Clinical Effectiveness of Silver Ion Products for Caries Control

Margherita Fontana, DDS, PhD

University of Michigan School of Dentistry
Department of Cariology, Restorative Sciences and Endodontics
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]

\[
Ca_{10}(PO_4)_6(OH)_2 + Ag(NH_3)_2F \rightarrow CaF_2 + Ag_3PO_4
\]

\[
+ \quad \text{NH}_4\text{OH}
\quad \text{Alkaline environment}
\]

- Antibacterial
- When in contact with dentin: Ag$_3$PO$_4$ (weakly soluble; turns black with sunlight or reducing agents) = Black, hard layer (>20mm deep enamel, Willerhausen et al., 2015; 50-200mm 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
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

Thus, use for caries control is “off label”
# Meta-analysis of studies using 38% SDF to arrest dentin caries

<table>
<thead>
<tr>
<th>Author, Year [Ref]</th>
<th>Method</th>
<th>% arrest of dentine caries</th>
<th>Risk of bias **</th>
</tr>
</thead>
</table>
| **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

Gao et al., 2016
Meta-analysis of studies using 38% SDF to arrest dentin caries

• 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)

Gao et al., 2016
Recommended UoM Technique (38% SDF)

- Caries removal does not offer any significant benefit in arresting caries (remove food debris)
- Dry lesion and saturate with SDF, wait ~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
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, Allison Scully, 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)
- **Opinions 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)
Enrollment

- Randomization across sites
  - 49 conventional restoration
  - 49 SDF

- Study Follow-up Period: 12 months

- Enrollment Period: 9 months
  - Enrollment began March, 2016 (UoM IRB: June 2015; Mott IRB: January 2016; 6 week wait for visits at Mott; Flint water-crisis issues almost halted recruitment between March-August 2016)
  - New Site added August, 2016*

- 98 total children
  - 49 children at Mott Children’s Health Center
  - 49 children at University of Michigan School of Dentistry Pediatric Clinic*
Inclusion Criteria

• Patients must be ages 2-10

• Presence of at least one active (soft) cavitated carious lesions in the primary dentition, extending into dentin (ICDAS 5 or 6) – Only one tooth will be selected for the study. All others will be restored and monitored according to the American Academy of Pediatric Dentistry (AAPD) guidelines

• The selected posterior (now also anterior teeth) tooth must have a one or two surface lesion (more than 1/3 of the crown of the tooth must be remaining) and must allow for direct application of SDF

• Study teeth will not have any spontaneous or elicited pain due to caries, tooth mobility, or signs of pulpal infection

• Selected primary teeth must have an anticipated exfoliation date greater than 12 months away
Exclusion Criteria

- Hereditary developmental defects such as Amelogenesis Imperfecta and Dentinogenesis Imperfecta
- Severe medical conditions that do not allow the child to be managed in the MCHC/UMSOD clinics
- Known allergy/sensitivity to dental materials being used, including SDF
- Inability of the child to cooperate for treatment, recall examinations, or periapical radiographs
- Wards of the State, for consenting reasons
<table>
<thead>
<tr>
<th>Time point</th>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>SDF or Conventional Restoration (RANDOM ALLOCATION)</td>
</tr>
<tr>
<td>1 month</td>
<td>Intermediate Contact *</td>
</tr>
<tr>
<td>2 months</td>
<td>Intermediate Contact</td>
</tr>
<tr>
<td>3 months</td>
<td><strong>Clinic Visit 2</strong> (Major &amp; minor failure assessment, pain, parent satisfaction)</td>
</tr>
<tr>
<td>4.5 months</td>
<td>Intermediate Contact</td>
</tr>
<tr>
<td>6 months</td>
<td><strong>Clinic Visit 3</strong> (Second SDF application, major &amp; minor failure assessment, pain, parent satisfaction, radiographs)</td>
</tr>
<tr>
<td>9 months</td>
<td>Intermediate Contact</td>
</tr>
<tr>
<td>12 months</td>
<td><strong>Clinic Visit 4</strong> (Major &amp; minor failure assessment, pain, radiographs, parent satisfaction, provider acceptability)</td>
</tr>
</tbody>
</table>

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

- **Intended to promote oral health**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>$50</td>
</tr>
<tr>
<td>Intermediate Contacts x 4</td>
<td>$10 x 4 = $40</td>
</tr>
<tr>
<td>3 month</td>
<td>$60</td>
</tr>
<tr>
<td>6 month</td>
<td>$70</td>
</tr>
<tr>
<td>12 month</td>
<td>$80</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$300</strong></td>
</tr>
</tbody>
</table>
Clinical Variables

- 5 trained and calibrated examiners
- Lesions will be assessed on:
  - Size (mm)
  - Dentin Color (yellow, brown, black)
  - Dentin Texture (soft, hard)
  - Periapical radiographs
- Success measured as Major (extractions, pulpotomies, etc.) and Minor Failures (caries progression, restoration needs repair, etc.)
- Both groups will receive OHI, F and diet instruction, sealants as necessary, traditional preventative care at recalls based on AAPD guidelines
<table>
<thead>
<tr>
<th></th>
<th>SDF Application</th>
<th>Conventional Restoration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success</strong></td>
<td>Caries arrested – dentin feels hard to explorer</td>
<td>Restoration appears satisfactory</td>
</tr>
<tr>
<td></td>
<td>No clinical signs or symptoms of pulpal pathology</td>
<td>No clinical signs or symptoms of pulpal pathology</td>
</tr>
<tr>
<td></td>
<td>Tooth exfoliated without major or minor failure</td>
<td>Tooth exfoliated without major or minor failure</td>
</tr>
<tr>
<td><strong>Minor Failure</strong></td>
<td>Caries progression – soft dentin, increase in lesion size clinically or radiographically</td>
<td>Secondary caries</td>
</tr>
<tr>
<td></td>
<td>Reversible pulpitis to be treated without pulpotomy or extraction</td>
<td>Restoration fracture or wear requiring repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of restoration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reversible pulpitis to be treated without pulpotomy or extraction</td>
</tr>
<tr>
<td><strong>Major Failure</strong></td>
<td>Pulpitis requiring pulpotomy or extraction</td>
<td>Pulpitis requiring pulpotomy or extraction</td>
</tr>
<tr>
<td></td>
<td>Abscess formation</td>
<td>Abscess formation</td>
</tr>
<tr>
<td></td>
<td>Caries progress to the extent that tooth is unrestorable</td>
<td>Abscess formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restoration loss leaving tooth unrestorable</td>
</tr>
</tbody>
</table>
Parent and Child Questionnaires

• Parent Questionnaires
  – Baseline, 3 months, 6 months, 12 months
  – Child’s oral hygiene, diet, opinion of appearance of child’s teeth, assessment for pain

• Child Questionnaires
  – Baseline, 3 months, 6 months, 12 months
  – Child’s opinion of how teeth look, any pain, ease of experience during the dental visit, pain during the dental visit

---

The next questions should be answered FOLLOWING today's treatment indicated by the study and prior to completion of the rest of the appointment.

1. How was your visit to the dentist today?
   - Easy
   - Some Easy & Some Hard
   - Hard

2. How did your visit to the dentist today feel?
   - Didn’t Hurt at All
   - Hurt a Little
   - Hurt a Lot
Current Participants

- MC-002
- MC-004
- MC-005
- MC-007
- MC-008
- MC-009
- MC-010
- MC-011
- MC-012
- MC-013

Baseline
1 month
2 month
3 month

Gender Distribution:
- Male: 5
- Female: 4

Age Distribution:
0
1
2
3
4
5
6
7
8
9
10

SCHOOL OF DENTISTRY
UNIVERSITY OF MICHIGAN
## Preliminary Findings: Child Questionnaire

### How do you feel about how your teeth look?

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Pre-tx)</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very Happy</td>
<td>Not Happy or Sad</td>
</tr>
<tr>
<td>SDF</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Conventional</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

### How do your teeth feel?

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Pre-tx)</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>They Feel Great</td>
<td>Sometimes They Hurt</td>
</tr>
<tr>
<td>SDF</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Conventional</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
# Preliminary Findings: Child Questionnaire

## How was your visit to the dentist today?

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Post-tx)</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Easy</td>
<td>Some Easy &amp; Some Hard</td>
</tr>
<tr>
<td>SDF</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Conventional</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

## How did your visit to the dentist today feel?

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Post-tx)</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Didn’t Hurt at All</td>
<td>Hurt a Little</td>
</tr>
<tr>
<td>SDF</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Conventional</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Preliminary Findings: Dentin

Dentin Color

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>3 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yellow</td>
<td>Brown</td>
<td>Black</td>
<td>Yellow</td>
<td>Brown</td>
</tr>
<tr>
<td>SDF</td>
<td>2</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conventional</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Dentin Hardness

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>3 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Soft</td>
<td>Hard</td>
<td>Soft</td>
<td>Hard</td>
<td></td>
</tr>
<tr>
<td>SDF</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Conventional</td>
<td>2</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Preliminary Findings: Treatment Time

• Conventional Treatment Time
  – Mean time: **23.5 minutes** (range 17-30 min; 2 treatments)

• SDF Treatment Time
  – Mean time: **6.3 minutes** (range 4-10 min; 7 treatments)
Providers’ Assessment

- Show feasibility and likelihood for future use

<table>
<thead>
<tr>
<th></th>
<th>Difficulty</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Easier</td>
<td>Harder</td>
</tr>
<tr>
<td>SDF</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Conventional</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preference</th>
<th>More Preferable</th>
<th>No Preference</th>
<th>Less Preferable</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDF</td>
<td>6</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Conventional</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>
Thank you!

QUESTIONS?