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J Dent Res 90(2):203-208, 2011

ABSTRACT

Tooth sensitivity is a common clinical problem. This multi-center randomized clinical trial assessed the effectiveness and safety of topical diammine silver fluoride. From two sites (Lima and Cusco, Peru), 126 adults with at least one tooth sensitive to compressed air were randomly assigned to either the experimental treatment or sterile water, and pain was assessed by means of a 100-mm visual analogue scale at 24 hours and 7 days. The diammine silver fluoride reduced pain at 7 days at both sites. At the Lima site, the average change in pain scores between baseline and day 7 for the silver fluoride group was -35.8 (SD = 27.7) mm vs. 0.4 (SD = 16.2) mm for the control group ($P < 0.001$). In Cusco, the average change in pain scores for the silver fluoride group was -23.4 (SD = 21.0) mm and -5.5 (18.1) mm for the control group ($P = 0.002$). No tissue ulceration, white changes, or argyria was observed. A small number of participants in the silver fluoride group experienced a mild but transient increase in erythema in the gingiva near the tooth. No changes were observed in the Gingival Index. We concluded that diammine silver fluoride is a clinically effective and safe tooth desensitizer.

KEY WORDS: tooth sensitivity, silver diamine fluoride, diammine silver fluoride, silver diamine fluoride, fluorides, topical.

DOI: 10.1177/0022034510388516

Received August 13, 2010; Revised September 3, 2010; Accepted September 3, 2010

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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.

Figure 1. Flow chart for clinical trial sites combined.

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 [$\text{Ag}(\text{NH}_3)_2\text{F}$, 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

Table 1. Tooth Sensitivity by Study Site and Condition

Study Site	Time	Condition		
Lima		Silver Fluoride (N = 37)	Control (N = 34)	P-value*
		Mean VAS (SD) [Range]	Mean VAS (SD) [Range]	
	Baseline	57.3 (26.7) [17, 99]	49.3 (19.3) [15, 84]	0.16
	24 hrs	28.2 (22.1) [2, 75]	52.1 (22.8) [16, 89]	
	Change from baseline	-29.1 (27.5) [-94, 10]	2.6 (15.3) [-44, 32]	< 0.0001
	7 days	21.5 (23.0) [1, 78]	49.9 (21.2) [9, 85]	
Cusco		Silver Fluoride (N = 26)	Control (N = 29)	P-value
		Mean VAS (SD) [Range]	Mean VAS (SD) [Range]	
	Baseline	51.7 (20.5) [22, 92]	51.6 (22.4) [16, 99]	0.98
	24 hrs	45.2 (24.1) [11, 87]	50.6 (22.0) [15, 95]	
	Change from baseline	-6.5 (13.1) [-34, 22]	-1.0 (11.7) [-37, 20]	0.11
	7 days	28.3 (21.8) [2, 94]	46.1 (24.4) [3, 92]	
	Change from baseline	-23.4 (21.0) [-56, 24]	-5.5 (18.1) [-77, 18]	0.0015

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

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

Study Site	Time	Condition		
Lima		Silver Fluoride (N = 37)	Control (N = 34)	
		n (%)	n (%)	P-value*
	Baseline	3 (8.1)	2 (5.9)	1.0
	24 hrs	3 (8.1)	2 (5.9)	1.0
	7 days	3 (8.1)	1 (2.9)	0.61
Cusco		Silver Fluoride (N = 26)	Control (N = 29)	
		n (%)	n (%)	P-value*
	Baseline	6 (23.1)	7 (24.1)	1.0
	24 hrs	10 (38.5)	2 (6.9)	0.0076
	7 days	3 (11.5)	3 (10.3)	1.0
Sites combined		Silver Fluoride (N = 63)	Control (N = 63)	
		n (%)	n (%)	P-value*
	Baseline	9 (14.3)	9 (14.3)	1.0
	24 hrs	13 (20.6)	4 (6.3)	0.035
	7 days	6 (9.5)	4 (6.3)	0.74

*Fisher's exact test

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 time-points), 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 3. Overall Gingival Index Score by Study Site and Condition

Study Site	Time	Condition		
Lima		Silver Fluoride (N = 37)	Control (N = 34)	P-value*
		Mean (SD) [Range]	Mean (SD) [Range]	
	Baseline	0.29 (0.24) [0.0, 1.2]	0.33 (0.35) [0.0, 1.5]	0.59
	24 hrs	0.28 (0.24) [0.0, 1.2]	0.35 (0.36) [0.0, 1.7]	
	Change from baseline	-0.01 (0.05) [-0.2, 0.1]	0.02 (0.07) [-0.2, 0.2]	0.076
	7 days	0.27 (0.23) [0.0, 1.2]	0.36 (0.39) [0.1, 1.8]	
Cusco	Change from baseline	-0.02 (0.09) [0.2, 0]	0.03 (0.13) [-0.5, 0.3]	0.076
		Silver Fluoride (N = 26)	Control (N = 29)	P-value*
		Mean (SD) [Range]	Mean (SD) [Range]	
	Baseline	0.47 (0.24) [0.1, 0.9]	0.38 (0.27) [0.0, 1.2]	0.19
	24 hrs	0.36 (0.21) [0.1, 0.8]	0.36 (0.24) [0.0, 1.2]	
	Change from baseline	-0.11 (0.16) [-0.6, 0.1]	-0.02 (0.12) [-0.3, 0.3]	0.020
Sites Combined	7 days	0.31 (0.19) [0.0, 0.8]	0.35 (0.26) [0.1, 1.2]	
	Change from baseline	-0.16 (0.27) [-0.8, 0.7]	-0.03 (0.09) [-0.3, 0.2]	0.023
		Silver Fluoride (N = 63)	Control (N = 63)	P-value**
		Mean (SD) [Range]	Mean (SD) [Range]	
	Baseline	0.36 (0.26) [0.0, 1.2]	0.35 (0.32) [0.0, 1.5]	0.72
	24 hrs	0.31 (0.23) [0.0, 1.2]	0.35 (0.31) [0.0, 1.7]	
	Change from baseline	-0.05 (0.12) [-0.6, 0.1]	0.00 (0.10) [-0.3, 0.3]	0.0023
	7 days	0.28 (0.22) [0.0, 1.2]	0.35 (0.33) [0.1, 1.8]	
	Change from baseline	-0.08 (0.20) [-0.8, 0.7]	0.00 (0.12) [-0.5, 0.3]	0.0028

*Two-sample test (unequal variances).

**Analysis of covariance, adjusted for study site, with heteroscedasticity-consistent standard errors.

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.

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).

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.*, 2006).

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.

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.

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