 < Group 1 < Group 2). SDF + KI treatment reduced secondary caries formation on GIC restoration, but it was not as effective as SDF treatment alone. Moreover, a perceptible staining on the restoration margin was observed, but the intensity of discolouration was less than that with solely SDF treatment.

Keywords: silver diamine fluoride; potassium iodide; secondary caries; glass ionomer; discolouration

1. Introduction

Secondary (recurrent) caries, which refers to the curious lesions affecting the margins of an existing restoration [1], is regarded as the most common reason for re-restoration of teeth in the long term [2]. It has been reported that more than 25% of restoration replacements of amalgam and resin composite were ascribed to secondary caries [3]. This fact has facilitated the development of dental materials that possess anti-cariogenic properties, such as fluoride-containing restorative materials [4]. Glass ionomer cements (GICs) can release fluoride ions to enhance remineralisation, and their abilities in fluoride release and recharge are superior to other restorative materials, such as compomers and giomers [4]. However, its antimicrobial effect is limited and inadequate to prevent secondary caries development [5].

The cariogenic bacteria of secondary caries are similar to those of primary caries, and consist primarily of Streptococci, Actinomyces naeslundii and Lactobacilli [2]. Studies have shown that silver diamine fluoride (SDF) has an intense antibacterial effect on cariogenic bacteria and can inhibit the...
growth of multi-species cariogenic biofilms on tooth surfaces [6–8]. SDF is a topical fluoride which is often used in high concentration (38%) for preventing and arresting dental caries [9]. SDF has recently been approved for clinical use by the United States Food and Drug Administration in 2015. A review concluded SDF as an effective, efficient, equitable and safe caries-preventive agent appearing to meet the World Health Organization’s Millennium Goals for 21st century medical care [10]. Clinical studies also showed the success of SDF in preventing and arresting dental caries [11,12]. A laboratory study found that the bond strength of restorations to dentine was not adversely affected by SDF using resin-based adhesives [13]. The application of SDF under GIC restorations has been demonstrated to produce a promising pulpal response and be effective in facilitating the formation of reparative dentine [14]. It also has been reported that prior treatment with SDF can increase resistance of cavity margins around GIC restorations to secondary caries development [5].

A significant disadvantage of SDF use, however, is black staining on teeth which can cause aesthetic concern [11]. A way that has been suggested of managing this problem is to apply a saturated solution of potassium iodide (KI) immediately after SDF application. It was suggested that discoloration of the carious lesion can be avoided while the caries arresting effect of SDF is not changed [15]. The suggested explanation is that the silver ions from the SDF solution will react with the iodide ions from the KI solution to form silver iodide. It was reported that the application of SDF + KI to dentine surfaces before the placement of GIC restorations did not affect the bond strength of GIC to dentine [16], and did not adversely interfere with the fluoride uptake into the adjacent demineralised dentine [15]. It would be desirable if KI could inhibit the staining formation associated with SDF without diminishing its effectiveness in preventing and arresting dental caries. Nevertheless, evidence from laboratory data is insufficient to support this claim. A search in PubMed found that there was no study reporting the effect of SDF + KI treatment in the prevention of secondary caries formation on GIC restorations, and quantifying the discoloration of tooth structure after the application of SDF + KI. Therefore, the objectives of this laboratory study were to investigate the effect of SDF + KI treatment on the prevention of secondary root caries development around direct GIC restorations, and to assess whether SDF + KI treatment could prevent discoloration of the dentine adjacent to GIC restorations. The first null hypothesis was that SDF + KI treatment has no effect on secondary caries prevention around GIC restorations. The second null hypothesis was that SDF + KI treatment has no staining effect on dentine along the restoration margin.

2. Results

Results of one-way ANOVA showed that the colour of the three groups was not significantly different at the baseline L* (p = 0.974), a* (p = 0.920) and b* (p = 0.352). L* axis represented lightness ranged from black (0) to white (100), a* axis described red (+a*) to green (−a*), and the b* axis represented yellow (+b*) to blue (−b*). The values relating to the chromatic coordinates L* a* b* and total colour change ∆E of the three groups are presented in Table 1 and Figure 1, respectively. For the intragroup analysis, there was a significant drop in the values of lightness (L*) in Group 1 from T (time point) 7 to T14 (p < 0.001), while Group 2 displayed a significant decrease in L* values from T0 to T1 (p < 0.001) (Table 1). The negative control did not show a noticeable colour variation at any time point (∆E < 3.7, p < 0.05) (Figure 1). Group 1 displayed a perceptible colour difference of ∆E > 3.7 at T14, whereas Group 2 presented a perceptible colour change from T1 onward (Figure 1). Pair-wise comparisons revealed that Group 1 (∆E = 22.5 ± 4.9) exhibited a colour difference inferior to that of Group 2 (∆E = 70.2 ± 8.3) at T14 (p < 0.001).
Table 1. Mean (±SD) values of L* a* b* coordinates of the three groups (n = 10).

<table>
<thead>
<tr>
<th>Group</th>
<th>Coordinates</th>
<th>T0</th>
<th>T1</th>
<th>T7</th>
<th>T14</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDF + KI</td>
<td>L*</td>
<td>90.2 ± 6.0</td>
<td>89.9 ± 5.1</td>
<td>88.6 ± 6.4</td>
<td>68.5 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>0.6 ± 0.9</td>
<td>0.6 ± 0.9</td>
<td>0.6 ± 0.7</td>
<td>4.2 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>b*</td>
<td>33.6 ± 4.7</td>
<td>33.4 ± 5.2</td>
<td>33.9 ± 3.1</td>
<td>34.0 ± 4.3</td>
<td>0.840</td>
</tr>
<tr>
<td>SDF</td>
<td>L*</td>
<td>89.5 ± 6.9</td>
<td>25.3 ± 4.1</td>
<td>27.4 ± 8.1</td>
<td>24.7 ± 5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>0.6 ± 1.0</td>
<td>4.5 ± 0.9</td>
<td>3.7 ± 1.6</td>
<td>3.9 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>b*</td>
<td>35.9 ± 5.1</td>
<td>12.2 ± 1.9</td>
<td>8.5 ± 4.4</td>
<td>9.6 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No treatment</td>
<td>L*</td>
<td>89.2 ± 5.2</td>
<td>88.4 ± 6.0</td>
<td>88.4 ± 6.1</td>
<td>88.0 ± 5.5</td>
<td>0.281</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>0.7 ± 1.1</td>
<td>0.6 ± 1.0</td>
<td>0.7 ± 0.9</td>
<td>0.6 ± 1.0</td>
<td>0.951</td>
</tr>
<tr>
<td></td>
<td>b*</td>
<td>32.8 ± 4.7</td>
<td>33.2 ± 4.1</td>
<td>32.5 ± 4.9</td>
<td>33.1 ± 4.1</td>
<td>0.702</td>
</tr>
</tbody>
</table>

T0: baseline (after preparation of the cavities), T1: after material filling (after setting for 1 day), T7: after thermal-cycling (7 days after material placement), and T14: after biofilm challenge (14 days after material placement). L* axis represented lightness ranged from black (0) to white (100), a* axis described red (+a*) to green (−a*), and the b* axis represented yellow (+b*) to blue (−b*). SDF: silver diamine fluoride; KI: potassium iodide.

Figure 1. Total colour change (ΔE) of the three groups. T1: after material filling (after setting for 1 day), T7: after thermal-cycling (7 days after material placement), and T14: after biofilm challenge (14 days after material placement). Columns displaying different letters indicate a significant difference (p < 0.05) between groups within each time point.

Representative images of micro-computed tomography (micro-CT) and Fourier transform infrared (FTIR) spectra from the three groups are displayed in Figures 2 and 3, respectively. The mean outer lesion depth (±SD) of Groups 1, 2 and 3 was 91 ± 7 µm, 80 ± 7 µm and 119 ± 8 µm, respectively (p < 0.001; Group 2 < Group 1 < Group 3). The values of the amide I: HPO₄²⁻ absorbance ratio of Groups 1, 2 and 3 were 0.50 ± 0.05, 0.43 ± 0.03 and 0.71 ± 0.05, respectively (p < 0.001; Group 2 < Group 1 < Group 3).
3. Discussion

SDF at a concentration of 38% was chosen as the positive control, because it is well known that it is effective in preventing and arresting dental caries [10,17]. Laboratory studies have illustrated that the topical application of a 38% SDF solution can inhibit the growth of cariogenic biofilms [6–8]. It has been suggested that 38% SDF possesses a strong inhibitory effect on the action of cysteine cathepsins [18] and matrix metalloproteinase [19], which are closely related to the collagen degradation of dentine. In addition, SDF treatment can increase the micro-hardness of carious lesions in dentine [20] and the
mineral density of carious lesions in enamel [21]. Clinical studies have shown that 38% SDF arrested
coronal caries in children [11] and prevented root caries in elderly patients [22]. However, SDF can
cause black staining of tooth structure which may not be acceptable to many patients from the aesthetic
point of view. A promising approach to solve this problem is to apply the KI solution immediately
after SDF treatment. To make this study more relevant to clinicians, SDF products readily available on
the market were used. Both Saforide and Riva Star contain 38% SDF and are commercially available.
Saforide was selected as positive control because it is the most common 38% SDF product used in
previous studies. The only commercial product of 38% SDF + KI available is Riva Star. Hence, it was
used in the experimental group.

There are various techniques available for disinfection of extracted teeth, for instance, γ irradiation,
ethylene oxide, and autoclaving. γ Irradiation can sterilise the teeth without altering the tooth
structure and the function of dentine. However, it requires expensive equipment, which is not easily
accessible [23]. It is believed that surface crazing and cracks were likely to have developed in the
GIC restorative material if sterilisation with ethylene oxide was adopted as a result of dehydration.
Therefore, autoclaving was used to sterilise the teeth in this study. Autoclaving is an effective, cheap,
simple and chemically safe method suitable for tooth sterilisation [24], which was been recommended
in previous laboratory studies [5,25]. Nevertheless, there was some concern with regard to the
high pressure and temperature required which may damage the dentinal structure or denature the
collagen. Although autoclaving of teeth may reduce the micro-hardness of dentine, the reduction in
micro-hardness is minimal and it does not affect the physical properties to the degree of compromising
strength [23]. Moreover, the dentine collagen structure can be weakened by autoclaving, but it would
not be destroyed to any major degree, because the molecular structure of dentine collagen has been
reported to remain relatively unaffected [25].

Secondary caries development has been commonly reported in two locations: along the cavity
wall adjacent to the restoration (namely wall lesion) [1], but also at the tooth surface next to the filling
material (namely outer lesion), similar to primary caries. The depth of these two kinds of lesions
has been commonly used to assess the inhibitory effect on the development of secondary caries [5].
An in situ study found that wall lesions only formed when there was a gap between the restoration
and the tooth, indicating that the presence of a gap is a crucial condition for the development of
a wall lesion [1]. Another laboratory study reported that wall lesions were only detected in the resin
composite group but not in the GIC group, and the possible explanation was that the shrinkage of
resin composites could cause contraction away from the cavity walls [5]. However, some researchers
have the concern that the “wall lesion” has been used indiscriminately, and it is uncertain whether
an entity like a wall lesion exists per se clinically [2]. Thus, the assessment of wall lesion depth was
not adopted in the current study. Moreover, this study did not find any recognisable wall lesion in all
specimens (data not shown). The reason could be there was no gap between the restorations and the
teeth, and the use of GIC which released fluoride and promoted remineralisation.

FTIR is an easy approach to identify the existence of molecular functional groups (namely, HPO$_4^{2-}$
and amide I) and thus was adopted in the current study. However, the instrument should be repetitively
calibrated, since the analog connection between the recording device and the monochromater position
is prone to misalignment and wear. The mineral of dentine is composed of hydroxyapatite, and
the organic matrix fraction is mainly composed of type I collagen. The HPO$_4^{2-}$ band in the FTIR
spectrum is representative of the mineral, while the amide I band represents the secondary structure of
collagen [26]. The ratio of amide I: HPO$_4^{2-}$ indicates the extent of demineralisation of dentine. In this
study, the amide I: HPO$_4^{2-}$ ratio was lowest in group SDF, followed by group SDF + KI and negative
control. This result demonstrated that SDF with or without KI, inhibited demineralisation of dentine
and prevented secondary caries formation.

Previous laboratory studies reported that both SDF solution and SDF + KI solution inhibited
cariogenic biofilm formation on demineralised dentine [27,28]. Moreover, the studies also found SDF
and SDF + KI could reduce the permeability of cariogenic bacteria through demineralised dentine
slices, and increase the resistance to further demineralization without significant differences between these two treatments [27,28]. In this study, SDF + KI solution could prevent secondary caries formation around GIC restorations, but it was not as effective as SDF. This finding might suggest KI may influence the effectiveness of SDF in preventing the formation of secondary root caries. The probable reason is that the application of KI solution might reduce the amount of silver ions. It is known that silver ions contained in the SDF solution play an important role in antimicrobial activities to hinder caries progression.

The aesthetic appearance of a restoration is an important concern of patients. Rather than assessing colour differences by the naked eye which is often subjective, our evaluation was to quantify colour changes using instrument-based measurements which are more precise with a high repeatability [29]. Silver ions in the SDF solution can blacken the tooth structure. It is suggested that the KI solution can react with SDF to form a bright yellow solid compound (silver iodide) [30], and this reaction could reduce the excess free silver ions which result in the black staining [27]. Although the bright yellow precipitates can be seen after the application of KI, the staining of tooth surfaces could still be detected in SDF + KI treatment group in this study. While KI was supposed to remove the staining caused by SDF, its effect has not been previously quantified. In this study, SDF + KI treatment led to discolouration of tooth surfaces although the intensity of the discolouration was less than that of SDF treatment. One possible explanation may be that the amount of the applied KI solution was not sufficient to lead to an excess of free silver ions remaining [30]. Besides, silver iodide is considered to be highly photosensitive which can dissociate into metallic silver and iodine by exposure to light. Hence, discolouration still occurred on tooth surfaces.

To our knowledge, this study is the first laboratory study to investigate the effectiveness of SDF + KI treatment in secondary root caries prevention around GIC restorations, and to quantify the discolouration on the restoration margins caused by SDF + KI. Based on the results of this study, the two null hypotheses were rejected. The results demonstrated that SDF + KI treatment could increase resistance of GIC restorations to the formation of secondary root caries, but was not as effective as SDF treatment. Moreover, in the long term, it was not effective in preventing discolouration of the restoration margin, but could reduce staining compared to that of SDF. It is noteworthy that this laboratory study is based on a laboratory model, which is different from the more complex clinical situation. The results cannot be extrapolated directly to the in vivo condition and caution is advised in the interpretation of the results.

4. Materials and Methods

4.1. Specimen Preparation and Materials Selection

The use of human teeth in this study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB UW 12-221). Thirty extracted sound human upper and lower premolars from 10 patients were collected with the patients’ consent. The premolars were stored in a 0.1% thymol solution at 4 °C before use and were used within 1 month of extraction. Box-shaped cavities (4 × 2 × 2 mm³) along the cemento-enamel junction were prepared on premolars. The cavities were prepared with a tungsten carbide bur (FG 330; SS White, Lakewood, NJ, USA) under copious water cooling. Then the teeth were sterilised by autoclaving at 121 °C [25]. The cavities were conditioned with 10% polyacrylic acid [5] and randomly allocated to the following three treatment groups:

- **Group 1 (SDF + KI),** the cavity was treated with SDF + KI (Riva Star, SDI, Bayswater, Australia). A layer of 38% SDF solution was topically applied to the cavity, immediately followed by a saturated KI solution until the creamy white solution turned clear. The reaction products were washed off with copious distilled water [28]. Then the cavity was dried with oil-free compressed air and filled with GIC (Fuji VII capsule, GC International, Tokyo, Japan).
- Group 2 (SDF), positive control—the cavity was treated with 38% SDF (Saforide; Toyo Seiyaku Kasei Co., Ltd., Osaka, Japan) for 3 min, followed by GIC restoration (Fuji VII capsule).
- Group 3 (no treatment), negative control, the cavity was filled with GIC (Fuji VII capsule).

The flow chart of the present study is shown in Figure 4. All procedures were performed with sterile instruments and gloves. The restored teeth were then stored at 37 °C and 100% humidity for 24 h. The restoration surfaces were finished and polished using 4000 grit sanding paper to confirm there was no excess over the cavity margins. To simulate the aging process, the restored teeth were thermocycled for 1500 cycles in 55 ± 5 °C and 10 ± 5 °C distilled water baths with a 32 s dwell time in each bath and a 14 s interval between baths [5]. Then the teeth were immersed in 70% alcohol for 60 s and air dried for 20 s before undergoing a cariogenic biofilm challenge [31].

**4.2. Cariogenic Biofilm Challenge**

Cariogenic bacteria used for biofilm challenge were *Streptococcus mutans* ATCC 35668 (American Type Culture Collection), *Streptococcus sobrinus* ATCC 33478, *Lactobacillus rhamnosus* ATCC 10863 and *Actinomyces naselundii* ATCC 12014 [26]. The microorganisms were cultured on blood agar plates for 24 h.
4.2. Cariogenic Biofilm Challenge

Cariogenic bacteria used for biofilm challenge were *Streptococcus mutans* ATCC 35668 (American Type Culture Collection), *Streptococcus sobrinus* ATCC 33478, *Lactobacillus rhamnosus* ATCC 10863 and *Actinomyces naselundii* ATCC 12014 [26]. The microorganisms were cultured on blood agar plates for 2 days (37 °C, anaerobically). Then, a single colony was picked from each agar plate and transferred to tubes containing brain-heart infusion (BHI) broth with 5% sucrose to prepare 24 h broth cultures at 37 °C under anaerobic conditions. After that, the bacterial cell pellets were harvested by centrifugation (1500 × g, 37 °C, 10 min). Bacterial suspensions were then prepared in BHI broth with 5% sucrose to a cell density of McFarland 2 (6 × 10^8 cells/mL) [5]. Each restored tooth was soaked in a well of a 12-well plate containing 500 µL of each bacteria culture. The plate was maintained in an anaerobic chamber at 37 °C for 7 days. The medium was refreshed daily [7] and Gram stain test of the used medium was performed to check contaminants.

4.3. Colour Assessment

Colour assessments (n = 10 per group) were taken at four time points: T0: baseline (after preparation of the cavities), T1: after material filling (after setting for 1 day), T7: after thermal-cycling (7 days after material placement), and T14: after biofilm challenge (14 days after material placement). The colour of the dentine surface adjacent to the restoration was observed using a VITA Easyshade® advanced portable dental spectrophotometer (VITA Zahnfabrik GmbH, Bad Säckingen, Germany). Each colour was elucidated three-dimensionally in space according to the Commission International del’Eclairage L* a* b* colour system. L* axis represented lightness ranged from black (0) to white (100), a* axis described red (+a*) to green (−a*), and the b* axis represented yellow (+b*) to blue (−b*). The instrument was calibrated with the manufacturer’s instruction before examination. The L*, a* and b* values were replicated three times by a single operator and the average values were recorded. The difference of colour between baseline and each time point was calculated based on the mathematical equation

\[ \Delta E = \left( (\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2 \right)^{1/2} \]  

The perceptibility threshold of \( \Delta E \), which the tooth colour change was clinically visible to the naked eye, was set at 3.7 units [32].

4.4. Outer Lesion Depth Assessment

The assessing method for outer lesion depth was adapted from Mei et al. [5]. The teeth (n = 10 per group) were scanned non-destructively in container tubes with water [33] using a SkyScan 1076 micro-CT (SkyScan, Antwerp, Belgium) to measure the outer lesion depth. The spatial resolution of 8 µm was used for scanning. The X-ray source was operated at 80 kV and 100 µA. A 1 mm thick aluminium filter was employed in front of the detector to eliminate low-energy radiation. Scanning results were reconstructed by the reconstruction software NRecon (SkyScan). Afterwards, reconstructed images were viewed by the data analysing software CTAn (SkyScan). From the reconstructed three-dimensional images, cross-sectional images of each tooth exhibiting lesion area were identified. Ten images were chosen by random sampling from those lesion images [34]. The outer lesion depth was quantified using ImageJ software [35].

4.5. Structural Evaluation of Dentine

The analysis of potential changes in the organic structure of restoration margins were performed by FTIR spectroscopy (UMA 500, Bio-Rad Laboratories, Hercules, CA, USA) with the infrared radiation ranging from 650 to 4000 cm\(^{-1}\) in wavelength number [8]. Spectra of the demineralised dentine adjacent to the restoration (n = 10 per group) were obtained by the average acquisition of data at the spatial resolution achieved with a 50 × 50 µm aperture. The ratio of the integrated area of collagen amide I absorbance between 1585 and 1720 cm\(^{-1}\) to that of HPO\(_4^{2-}\) absorbance between 900 and 1200 cm\(^{-1}\) was calculated. The value of the amide I: HPO\(_4^{2-}\) absorbance ratio indicated the extent of demineralisation of root dentine as a result of the activity of the cariogenic biofilm [8].
4.6. Statistical Analysis

All data were assessed for normality using the Shapiro–Wilk test ($p > 0.05$). Repeated measures analysis of variance (ANOVA) was applied to evaluate $L^*$, $a^*$ and $b^*$ values over time within each group. One-way ANOVA with Bonferroni post hoc test was used to detect differences in $\Delta E$ (at different time points), outer lesion depth and amide I: HPO$_4^{2-}$ between groups. One-sample Student’s $t$-test was used for each group at different time points to test whether the color change significantly different from the standard as 3.7. All analyses were conducted using IBM SPSS Version 20.0 software (IBM Corp., Armonk, NY, USA). The level of significance was set at 5%.

5. Conclusions

SDF + KI treatment inhibited development of secondary caries on GIC restorations, but was not as effective as SDF treatment alone. Moreover, SDF + KI treatment caused a perceptible staining at the restoration margin, but the intensity was less than that with purely SDF treatment.

Acknowledgments: The authors thank Samantha Li for her statistical advice. This study was supported by the Research Grant Council General Research Fund (No. 760413M).

Author Contributions: May Lei Mei and Chun-Hung Chu conceived and designed the experiments. Irene Shuping Zhao performed the experiments and analysed the data. Irene Shuping Zhao and Chun-Hung Chu wrote the paper. Michael F. Burrow revised the paper. Edward Chin-Man Lo and Chun-Hung Chu supervised the work. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>SDF</td>
<td>Silver diamine fluoride</td>
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<tr>
<td>KI</td>
<td>Potassium iodide</td>
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<tr>
<td>GIC</td>
<td>Glass ionomer cement</td>
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<tr>
<td>Micro-CT</td>
<td>Micro-computed tomography</td>
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<tr>
<td>FTIR</td>
<td>Fourier transform infrared</td>
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References


A systematic review of silver diamine fluoride: Effectiveness and application in older adults

Amruta D. Hendre1 | George W. Taylor1 | Elisa M. Chávez2 | Susan Hyde1

Objective: This systematic review examines the effectiveness of silver diamine fluoride (SDF) in the management of caries in older adults.

Background: Silver diamine fluoride has been extensively researched and proven effective for caries prevention and arrest in children. Limited studies support its effectiveness in adult and older adult populations.

Materials and methods: Multiple databases were searched according to specified inclusion-exclusion criteria. Quality assessment used modified Centre for Evidence-Based Medicine worksheets.

Results: Three randomised controlled trials were identified that addressed the effectiveness of SDF on root caries in older adults, but none addressed coronal caries. Root caries prevented fraction and arrest rate for SDF were significantly higher than placebo. The prevented fraction for caries prevention for SDF compared to placebo was 71% in a 3-year study and 25% in a 2-year study. The prevented fraction for caries arrest for SDF was 725% greater in a 24-month study and 100% greater than placebo in a 30-month study. No severe adverse effects were observed.

Conclusion: This systematic review evaluates the use of SDF for both root caries prevention and arrest in older adults. Existing reports of SDF trials support effectiveness in root caries prevention and arrest, remineralization of deep occlusal lesions and treatment of hypersensitive dentin.

KEYWORDS
arrest, caries, older adults, prevent, safety, silver diamine fluoride, systematic review

1 INTRODUCTION

In 2030, 19% of the U.S. population will be aged 65 years or older, and 2.3% over age 85.1 The number of adults aged 65 years and older per 100 working-age adults will increase from 0.22 in 2010 to 0.35 in 2030, indicating a growing burden on the healthcare system.1 Nationally, 19% of community-dwelling adults in the United States aged 65 and older have untreated coronal caries.2 The most current estimates for root caries prevalence in U.S. adults aged 65 and older are 14%, with 12% for non-Hispanic Whites and 31% and 30% for Mexican Americans and African Americans, respectively.3 The rise in the proportion of older adults in the population living with chronic disease, the longer retention of natural teeth, combined with pre-existing dental restorations and persistent caries experience is poised to create a dental public health crisis.4

The World Health Organization (WHO) has included oral health as an important component of their active ageing policy, which promotes healthy living, disease prevention and focusing on improving the quality of life of older adults.5 In concordance with the WHO global goals for 2020, Healthy People 2020 has included for the first time objectives to reduce the proportion of older adults with untreated coronal and root caries.6,7 In order to achieve these objectives, it is important to consider how the oral health needs of an older population change with fluctuations in functional status and level of dependency over a
lifet ime. The goals for oral health and the factors that influence the provision of care may vary with different stages of dependency.9

Silver diamine fluoride (SDF) is an emerging caries preventive treatment option that is inexpensive, safe and easily accessible.9 Treatment with SDF requires minimal instrumentation and application at less frequent intervals than other caries preventive materials. Current evidence supports SDF use in children.10,11 However, older adults, especially those with high caries risk and/or with limited to no access to dental services due to economic, social or functional challenges, may benefit from this treatment as well.

1.1 Background of SDF

Silver nitrate was first used to arrest caries in the 19th century. Rapid development to create more effective formulations occurred during the 20th century starting with Howe’s ammoniacal silver nitrate, followed by silver fluoride, and later SDF. Since 1970, a solution of 38% SDF has been widely used outside the United States, primarily for caries prevention and arrest in children.12 The U.S. Food and Drug Administration (FDA) approved the use of SDF as a desensitising agent in 2014. In January 2016, a new Code on Dental Procedures and Nomenclature (CDT) D1354 allowed billing claims for off-label use of SDF as an interim caries arresting medicament.13,14 Thirty-eight per cent SDF is an alkaline (pH 10) colourless solution, containing 24%-27% silver (Ag), 8.5%-10.5% ammonia (NH₃) and 5.0%-6.0% fluoride (F).15

SDF affects the tooth structure and the caries process. The effect on enamel is primarily due to fluoride, while the effect on dentin is predominantly due to silver.16,17 Formation of silver phosphate turns SDF-treated carious lesions black.18 SDF does not affect the bond strength of composite resin to noncarious dentin, but may reduce bond strength to caries-affected dentin.19,20 SDF is compatible with glass-ionomer cements (GIC) and may increase resistance of GIC and composite restorations to secondary caries.21,22

Excavation of caries is not required prior to application. Teeth are air-dried, and SDF is applied to the carious lesions using a microbrush for 1 minute and rinsed.9 The effect of SDF diminishes over time, therefore follow-up applications are required as the lesion can revert to further carious demineralization in 24 months.23 The recommended safest maximum dose of SDF per visit is 1 drop/10 Kg.9

Although numerous randomised clinical trials have been conducted in children, very few randomised controlled24-26 trials have been conducted in older populations. The purpose of this report is to provide a systematic review of the evidence regarding the effectiveness of SDF in arresting or preventing root caries in older adults.

2 METHODS

2.1 Search strategy

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA).27(Figure 1)

Databases used:
PubMed, PubMed Clinical Queries, EMBASE, the American Dental Association’s Evidence-Based Dentistry Website, Cochrane Library, Web of Science, repository of the Journal of the American Dental Association and Google Scholar.

1) Search terms (MeSH, Brand names, Other terms) for SDF:
“Silver Diamine Fluoride” OR “Diammine Silver Fluoride” OR “Ammonical Silver Fluoride” OR Silver Ammonia Fluoride” OR “Silver Fluoride” OR “Quaternary Ammonium Compounds”(MeSH) OR “Saforide” OR “Riva-Star” OR “Silver Nitrate + Caries”

2) MeSH terms for caries in older adults:
“Elderly + Caries + Silver” OR “Dental Caries + Therapy + Silver” OR “Older Adult + Care Management + Dental” OR “Cariostatic Agents + Therapeutic + Elderly” OR “Dental Atraumatic Restorative Treatment/Methods” OR “Dental Caries + Prevention + Control + Silver” OR “Dental Caries + Drug Therapy” OR “Aged” OR “Frail” OR “Institutionalized”.

FIGURE 1 Search strategy

PubMed, PubMed Clinical Queries, EMBASE, the American Dental Association’s Evidence-Based Dentistry Website, Cochrane Library, Web of Science, repository of the Journal of the American Dental Association and Google Scholar were searched for articles published from 1946 to November 2015 with monthly runs of search terms in PubMed through August 2016.

A literature search was conducted under two broad categories:

- Silver diamine fluoride: Under search terms (MeSH, Brand names, Other terms) “Silver Diamine Fluoride” OR “Diammine Silver Fluoride” OR “Ammonical Silver Fluoride” OR Silver Ammonia Fluoride” OR “Silver Fluoride” OR “Quaternary Ammonium Compounds”(MeSH) OR “Saforide” OR “Riva-Star” OR “Silver Nitrate + Caries”
- Caries in older adults: Under search terms “Elderly+Caries+Silver” OR “Dental Caries+Therapy+Silver” OR “Older Adult+Care Management+Dental” OR “Cariostatic Agents+Therapeutic+Elderly” OR “Dental Atraumatic Restorative Treatment/Methods” OR “Dental Caries+Prevention+Control+Silver” OR “Dental Caries+Drug Therapy” OR “Aged” OR “Frail” OR “Institutionalized”.

We continued to update our search through monthly runs of our search terms in PubMed. The bibliographies of the selected manuscripts were subsequently hand-searched.

2.1.1 Inclusion criteria

Type of study: randomized controlled trials, cohort studies; Dentition: permanent; Population: adults aged 18 and older, community dwelling,
or institutionalized; Treatment outcomes: caries prevention, arrest, remineralization; Language: English.

2.1.2 Exclusion criteria

Type of report: systematic reviews, meta-analysis, case reports, in vitro studies, comments on articles, reports on caries in older adults that excluded SDF, and narrative reviews; Dentition: studies of primary dentition, exclusively; Population: children and animals; Language: any other than English.

Clinical trials included in this systematic review are registered with the Hong Kong University Clinical Trials Registry (available from: http://www.hkuctr.com/search) and the U.S. National Institutes of Health Registry (available from: https://clinicaltrials.gov) (clinical trial registration numbers: HKUCTR-343, HKUCTR-1297, HKUCTR-1583 and NCT02360124).

2.2 Data extraction

Summary tables were used to organise the study characteristics and results for each study (Table 1). Prevented fraction (PF), number needed to treat (NNT) and relative risk (RR) were calculated by the authors of this review to augment the results reported by Zhang et al and Li et al.

2.3 Quality assessment

The critical appraisal worksheet for randomised controlled trials from the Oxford Centre for Evidence-based Medicine (CEBM 2005) provided the framework to assess the quality and risk of bias of the selected articles. All four authors recorded their findings in an assessment table (Table 2) and discussed disagreements until achieving consensus. The appraisal worksheet was slightly modified: Question 3b was added to the therapy appraisal for clinical trials to gauge inter-examiner calibration.

2.4 Clinical recommendations

To thoroughly evaluate the published evidence regarding its safety and effectiveness before making clinical recommendations, the authors also reviewed studies on remineralization by Sinha et al and hypersensitivity and safety by Castillo et al. These studies were conducted in younger adult populations but provided evidence to support extending SDF application for use in coronal caries.

3 RESULTS

The initial search identified 2931 articles. Category #1 “SDF” yielded 509 articles. Search for articles in category #2, “caries in older adults,” yielded 2419 articles. An additional 3 articles were subsequently identified. After removing duplicates and applying inclusion and exclusion criteria, 176 abstracts were selected for initial review by all authors. Eighteen articles were selected for full review. One article, published in May 2016, was identified during a monthly search rerun. Three articles were selected for final inclusion in this systematic review (Figure 2).

Selected RCT’s investigated the effect of SDF on root caries compared to other preventive agents or placebo. Measures used to quantify findings of the studies reviewed are shown in Table 1. Our search did not find studies investigating effect of SDF on coronal caries.

4 ASSESSMENT OF CLINICAL TRIALS REVIEWED

Using the quality assessment framework, Zhang et al met all CEBM criteria, while Li et al and Tan et al met 8 of 9 CEBM criteria. All three studies exhibited a low degree of bias. (Tables 1 and 2)

All three RCT’s investigated the effect of SDF on root caries and reported a significant effect of SDF on the prevention and/or arrest of root caries. Effectiveness of SDF was measured using the following parameters:

- **Number needed to treat (NNT)**: number of patients required to treat in the intervention group(s) in order to prevent a root surface caries lesion from occurring or to prevent a carious root surface from progressing relative to the control group.
- **Prevented fraction (PF)**: reduction in the rate of incident caries surfaces or the increase in the rate of preventing root surface caries from progressing in the intervention group(s) relative to the control group.
- **Mean number new carious surfaces and mean number of arrested root surfaces.**
- **Relative risk (RR)**: how much more likely new root surface caries will occur, or existing root surface caries will be prevented from progressing in the intervention group(s) relative to the control group.
- **Arrest rate**: percentage of active carious lesions at baseline that subsequently became arrested per time period at 12, 24, 30 months. We calculated PF, NNT and RR for Zhang et al and Li et al to increase homogeneity of the reported results.

Tan et al investigated the effect of 38% SDF on root caries prevention in institutionalized older adults and found the preventive effect of SDF was comparable to other preventive agents and greater than placebo. The effectiveness of annual application of SDF was compared with four quarterly applications of 5% sodium fluoride varnish (NaF), 1% chlorhexidine varnish (CHX) and placebo. Each group received oral hygiene instruction (OHI). The NNT for preventing new caries was 2.5, 3.1 and 3.2 for SDF, NaF and CHX varnish, respectively. The PF, compared to placebo and OHI, was 71%, 64% and 57% for SDF, NaF and CHX varnish, respectively (P<.001).

Zhang et al investigated the effect of SDF on root caries prevention and arrest and concluded annual SDF application is more effective than placebo in arresting and preventing root caries. In that study, community-dwelling older adults were randomly assigned to...
The PF and NNT have negative values for arrested caries because the formulae for PF and NNT are designed to yield positive values when the incidence of the adverse outcome (or event) is higher in the control group than in the intervention group. In the case of arrested caries, the event is a beneficial outcome (arrested caries surfaces) and is actually greater in the intervention group, thus yielding negative values for PF and NNT. Nevertheless, the interpretation for PF and NNT ignores the negative signs and uses the absolute value.

### TABLE 1 Summary of randomised clinical trial studies

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Sample size, loss to follow-up</th>
<th>Type of study, duration</th>
<th>Study population, ages, inclusion criteria</th>
<th>Treatment protocols included</th>
<th>Outcomes</th>
<th>Results</th>
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<tbody>
<tr>
<td>Tan et al24 2010 Hong Kong</td>
<td>Baseline N=306 loss to follow-up: N=247 (19%) at 1 y N=227 (26%) at 2 y N=203 (34%) at 3 y</td>
<td>RCT 3 y</td>
<td>Elders. mean age 78.±6.2 y. At least 5 teeth with exposed roots. No serious medical problems. Basic self-care ability. Living in 21 residential and nursing homes.</td>
<td>Grp.1 OHI+water (placebo) q 3 mo. Grp.2 OHI+CHX varnish q 3 mo. Grp.3 OHI+NaF varnish q 3 mo. Grp.4 OHI+annual application of SDF solution.</td>
<td>Development of new caries on the exposed sound root surfaces.</td>
<td>PF/NNT/RR for prevention of new carious surfaces compared to OHI+Placebo OHI+CHX 57%/3.2/0.27 OHI+NaF 64%/3.1/0.26 OHI+SDF 71%/2.5/0.19 Mean number of new root caries surfaces OHI+Placebo 2.5 OHI+CHX 1.1 OHI+NaF 0.9 OHI+SDF 0.7 3 intervention groups had significantly lower mean number of new root caries surfaces than the control group at 3 y (P&lt;.001).</td>
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<tr>
<td>Zhang et al25 2013 Hong Kong</td>
<td>Baseline N=266 loss to follow-up: N=227 (15%) at 2 y</td>
<td>RCT 2 y</td>
<td>Elders. Age 60-89 y. At least 5 teeth with exposed roots. No serious medical problems. Basic self-care ability. Community dwelling from 11 elderly centres.</td>
<td>Grp.1 OHI+Water (placebo) q 12 and 24 mo. Grp.2 OHI+SDF q 12 and 24 mo. Grp.3 (OHI+SDF) q 12 and 24 mo Oral hygiene education programme (OHE) q 6 mo.</td>
<td>Prevention and arrest of new carious surfaces on exposed roots.</td>
<td>PF/NNT/RR for prevention of new carious surfaces compared to OHI+Placebo OHI+SDF 25%/3.0/0.75 OHI+SDF+OHE 47%/1.59/0.53 PF/NNT/RR for arrest of root surface caries compared to OHI+Placebo OHI+SDF 600%/4.17/7.0 OHI+SDF+OHE -725%/3.45/8.25 Mean number of new/arrested root caries surfaces OHI+Placebo 1.33/0.04 OHI+SDF 1.00/0.28 OHI+SDF+OHE 0.70/0.33 OHI+SDF had significantly better effect on prevention (P&lt;.05) and arrest (P&lt;.05) of root caries than OHI alone. Additional improvement in prevention and arrest with adding OHE to OHI+SDF (P&lt;.05).</td>
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<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Sample size, loss to follow-up</th>
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<tr>
<td>Li et al24 2016 Hong Kong</td>
<td>Baseline N=83 Baseline root surfaces with active caries lesions n=156 Loss to follow-up at 30 mo: N=16 (19%)</td>
<td>RCT 30 Months</td>
<td>Elders. Age 72.2±5.2 y. No serious medical problem. No salivary gland malfunction. No cognitive problems in communication. Basic self-care ability. One or more teeth with active root caries.</td>
<td>Grp.1 OHI+Soda water (placebo) q 12 and 24 mo. Grp.2 OHI+SDF q 12 and 24 mo. Grp.3 OHI+SDF+KI q 12 and 24 mo. Individual OHI+tooth brush+interdental brush +fluoridated tooth paste provided at each exam q 6 mo to all participants.</td>
<td>Arrest rate of carious root surfaces. Assess colour of arrested carious lesions.</td>
<td>Arrest rate at 12/24/30 mo. OHI+Placebo 32.1%/28.6%/45% OHI+SDF 61%/82.1%/90% OHI+SDF+KI 75.9%/85.4%/92.5% PF/NNT/RR for arrest of root surface caries compared to OHI+placebo SDF+OH 100%/1.8/2.0 The arrest rate in SDF and SDF+KI groups were statistically significant compared to placebo (P&lt;.001), while there was no statistically significant difference in arrest rates between SDF and SDF+KI groups (P&gt;.05). There was no statistically significant difference between colour distribution of arrested lesions in SDF and SDF+KI groups (P&gt;.05).</td>
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CHX, chlorhexidine; F, fluoride; Grp, group; N, number of participants; NaF, sodium fluoride; OHE, oral hygiene education programme; OHI, oral hygiene instructions; q3 months, every 3 months; RCT, randomised controlled trial; RR, relative risk; SDF, silver diamine fluoride; KI, potassium iodide; NNT, number needed to treat; PF, preventive fraction; RR, relative risk.

The PF and NNT have negative values for arrested caries because the formulae for PF and NNT are designed to yield positive values when the incidence of the adverse outcome (or event) is higher in the control group than in the intervention group. In the case of arrested caries, the event is a beneficial outcome (arrested caries surfaces) and is actually greater in the intervention group, thus yielding negative values for PF and NNT. Nevertheless, the interpretation for PF and NNT ignores the negative signs and uses the absolute value.
three groups who received one of the following: (i) annual application of 38% SDF on root caries and on sound exposed root surfaces with oral hygiene instruction (SDF/OHI); (ii) SDF application and oral hygiene instruction supplemented with tailored biannual oral hygiene education (SDF/OHI+OHE); or (iii) oral hygiene instruction and placebo (OHI+P), the control group.25

The mean increments of new root caries surfaces in Zhang et al25 were 0.70, 1.00, and 1.33, respectively, for the (SDF/OHI+OHE), (SDF/OHI), and (OHI+P) groups (P<.05). Our calculated PF (ie 1–RR) was 25% for (SDF/OHI) group and 47% for (SDF/OHI+OHE) group, using the control group as the referent group. For NNT, to prevent one new root caries surface, the (SDF/OHI) and (SDF/OHI+OHE) groups required treating 3.03 and 1.59 patients, respectively.

The mean number of arrested root caries surfaces for Zhang et al25 was 0.33 (SDF/OHI+OHE), 0.28 (SDF/OHI), and 0.04 (OHI+P) (P<.01). The RR for caries arrest was 7 for (SDF/OHI) and 8.25 for (SDF/OHI+OHE), respectively. This means participants who received (SDF/OHI) or (SDF/OHI+OHE) had a sevenfold or 8.25 greater chance of experiencing caries arrest, respectively, than those who received (OHI+P). The PF for arrested caries was 600% greater in the (SDF/OHI) group and 725% greater in the (SDF/OHI+OHE) than in the (OHI+P) group. The NNT to arrest one carious surface was 4.17 for (SDF/OHI) and 3.45 for (SDF/OHI+OHE).

Li et al26 investigated the effectiveness of SDF in arresting root caries in community-dwelling older adults and assessed the effectiveness of potassium iodide (KI) for reducing the colour of the arrested lesions. SDF was effective in arresting caries, KI had no effect on the arrest rate, and all arrested lesions eventually changed colour to the characteristic black stain. Effectiveness of annual application of 38% SDF was compared with annual application of 38% SDF immediately followed by KI application (SDF+KI), and with annual application of soda water used as placebo. Individualised oral hygiene instructions were provided to all participants at baseline and subsequently every 6 months. The caries arrest rate at the 30-month follow-up was 90% in the SDF group, 93% in the (SDF+KI) group and 45% in the placebo group (P<.001).26

5 | DISCUSSION

Our search for studies on SDF in older populations resulted in only 3 well-conducted randomised clinical trials on root caries.24-26 None investigated SDF treatment of coronal caries in older adults. We extended our search to include SDF safety, remineralization and desensitization studies in adults aged 18-65 but found no systematic reviews or meta-analyses of these topics.

All three studies were high quality and had a low degree of bias. While Zhang et al study clearly met all evaluation criteria, the description of the equal treatment of the study groups was unclear in the Tan et al study, and the description of the similarity of the groups at baseline was unclear in the Li et al study.

Taken together, the three clinical trials reviewed support the use of SDF for prevention and arrest of root caries in older adults. The PF...
for prevention was lower in the Zhang et al study than that in the Tan et al study. This difference could be due to differences in study duration, number of SDF applications during the study and health status of the study groups. Although the PF differed, the mean numbers of new caries in both studies were similar. Importantly, only one application of SDF was required to achieve results comparable to four applications of either NaF or CHX varnish. Similar to this systematic review, a meta-analysis of root caries prevention and arrest in older adults by Wierichs et al that reviewed the studies by Tan et al and Zhang et al found fewer new carious root surfaces with a mean difference of −0.33 (95% CI = −0.39, −0.28) in SDF-treated teeth than placebo. Additionally, a systematic review of root caries prevention in older adults by Gluzman et al that reviewed the study by Tan et al, reported that SDF reduced incidence of new root surface caries by 72%. SDF effectively arrested root caries in the studies assessing root caries arrest. The arrest rate for SDF and SDF-KI groups in the Li et al. study was 2 times (200%) greater than placebo, while Zhang et al reported the arrest rate being 6 times (600%) greater for the SDF group and 7.25 times (725%) greater for the (SDF+OHE) group than placebo. All participants in the Li et al study received individualised OHI, instructions for using manual toothbrush and interdental brush and received fluoride toothpaste during each follow-up examination every 6 months. The difference in arrest rates between Zhang et al and Li et al studies could be due the difference in their placebo groups where in addition to individualised oral hygiene instructions, the placebo group in the Li et al study received one fluoride toothpaste tube and a manual toothbrush at each visit. For the Zhang et al study, as a part of OHE, the (SDF+OHI+OHE) group was engaged in establishing their oral hygiene goals and were evaluated every 6 months.

KI application following SDF application inhibits biofilm formation and improves fluoride uptake from glass-ionomer fillings. The formation of silver iodide in SDF+KI reaction is thought to reduce staining. However, Li et al reported KI application had no effect on reducing the characteristic black stain of SDF (P = .05). Carious lesions turned yellow immediately after KI application, but after 30 months, the colour of arrested lesions in the SDF and SDF-KI groups was similar. KI application may delay the staining process but eventually the arrested lesion will darken.

Our search found no studies testing the effect of SDF on coronal caries in older populations. However, SDF studies in children aged 18-36 months dominate the literature and provide evidence supporting the effectiveness of SDF in the prevention and arrest of coronal caries, with results comparable to other caries preventing and arresting agents such as NaF varnish, CHX, sealants and GIC. SDF was significantly more effective than no treatment in children.

Evidence suggests SDF is effective in reducing pain in hypersensitive dentin in permanent teeth. Castillo et al reported significant reduction in the pain response of hypersensitive teeth, 24 hours after initial SDF application. Sensitivity continued to diminish further during the 7-day study period. Sinha et al demonstrated effectiveness of SDF as a remineralizing agent and possible use as an indirect pulp capping agent in deep carious lesions.
Dental caries is caused by demineralization of tooth structure following loss of calcium and phosphate ions. Hypersensitivity is an early sign of demineralization. Although older adults may not report hypersensitivity, the process of demineralization continues. SDF enhances deposition of calcium and phosphate ions, remineralization of tooth structure and reversal of the disease process. Based on findings from studies in children, as well as from Sinha et al (average age 43-44 years old) studies, SDF could be effective in arresting and preventing coronal caries in older adults. SDF application on coronal surfaces may help retention of natural teeth and increase their resistance to many of the risk factors for caries such as xerostomia, poor oral hygiene and low pH that are more prevalent in older adults coping with chronic diseases and functional impairments.

Professional application of SDF is considered safe. No serious adverse effects are reported from clinical trials of SDF. A pilot study by Vasquez et al addressed safety and reported that the serum concentrations for fluoride and silver were significantly less than the U.S. Environmental Protection Agency’s oral reference dose for daily fluoride exposure and lifetime silver exposure. No significant mucosal changes were noticed.

SDF is inexpensive relative to other caries preventive agents. A simulated study about cost-effectiveness of root caries preventive treatment concluded that SDF application is more effective and less costly in high-risk populations.

6 | KNOWLEDGE GAP ANALYSIS

There is no established frequency for SDF application; suggested frequencies in children range from annual to biannual to three consecutive weekly applications followed by semi-annual recall applications. Increased frequency is linked to a greater arrest rate over the first 6-12 months in children. Annual application of SDF effectively prevents and arrests root caries in older adults who are capable of self-care and are not affected by serious medical conditions. Multiple applications may benefit a more dependent and at-risk older population. Clinicians should use their clinical judgement about application frequency based on current evidence and individual caries risk factors. More studies are required to determine effective application frequency for caries prevention and arrest rates in older adults, at different stages of dependency and risk.

The studies included in this report were conducted in locales with community water fluoridation. However, in the United States, water fluoridation is not uniform. Black staining of carious lesions by SDF was reported to be acceptable by parents and young children, possibly because primary teeth exfoliate. Future studies should evaluate aesthetic acceptability for older adults and ways to reduce staining in permanent dentition. Acceptability may also vary depending on patient expectations.

The few clinical trials focused on older adults indicate SDF is effective in the prevention and arrest of root caries for this population. However, additional clinical trials in heterogeneous populations of older adults, investigating root, coronal, primary and secondary caries, would be beneficial to better establish the full range of optimal use.

7 | RECOMMENDATIONS

Our recommendations for the use of SDF in older adults are based on the current state of evidence found in this systematic review. The Seattle Care Pathway (SCP) provides an evidence-based approach to oral care for older adults. SCP is a framework for dental providers to assess the risks, needs and barriers to oral health care for older adults and determine best practices for prevention and treatment based upon functional status. The schema assists practitioners in appropriate assessment, prevention, treatment and communication strategies, based on functional dependency and is adaptable to patients’ needs and population-based needs. The pathway provides an important framework through which standardised care can be delivered to patients throughout the dependency continuum with consistent outcomes.

Following SCP criteria and the results of this review, SDF is appropriate for a wide spectrum of seniors, from those who are independent with high to extreme caries risk to highly dependent older adults with limited access to care and increased caries risk. SDF could be used as a standalone measure or in conjunction with oral hygiene education as a standalone measure or in conjunction with oral hygiene education and other treatment.

Some states permit dental hygienists, dental assistants, physicians, nurses and their assistants to apply SDF for the control of caries, thereby increasing access to care for many older adults. Communication between patients, care givers and healthcare providers, is crucial for setting expectations and achieving successful outcomes. SDF is an appropriate option to manage dentin sensitivity and for caries prevention and management to optimise oral health across the life course.

8 | CONCLUSION

This systematic review evaluates the use of SDF for both root caries prevention and arrest in older adults. Existing reports of SDF trials support effectiveness in root caries prevention and arrest, remineralization of deep occlusal lesions and treatment of hypersensitive dentin.


Compendium of Continuing Education article provides an overview on the use of Silver Diamine Fluoride in dental treatment.

May L. Mei, BDS, MDS, PhD; Edward Chin-Man Lo, BDS, MDS, PhD; and Chun-Hung Chu, BDS, MDS, PhD.

ABSTRACT

The use of a topical fluoride solution, namely silver diamine fluoride (SDF), in dental treatment has been drawing increasing attention. SDF has been used in some countries in Asia, including Japan and China, as a caries-arresting and anti-hypersensitivity agent. It was recently cleared by the Food and Drug Administration in the United States as a fluoride to manage hypersensitive teeth. Topical application of SDF is a noninvasive procedure that is quick and simple to use. Promising results of laboratory studies and clinical trials have suggested that SDF is more effective than other fluoride agents to halt the caries process. A review concluded that SDF is a safe, effective, efficient, and equitable caries control agent that has a potentially broad application in dentistry and may meet the criteria of both the WHO Millennium Development Goals and the US Institute of Medicine’s criteria for 21st century medical care. This article provides an overview of the clinical use of SDF in dental treatment.

Please use the link below to access the full article.

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Additional Articles of Interest


Zhao Y, Ni C, Hu J.


pling tubes. Evans RA(1), Smith WL, Nguyen NP, Crouse KL, Crouse CL, Norman SD, Jakubowski EM.


59. Parental Acceptance of the Use of Diamine Silver Fluoride in Children Aged 0 to 3 Years in the City of Cascavel, PR, Brazil Thaisa Cezária TRICHES, Mabel Mariela Rodríguez CORDEIRO, Juliana Garcia Mugnai Vieira SOUZA, Eduardo Karam SALTORI, Beatriz Helena Sottile FRANÇA


64. The effectiveness of the biannual application of silver nitrate solution followed by sodium fluoride varnish in arresting early childhood caries in preschool children: study protocol for a randomised controlled trial. Chu


