Clinical Effectiveness of Silver Ion Products for Caries Control

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Topics

- Silver products used for caries control
- SDF in the US
- RCT studies on primary teeth-Implications for evidence-based technique
- UoM ongoing RCT

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Silver Compounds

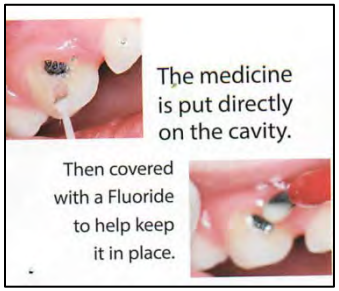

Table 1 – Use of silver compounds for caries management in dentistry.

Period	Advances
Up to 1900	$AgNO_3$ used in caries management
1917	Howe's solution ($AgNH_3NO_3$) invented and used up to 1950s
1970s–1990s	AgF used alone and combined with SnF_2 in clinical studies in Western Australia
1970s	Development of SDF in Japan supported by Central Pharmaceutical Council of the Ministry of Health and Welfare
1990s	SDF was recommended for young children in Brazil
2000s	Randomized controlled clinical trials on SDF and other preventive treatments
2000s	Addition of silver particle into restorative materials

Peng et al., 2012

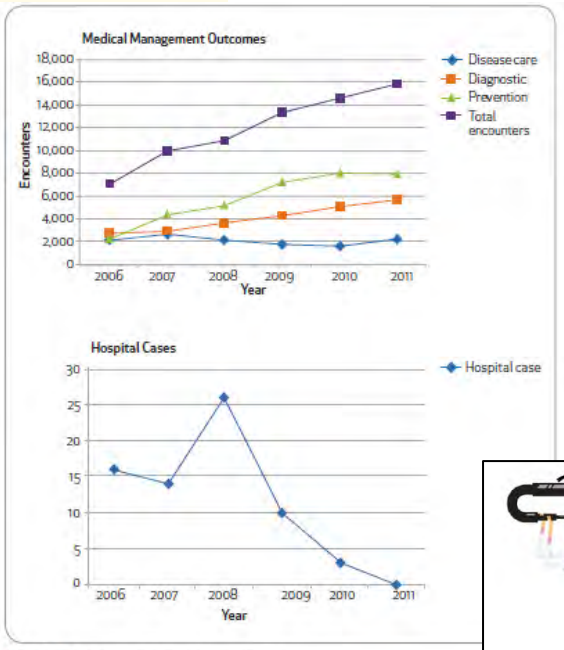

FIGURE 9. Medical management outcomes and hospital cases.

$AgNH_3NO_3$: Howe's ammoniacal silver nitrate solution

Table 2 – Clinical evidence for silver compounds utilization (1905–2011).

Author	Type of study, duration, and intended effect on caries	Treatment protocol and results	Outcome
(1) $AgNO_3$			
Prime J 1935[13]	Case report Caries arresting	$AgNH_3NO_3$ single application: 2 permanent upper incisors	$AgNH_3NO_3$ was useful for arresting caries
Klein H 1942[14]	Cohort (5 y) Caries prevention	$AgNH_3NO_3$ single application: 37 teeth Control (no treatment): 55 teeth 79% of treated and 77% of the untreated permanent molars became carious at recall	$AgNH_3NO_3$ was not effective in preventing caries
Seltzer S 1942[8]	Cohort (1 y) Cavity sterilising and restoration	$AgNH_3NO_3$ single application: 9 teeth Control (no treatment): 12 teeth Sealed by *gutta percha* and amalgam restoration, 22% vs 8% showed no bacteria respectively	$AgNH_3NO_3$ had limited sterilising effect
Schultz-Haudts S 1956[15]	Cohort (1 y) Caries arresting	Excavation + $AgNH_3NO_3$ single application: 136 class II carious lesions Excavation alone: 93 class II carious lesions The "caries arresting rate" was 82% and 17% respectively	"$AgNO_3$ has caries arresting effects in primary teeth."

$$Ca_{10}(PO_4)_6(OH)_2 + AgNO_3 \rightarrow Ca(NO_3)_2 + Ag_3PO_4 + Ag_2O + H_2O$$

Re: K102973
Trade/Device Name: Silver Dental Arrest
Regulation Number: 21 CFR 872.3620
Regulation Name: Cavity Varnish
Regulatory Class: Class II
Product Code: PHR
Dated: April 19, 2014
Received: April 22, 2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(If known)*
K102973

Device Name
Silver Dental Arrest

Indications for Use *(Describe)*
Treatment of Dental Hypersensitivity. For use in adults over the age of 21.

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Thus, use for caries control is "off label", similar to use of Fluoride Varnish

38% (55,800 ppm F) Silver Diamine Fluoride-SDF

[e.g., Saforide, Advantage Arrest (US); ammonia and AgF combined to form a diamine silver ion complex $Ag(NH_3)_2+$; claimed to be more stable than AgF, and can be kept at constant concentration for a longer time; pH=8-10]

$$Ca_{10}(PO_4)_6(OH)_2 + Ag(NH_3)_2F \rightarrow CaF_2 + Ag_3PO_4$$
$$+ \quad NH_4OH$$
Alkaline environment

- **Antibacterial**
- **When in contact with dentin: Ag_3PO_4 (weakly soluble; turns black with sunlight or reducing agents)= Black, hard layer (>20μm deep enamel, Willerhausen et al., 2015; 50-200μm in dentin; Chu and Lo, 2008)**
- **Metallic taste; transient gingival and mucosal irritation (Llodra et al., 2005)**
- **To counter stain: KI (in vitro suggests same effect on biofilm, Knight et al., 2005)**
- **Low cost, easy to use**

Rosenblatt et al., 2009

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Studies on Primary Teeth (some include also permanent teeth)	
Chu et al. (2002) (Lo et al., 2001)	• After 1.5 and almost 3 years, 38% SDF arrests lesions better than FV and nothing (1x/year: PF ~ 70-84%; better than FV ~44-56%) • **No need for prior excavation**
Llodra et al. (2005)	• 2x/year better than nothing in prevention and arrest • Preventive effect higher in primary than permanent teeth (primary teeth PF 79% and 64% in permanent teeth)
Yee et al. (2009)	• After 2 years, 38% more effective than 12% SDF (and 12% equal to no treatment) • Effectiveness decreases over time
Zhi et al. (2012)	• Annual application of 38% SDF or glass ionomer can arrest active dentine caries. • **Increasing the frequency of application to every 6 months can increase the caries arrest rate of SDF application [Caries arrest rates were 79%-1X/year, 91%-2x/year**, and 82%-control, respectively (p=0.007).]
Santos et al. (2012)	• After 1 year, 30% SDF was more effective than IRT for arresting caries in primary teeth.
Duangthip et al. (2015)	• Annual or three consecutive weekly applications of SDF solution is more effective in arresting dentine caries in primary teeth than three consecutive weekly applications of NaF varnish.
Santos et al. (2014)	• After 1 year, Nano-AgF was more effective in arresting cavitated lesions than no treatment (PF:50%)

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Authors (Year)	Target	Surface	Groups	Results
Chu et al. (2002) (Lo et al., 2001 reported 18 month data)	Children 3-5 (China); N=375 Low F= 0.2 ppm HIGH CARIES= dmfs of anterior teeth: 4.66	Cavitated lesions in anterior primary teeth (RCT; 30 months; 1 blinded calibrated examiner; exams every 6 months; outcome= caries arrest-hardness)	5 groups: 38% SDF annually (with or without excavation) vs. FV applied every 3 months (with or without excavation) vs. control (no treatment)	SDF groups had higher caries arrest rates than those of NaF groups and control (respective mean numbers of arrested caries tooth surfaces in the five groups were 2.5, 2.8, 1.5, 1.5 and 1.3). All arrested lesions, regardless of group, were darker **Conclusion** **1)SDF arrests lesions better than FV and nothing (1x/year: PF ~ 70-84%; better than FV ~44-56%)** **2)No need for prior excavation**

(Comments: ethical concern regarding the no treatment, study quality good; low risk of bias. “In this study, only the upper primary incisors and canines were involved, because caries in the three- to four-year-old Chinese children was mainly found in these teeth”)

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Authors (Year)	Target	Surface	Groups	Results
Llodra et al. (2005)	Children 6-15 (Cuba); N=452 Low F= 0.09ppm dmfs: 3.5-3.6 (primary teeth data were gathered for the surfaces of only canines and molars. In permanent teeth, data were gathered only on first molars) Note: All schools had a preventive program (OHI, dietary recomm., and 0.2% NaF mouthrinses every 2 wks)	Cavitated lesions of primary and permanent teeth and occlusal surfaces of any first permanent molars that had erupted. (RCT, 36 months; 2 blinded calibrated examiners; exams every 6 months; outcome: caries arrest-hardness)	38% SDF every 6 months for 3 min (no tissue removal in primary teeth; yes for permanent teeth) vs. nothing	Mean # of new decayed surfaces in primary teeth during the study was 0.29 in the SDF group *vs.*1.43 in controls. The mean of new decayed surfaces in first permanent molars was 0.37 in the SDF group *vs.* 1.06 in controls. With respect to the therapeutic effect of SDF (arrest of caries), around 77% of treated active lesions became inactive, both in primary teeth and in first permanent molars. A hypothetical risk attributed to SDF is its possible toxicity to the pulp. This concern was not supported by the present results **Conclusion:** 1)**2x/year better than nothing in prevention and arrest** 2)**Preventive effect higher in primary than permanent teeth (primary teeth PF 79% and 64% in permanent teeth)**

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(Comments: “In the present study, the baseline level of caries was much higher in deciduous teeth (mean of > 3 surfaces with caries) than in first permanent molars (0.3 surfaces with caries), which may explain the greater efficacy of the SDF solution in the deciduous dentition.”)

Authors (Year)	Target	Surface	Groups	Results
Yee et al. (2009)	Children 3-9 (Nepal); N=976 Low F=0.03ppm dmft: 4.6	Active cavitated lesions in primary teeth (anterior and posterior) (RCT; 24 months; calibrated dentist and therapist baseline exams, all follow up exams by blinded therapist; exams at 6, 12 and 24 months)	1 application (2min): 38% SDF + tannic acid made from tea as a reducing agent vs. 38% SDF vs. 12% SDF vs. nothing (control)	# of arrested lesions was significantly higher in groups treated with 38% SDF than 12% SDF and control group. No difference between 38% SDF alone and the group treated with 38% SDF + tannic acid (to accelerate deposition of silver phosphate). There was no effect of the 12% SDF alone application **Conclusion:** **1)38% more effective than 12% SDF** **2)Effectiveness decreases over time**

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Authors (Year)	Target	Surface	Groups	Results
Zhi et al. (2012)	Preschool Children 3-4 (China), N=212 Mean dmft: 5.1	Cavitated active dentine lesions in primary teeth (RCT, 3 years, exams every 6 months, 1 calibrated blinded examiner)	38% SDF annually vs. SDF biannually vs. Glass ionomer filling	Caries arrest rates were 79%, 91% and 82%, respectively (p=0.007). **Conclusion:** **1)Annual application of either SDF solution or high fluoride-releasing glass ionomer can arrest active dentin caries.** **2)Increasing the frequency of application to every 6 months can increase the caries arrest rate of SDF application.**

(Comments: blinding of filling impossible; study quality good; low risk of bias)

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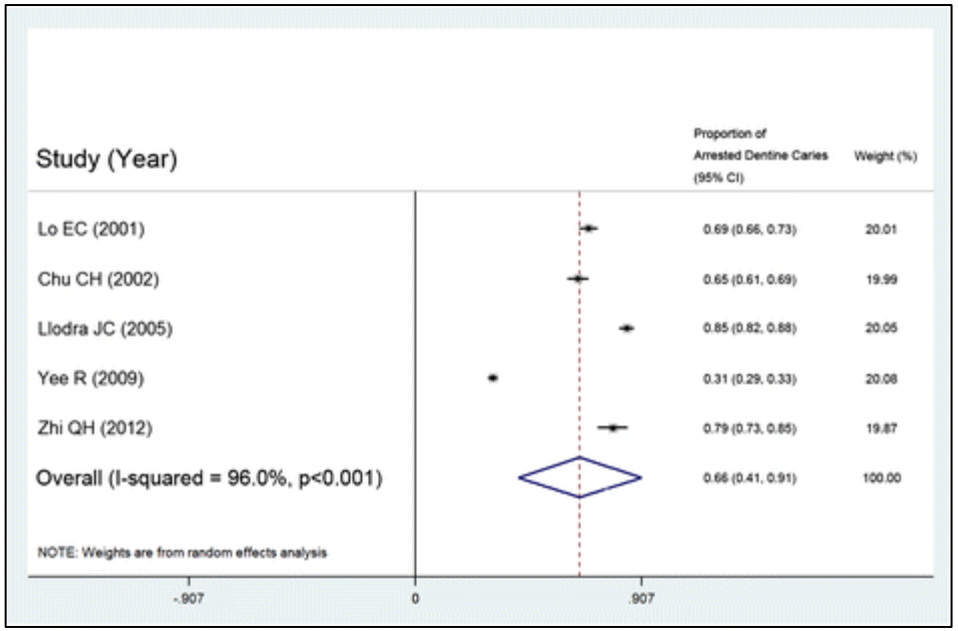
Meta-analysis of studies using 38% SDF to arrest dentin caries

Author, Year [Ref]	Method	% arrest of dentine caries	Risk of bias ** A	B	C	D	E	F
Santos et al, 2014 [17]	Primary teeth, 12-month Gp1 - Nano-AgF (n=63) Gp2 - No treatment (n=67)	Gp1>Gp2 (p=0.003)	⊕	⊕	⊕	⊕	⊕	⊖
Santos et al, 2012 [16]	Primary teeth, 12-month Gp1 - 30% SDF (n=183) Gp2 - GI (n=162)	Gp1>Gp2 (p<0.001)	○	○	⊖	⊕	⊕	⊕
Zhi et al, 2012 [14]	Primary teeth, 24-month Gp1 - 38% SDF annually (n=218) * Gp2 - 38% SDF semi-annually (n=239) GP3 - Glass ionomer annually (n=262)	Gp2>Gp1,Gp3 (p=0.007)	⊕	○	⊕	⊕	⊕	⊕
Yee et al, 2009 [15]	Primary and permanent teeth, 24-month Gp1 - 38% SDF (n=3,396) * GP2 - 12% SDF (n=1,652) Gp3 - No treatment (n=1,590)	Gp1>Gp2,Gp3 (p<0.001)	⊕	○	⊕	⊕	⊕	⊕
Llodra et al, 2005 [13]	Primary and permanent teeth, 36-month Gp1 - 38% SDF semi-annually (n=675) * Gp2 - No treatment (n=658)	Gp1>Gp2 (p<0.001)	○	○	⊕	○	⊕	⊕
Chu et al, 2002 [12]	Primary teeth, 30-month Gp1 - 38% SDF annually (n=641) * Gp2 - 5% NaF every 3 months (n=576) GP3 - No treatment (n=273)	Gp1>Gp2,Gp3 (p<0.001)	⊖	○	⊕	⊕	⊕	⊕
Lo et al, 2001 [11]	Primary teeth, 18-month Gp1 - 38% SDF annually (n=641) * Gp2 - 5% NaF every 3 months (n=576) GP3 - No treatment (n=273)	Gp1>Gp2,Gp3 (p<0.001)	⊖	○	⊕	⊕	⊕	⊕

Nano-AgF Nano silver fluoride, *SDF* Silver diamine fluoride, *GI* Glass ionomer
* Data included for meta-analysis. (Fig. 3)
** Risk of bias legend:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
⊕ = Low risk, ⊖ = High risk, ○ = Unclear risk



- **Systematic search 1948-2014 was [(fluoride) AND (remineralisation OR remineralization OR arresting) AND (children caries OR early childhood caries)]**

- **Meta-analysis (5 papers) using 38 % SDF= overall proportion of arrested dentin caries was 65.9 % (95 % CI: 41.2 % - 90.7 %; p < 0.001)**

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Gao et al., 2016

Other Outcomes or Ongoing Studies				
Authors (Year)	**Target**	**Surface**	**Groups**	**Results**
Shah et al. (2013)	Children	Plaque and salivary *S. mutans* scores	SDF vs. fluoride varnish vs. APF gel.	• Significant reduction was found in plaque score as well as *S. mutans* counts irrespective of group division. • On intergroup comparison, no statistically significant difference was found in plaque score, but significant reduction in *S. mutans* counts was found in SDF as compared with the other 2 groups
Mattos-Silveira et al. (2015)- **Ongoing trial**	Children 3-10 (Brazil), N=141	Approximal surfaces with incipient lesions in primary or permanent teeth (RCT)	flossing vs. SDF vs. resin infiltration	• Children allocated in the infiltration group showed higher levels of discomfort than those in the SDF and control groups

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Recommended UoM Technique (38% SDF)

- **Caries removal does not offer any significant benefit in arresting caries (remove food debris)**
- **Dry lesion and apply SDF, wait ~1-3 min before rinsing with water**
- **Be careful not to touch soft tissues or other surfaces (tongue, cheek, etc.; or clothes, dental operatory, etc.)**
- **Biannual application better than annually**
- **Application of reducing agent (10% SnF_2 or tannic acid) shows no additional benefit in effect of SDF**

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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)

FIGURE 4. UCSF special consent form.

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New code CDT 2016 code

D1354 - Interim caries arresting medicament application

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

SDF can be billed under…

D1208 -Topical application of fluoride
D9910 - Application of a desensitizing medicament, per visit
D1999 - Unspecified preventive procedure by report

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The Effectiveness of 38% SDF as a Treatment for Caries Lesions in Comparison to Traditional Restorative Techniques: A 12 Month Randomized Controlled Trial

Whitney Yang, Margherita Fontana, George Eckert

To Evaluate:

- **Effectiveness of treatment** of cavitated caries in children by application of SDF in comparison to conventional restorative treatments (Hyp: Both effective)
- **Perceptions of parents and patients** to both treatment modalities and their levels of acceptability (Hyp: Both acceptable)
- **Perceptions of dental providers** in terms of ease of use and clinical time spent (Hyp: SDF easier)
- **Cost-effectiveness** of the two treatment approaches regarding both practitioner chair time and material-based cost (Hyp: SDF: cheaper)

Time point	Visit
Baseline	**SDF or Conventional Restoration (RANDOM ALLOCATION)**
1 month	Intermediate Contact *
2 months	Intermediate Contact
3 months	**Clinic Visit 2 (**Major & minor failure assessment, pain, parent satisfaction)
4.5 months	Intermediate Contact
6 months	**Clinic Visit 3** (Second SDF application, major & minor failure assessment, pain, parent satisfaction, radiographs**)**
9 months	Intermediate Contact
12 months	**Clinic Visit 4 (**Major & minor failure assessment, pain, radiographs, parent satisfaction, provider acceptability**)**

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* Intermediate Contacts: Attrition prevention, update contact information, follow-up on pain

- **Low cost, easy to use**
- **Arrest cavitated advanced lesions (PF: ~66-90%)**
- **Evidence limited, but some studies of good quality suggest this is an important alternative for some lesions in some patients to help control dental caries at the tooth level**

QUESTIONS?

Thank you!

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