A Clinical Study to Assess the Effect of a Stabilized Stannous Fluoride Dentifrice on Hypersensitivity Relative to a Marketed Sodium Fluoride/Triclosan Control

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Abstract

- **Objective:** To evaluate the efficacy of a marketed stabilized stannous fluoride (SnF_2) dentifrice in reducing dentinal hypersensitivity as compared to a marketed sodium fluoride (NaF)/triclosan dentifrice over an eight-week period.
- **Methods:** Adults with confirmed dentinal hypersensitivity were enrolled in this randomized and controlled, parallel group, double blind, eight-week, single-center clinical trial. Random assignment to one of two dentifrice test groups via age, gender, and thermal sensitivity of enrolled test teeth was performed at baseline, with subjects assigned to twice-daily unsupervised brushing with either the marketed SnF_2 dentifrice (Oral-B® Pro-Expert, 0.454% SnF_2 plus 0.077% NaF) or the marketed 0.32% NaF with 0.3% triclosan/copolymer dentifrice control (Colgate® Total® Advanced). Tactile sensitivity (Yeaple Probe) and thermal sensitivity (air-blast/Schiff Air Index) evaluations of the selected test teeth were performed at baseline pre-treatment, and again at Weeks 2 and 8 of product use to compare the dentifrices' relative hypersensitivity protection effectiveness.
- **Results:** Ninety-seven (97) of the 100 enrolled subjects completed the trial and were fully evaluable. At both Week 2 and Week 8, for both the thermal and tactile evaluation measurements, subjects brushing with the marketed SnF_2 dentifrice experienced statistically significantly ($p < 0.0001$) superior average dentinal hypersensitivity improvement versus subjects assigned to the NaF/triclosan control dentifrice. Between groups, superior relative mean reduction in thermal Schiff Air Index favored SnF_2 by 24% at Week 2 and 68% at Week 8, while greater relative mean tactile Yeaple Probe benefits were observed for SnF_2 relative to the control by 114% after Week 2 and 184% at Week 8. The dentifrices were well-tolerated.
- **Conclusion:** Twice-daily brushing with a marketed SnF_2 dentifrice provided superior dentinal hypersensitivity improvement versus a commercially available NaF/triclosan dentifrice, with significantly ($p < 0.0001$) greater relief after two weeks, and even larger relative benefits at eight weeks.

(J Clin Dent 2014;25:13–8)

Introduction

A welcome trend is the increasing attention given to developing easily accessible, yet effective products to ameliorate the common patient complaint of dentinal hypersensitivity, generally defined as an acute, transient pain arising from exposed dentin in response to exogenous stimuli, and not explainable by other dental pathologies or defects.[1,2] Perhaps thought of by many laypersons as an annoying, but relatively benign problem when contrasted with other adverse clinical entities, in fact dentinal hypersensitivity can significantly impact daily quality of life around food and drink, and lead to patient neglect behaviors, such as not performing oral hygiene in sensitive areas and foregoing clinical examinations. These avoidance practices, motivated by anticipation of pain, can compound patient issues rather than reduce suffering over time, leading to additional conditions requiring more extensive restoration.

Dentinal hypersensitivity is primarily associated with gingival recession, which can result from overly aggressive tooth brushing and periodontal disease.[3] Tooth wear may also result in hypersensitivity; frequently consuming popular acidic beverages can precipitate chemical erosion of tooth enamel or cementum that exposes dentin, leading to chronic discomfort when untreated.[4-7] With lifespans and total number of dentate years generally increasing worldwide, the cumulative additive effects of lifestyle choices and unavoidable wear will likely keep dentinal hypersensitivity prevalence at current or even higher levels in the absence of effective intervention.[8] Existing prevalence data vary by locale and studied population, but published reports have estimated that perhaps one-third to one-half of adults are afflicted by dentinal hypersensitivity, with the condition typically more common in females than males, significantly more prevalent in periodontal patients as well as those exposed to dietary and gastric acids, and most frequently impacting the cervical regions of premolars and canines.[9-16]

When dentin is exposed via a chemical or mechanical insult, external stimuli (tactile, thermal, or osmotic) can generate a heterogenic spectrum of discomfort of variable intensity, which may be very pronounced in some individuals. A widely accept-

ed theory of causation, known as Brännström's Hydrodynamic Theory,[17] indicates this acute transient pain response is attributable to the rapid movement of fluid instigating nerve receptor stimulation in exposed open patent dentinal tubules. While some products for dentinal hypersensitivity management (*e.g.*, potassium-based) attempt to interfere with pain-causing nerve response in the pulp, other researchers have focused on formulating antisensitivity products with ingredients that occlude open dentin tubules, thus blocking the sequence of pain generation at its source. One such desensitizing agent, with well-replicated laboratory and clinically proven benefits, is stannous fluoride (SnF_2), which forms durable smear layers on tooth surfaces that occlude open dental tubules and thus impede the pulpal nerve arousal brought about by external stimuli, such as cold air exposure.[18,19] *In vitro* investigations, including those conducted by von Koppenfels,[20] Zsiska, *et al.*,[21] and White, *et al.*[22] have demonstrated the ability of SnF_2 compounds to rapidly form chemical precipitates that obstruct dentinal tubules, thus creating an occlusive barrier on the exposed dentin that resists the mechanical and chemical affronts typically experienced as pain by hypersensitivity sufferers.

While SnF_2 has been utilized in toothpastes for decades,[23] contemporary advances in stabilization via formulation innovation have rendered SnF_2 a reliable and highly efficacious desensitizing agent in formulations that simultaneously offer multiple therapeutic benefits.[24] The clinical superiority of a stabilized 0.454% SnF_2 dentifrice (Crest® Pro-Health™, Procter & Gamble, Cincinnati, OH, USA) relative to non-SnF_2 dentifrice controls in reducing dentinal hypersensitivity in confirmed hypersensitivity sufferers has been described in several published reports.[25-28] Schiff and colleagues compared SnF_2 dentifrice to NaF controls in two independent investigations and found that SnF_2 significantly outperformed the others in pain reduction after both four and eight weeks of home use, with relative benefits of up to 44% and 71% for thermal and tactile sensitivity, respectively.[27,28]

Recently, the ability to provide antisensitivity relief through the occlusion of dentinal tubules with silica has been reported for an NaF/triclosan dentifrice marketed in the United Kingdom.[29] The aim of the eight-week clinical study reported herein was to assess the efficacy in reducing dentinal hypersensitivity by a marketed 0.454% SnF_2 dentifrice when compared to a marketed NaF/triclosan control dentifrice at both short-term (two weeks) and longer time points, using two validated effectiveness measurements.

Materials and Methods

This double blind, randomized and controlled, eight-week, parallel group clinical investigation evaluated the relative benefits of two commercially available fluoride dentifrices in subjects with pre-existing moderate dentinal hypersensitivity:

- 0.454% SnF_2 plus 0.077% NaF (1450 ppm fluoride), marketed in the United Kingdom as Oral-B® Pro-Expert dentifrice (Procter & Gamble, Gross Gerau, Germany); and
- 0.32% NaF (1450 ppm fluoride) with 0.3% triclosan, marketed in the United Kingdom as Colgate® Total® Advanced dentifrice (Colgate-Palmolive, Dublin, Ireland).

Prior to study initiation, an independent Institutional Review Board reviewed and provided approval of the study protocol and subject consent form. Generally healthy adult volunteers between 18 and 65 years of age, providing written informed consent, and possessing at least two teeth demonstrating reproducible sensitivity to thermal and tactile stimuli were potentially eligible for study inclusion. For enrollment at the baseline visit, participants were additionally required to be current users of a non-desensitizing fluoride dentifrice.

Volunteer participants were excluded from enrollment if any of the following criteria applied: gross oral neglect or the need for extensive dental therapy; daily usage of anticonvulsant medications, sedatives, tranquilizers, or any other mood altering drugs; pregnancy or lactation; chronic disease associated with intermittent episodes of pain or constant daily pain, such as arthritis; participation in a desensitizing dentifrice clinical study within the preceding two months; or receipt of a dental prophylaxis within two weeks of the study baseline visit. The use of antihistamines, analgesics, and anti-inflammatory drugs was prohibited within 48 hours prior to all study visits.

Enrolled subjects attended three study visits: Baseline, Week 2, and Week 8. At the baseline study visit, subject medical and dental histories were reviewed, followed by a comprehensive oral soft and hard tissue evaluation. The clinical examiner subsequently assessed the presence or absence of dental hypersensitivity deemed moderate in severity via the Yeaple Probe[27,28] tactile evaluation, performed twice consecutively on potentially eligible sensitive test teeth, where enrollment required responsiveness to a Yeaple Probe force setting of 10 grams both times. This was followed within a minimum of five minutes by a thermal sensitivity evaluation using the Schiff Air Sensitivity examination,[30] with required Schiff Air Sensitivity scale scores greater than 1. If subjects displayed responsiveness to the hypersensitivity evaluations and met all other study eligibility criteria, they were enrolled in the clinical trial.

The clinical examiner selected two test teeth (canine or premolar) for each enrolled subject in different quadrants and displaying signs of facial/cervical erosion, abrasion, or gingival recession. Sensitive teeth were not selected as test teeth if they were fully crowned or had extensive caries or cracked enamel. Test teeth could not have deep, defective, or facial restorations, or serve as abutments for fixed or removable partial dentures. Additional disqualifying characteristics for test teeth included bleeding on probing, scaling and root planing, or periodontal surgery within the preceding three and six months, respectively, prior to study inception.

Following the sensitivity measurements, participants were randomly assigned to either the SnF_2 or the NaF/triclosan dentifrice test group; randomization occurred using an encoded computer program following subject stratification according to age, gender, and baseline cold air sensitivity scores for enrolled teeth. In a clinical site room area not accessible to the clinical grader for purposes of assuring study blinding, subjects were provided with identically appearing kits containing their assigned study dentifrice (packaged with toothpaste identity disguised), an Oral-B® Indicator regular soft manual toothbrush (Procter & Gamble, Cincinnati, OH, USA), a timer, and verbal and writ-

ten brushing instructions, and told to use the assigned study products in place of their normal oral hygiene for the duration of the study. Subjects were directed to brush thoroughly at home twice daily, once each morning and evening, for one timed minute after applying enough of their assigned toothpaste to cover the top of the toothbrush bristles.

At two weeks post-baseline and again at Week 8, subjects returned for clinical evaluations to determine the desensitizing effects of twice-daily brushing with their assigned test dentifrice. Evaluation visits were consistently scheduled for either morning or afternoon to minimize any intra-subject diurnal pain/discomfort variation. At both Week 2 and Week 8, after confirmation of continuing study eligibility, evaluable subjects received an oral hard and soft tissue evaluation to assess any product effects. Product desensitizing efficacy testing was then performed on the selected test teeth using the same procedures as at baseline; the Yeaple Probe tactile evaluation followed by the cold air blast examination.

Efficacy Assessments

Tactile Sensitivity. A pre-calibrated Yeaple Probe[27,28] (Model 200A Yeaple Electronic Force Sensing Probe, XinX Research, Inc., Portsmouth, NH, USA) evaluated baseline and Weeks 2 and 8 tactile sensitivity. The clinical examiner used a #16 explorer tip and made two horizontal sweeps with the probe tip, keeping it perpendicular to the root surface of the tested tooth, across the facial surfaces of the sensitive area at each force setting. At baseline, testing began at 10 grams of force, and where a pain response was elicited, teeth were re-challenged at 10 grams; only those teeth responding positively to both challenges could be designated as test teeth. At the Week 2 and Week 8 visits, testing was initiated at 10 grams and increased as applicable by 10 grams incrementally to 50 grams, with each successive challenge increasing until a subject's "yes" pain response was repeated. If a second "yes" was not obtained, the force setting was increased to the next level until a force setting elicited two consecutive "yes" responses (recorded as the threshold). If no sensitivity was noted up to 50 grams, 50 grams was recorded as the threshold.

Thermal Air Sensitivity. Thermal sensitivity was determined at study baseline and Weeks 2 and 8 utilizing the Schiff Air Sensitivity Index.[30] A one-second application of cold air was delivered to study test teeth from a standard dental unit syringe at a temperature of 70° ± 5°F and pressure of 40–60 psi. Subject response to the cold air blast was quantified with the Schiff Air Sensitivity Index using the following scale:

0 – Tooth/subject did not respond to air stimulus.
1 – Tooth/subject responded to air stimulus but did not request discontinuation of stimulus.
2 – Tooth/subject responded to air stimulus and requested discontinuation or moved from stimulus.
3 – Tooth/subject responded to air stimulus, considered stimulus to be painful, and requested discontinuation of the stimulus.

Statistical Analyses

Pre-study sample size calculations indicated that 47 subjects per group completing the trial would provide a minimum of 80% power to detect a mean difference between test dentifrices for the sensitivity assessments, using two-sided testing with a 5% significance level. This estimate assumed the effect size (mean treatment difference divided by the standard deviation) was approximately 0.60 or higher. The total sample size estimate of roughly 100 subjects allowed for approximately a 5% dropout rate.

The tooth-level scores were averaged for each subject to derive a subject-level score, and subject-level scores were calculated for each sensitivity efficacy measurement and visit. Between-group comparisons of the subject-level data were performed for the baseline, Week 2, and Week 8 time points. Since baseline tactile Yeaple Probe scores were 10 for all subjects, between-group comparisons were performed at post-baseline visits using analysis of variance. For the thermal Schiff Air Index, analysis of covariance was performed, adjusting for the baseline score as a covariate and the model estimated different variances for each dentifrice group. Standard errors (SE) of the means were reported quantifying the uncertainty of that estimate. Statistical comparisons utilized two-sided testing with a 0.05 significance level. Demographic, baseline, and safety data were summarized overall and by treatment group. Common summary statistics of the subject level data, such as means, standard deviations (SD), and percentages, were calculated. Between-group comparisons for age used analysis of variance; the Chi-squared test was used for gender.

Results

A total of 100 adult subjects (50 per group) were enrolled and randomized to one of the two test dentifrice groups at baseline. Three subjects (one in the SnF_2 group and two in the NaF/triclosan control group) were lost to follow-up after the Week 2 visit, thus 97 subjects (97%) completed the entire eight-week trial and were fully evaluable for statistical analyses. The mean age of the study population was 45.5 years, with a range of 21 to 65 years. Female subjects accounted for 79% of all participants. With respect to age and gender, the test groups were well balanced ($p \geq 0.24$). Table I summarizes the baseline demographic characteristics.

Tactile Sensitivity

The outcomes of the Yeaple Probe evaluations to assess the relative effects of the SnF_2 and NaF/triclosan dentifrices on tactile dentinal hypersensitivity are presented in Table II and Figure 1. At baseline, per study eligibility criteria, scores were 10 grams of force for all enrolled subject study teeth. Higher scores were

Table I
Baseline Subject Demographics

	SnF_2	NaF/triclosan	Total
Characteristic	N = 50	N = 50	N = 100
Mean Age (SD)[a]	46.6 (9.88)	44.4 (8.70)	45.5 (9.32)
Age Range	25-64	21-65	21-65
Female (N, %)[b]	40 (80%)	39 (78%)	79 (79%)
Male (N, %)[b]	10 (20%)	11 (22%)	21 (21%)

SD = standard deviation; N = number of subjects
[a]Two-sided analysis of variance (ANOVA) was used to compare mean age between the two groups (p = 0.24).
[b]Two-sided Chi-Square test was used to assess balance of percentage between the two groups for gender (p = 0.81).

Table II
Treatment Comparisons for Tactile and Thermal Sensitivity

Measure	Mean (SE) Baseline Score	Analysis of Variance Mean (SE) Week 2 (N = 100)[a]	Week 8 (N = 97)[a]
Tactile (Yeaple Probe)[b]			
SnF_2	10 (0)	25.20 (0.78)	37.25 (0.57)
NaF/triclosan	10 (0)	11.80 (0.49)	13.13 (0.68)
SnF_2 greater benefit vs. control		114%	184%
2-sided p-value		p < 0.0001	p < 0.0001
		Analysis of Covariance Adjusted Mean (SE)	
Thermal (Schiff Air Index)[c]			
SnF_2	2.63 (0.044)	1.51 (0.050)	0.61 (0.050)
NaF/tricosan	2.65 (0.042) (p = 0.74)[d]	2.00 (0.066)	1.90 (0.077)
SnF_2 greater benefit vs. control		24%	68%
2-sided p-value		p < 0.0001	p < 0.0001

SE = standard error; N = number of subjects
[a]Week 2: 50 subjects/group; Week 8: 49 and 48 subjects in SnF_2 and control, respectively.
[b]Yeaple Probe scores are in grams (g), and higher scores indicate less tooth sensitivity. All subjects had a baseline score of 10.
[c]Lower Schiff Air Index scores indicate less tooth sensitivity, and means were adjusted due to the baseline covariate.
[d]Baseline mean comparison between groups used analysis of variance.

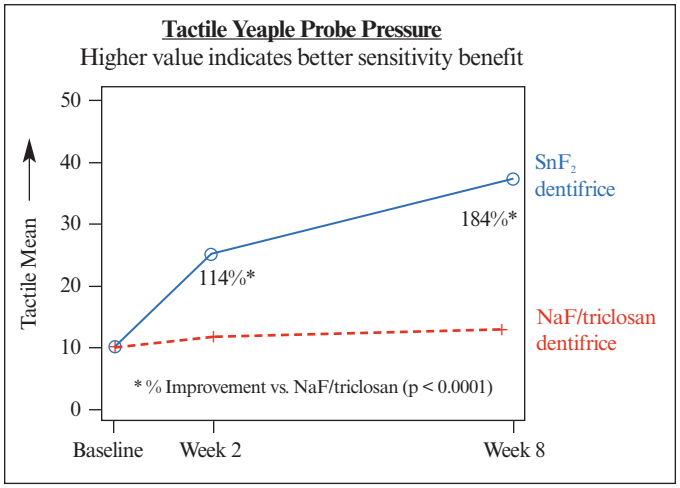

Figure 1. *Mean Yeaple Probe by dentifrice and visit, where higher averages indicate greater tolerance to tactile sensitivity stimulus.*

indicative of a better tolerance of the tactile sensitivity stimulus. Following twice-daily brushing with the assigned test dentifrice, at Week 2 post-baseline the mean (SE) tactile sensitivity scores for the SnF_2 and NaF/triclosan groups were 25.2 (± 0.8) and 11.8 (± 0.5), respectively. Higher Yeaple Probe scores indicate less tooth sensitivity, and the statistically significantly ($p < 0.0001$) higher mean score for SnF_2 users compared to NaF/triclosan users signified a 114% greater desensitizing benefit for SnF_2. At Week 8, both dentifrices produced additional desensitizing improvement beyond that measured at Week 2. Mean (SE) Yeaple Probe scores were 37.2 (± 0.6) with use of SnF_2, and 13.1 (± 0.7) for the NaF/triclosan control group, representing a 184% significantly greater hypersensitivity benefit for SnF_2 versus the NaF/triclosan control dentifrice ($p < 0.0001$).

Thermal Sensitivity

Table II and Figure 2 depict the Schiff Air Index thermal sensitivity effectiveness results. At baseline, there were no statistically significant between-group differences, with SnF_2 and NaF/triclosan control group mean scores of 2.63 and 2.65, respectively ($p = 0.74$). For thermal Schiff Air Index, lower scores indicate less sensitivity to thermal stimulus. After two weeks of unsupervised twice-daily assigned dentifrice use, the SnF_2 group demonstrated a significantly ($p < 0.0001$) greater reduction in thermal sensitivity relative to the NaF/triclosan control, with Schiff Air Index adjusted means (SE) of 1.51 (± 0.05) for SnF_2 and 2.00 (± 0.07) for NaF/triclosan. The Week 2 thermal sensitivity mean reduction for the SnF_2 group relative to the NaF/triclosan control group was 24%. By Week 8, the mean difference between groups increased further favoring the SnF_2 dentifrice compared to the NaF/triclosan dentifrice, with a statistically significant ($p < 0.0001$) reduction of 68% in thermal Schiff Air Index sensitivity, with adjusted means (SE) of 0.61 (± 0.05) and 1.90 (± 0.08), respectively.

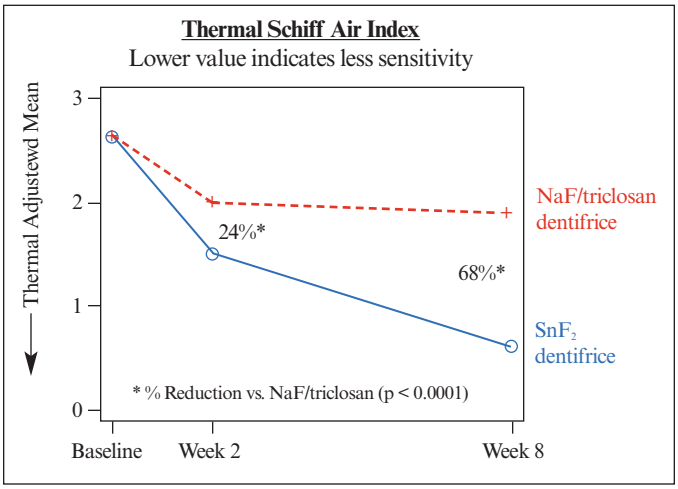

Figure 2. *Adjusted mean Schiff Air Index by dentifrice and visit, where lower averages indicate less sensitivity to thermal stimulus.*

Safety

Both study dentifrices were well tolerated, with no reported or clinically observed adverse events.

Discussion

Unlike conditions such as gingivitis which can sometimes go unnoticed, the manifestations of dentinal hypersensitivity are by definition completely obvious to the sufferer. Accordingly, those afflicted must either compensate by attempting to constantly avoid sources of pain or, preferably, seek treatment to alleviate the acute discomfort brought on by what are, for most people, innocuous thermal, chemical, and/or mechanical stimuli. Both in-office and over-the-counter dentinal hypersensitivity treatments are available.[3] For many, an antisensitivity product which is not only effective but value-oriented, simple to access, and esthetically pleasing is an attractive treatment option. Because

changing oral hygiene routines long-term is notoriously challenging,[31] simply replacing one's regular dentifrice with a toothpaste that offers rapid desensitizing relief may be a winning home management solution with maximum compliance. If the dentifrice provides additional clinically proven therapeutic and cosmetic benefits beyond desensitizing, the patient now has a convenient one-source product targeting their most pressing oral/dental health needs.

There is a sizable body of published clinical research on stabilized SnF_2 dentifrice, both substantiating its method of action and supporting its predictable rapid and clinically meaningful desensitizing benefits against a number of different positive and negative controls.[18-22,24-28] The results of this current trial are again consistent with prior investigations, where the stabilized 0.454% SnF_2 dentifrice significantly outperformed the control dentifrice; in this instance with relative benefits of 68% and 184% significantly less thermal and tactile sensitivity, respectively, versus the NaF/triclosan dentifrice by Week 8 following twice-daily brushing. And as in the previous clinical studies, the robust desensitizing relief provided by the SnF_2 dentifrice was noticeable in as early as two weeks, as demonstrated by the statistically significant improvements compared to the marketed control, and continued to increase in magnitude with ongoing usage out to eight weeks. Such rapid and incrementally increasing desensitizing relief brought about by simply changing one's dentifrice in the already established practice of tooth brushing is likely to be encouraging and motivational.

An awareness of the published literature is helpful to the clinician in making product recommendations to patients. As dentinal hypersensitivity is diagnosed and evaluated over time primarily based on subjective input, well-controlled comparative research is essential in evaluating the relative merits of different dentifrices with hypersensitivity reduction claims. In this clinical trial, careful attention was used to avoid potential confounding factors, including use of well-validated measures of sensitivity, subject scheduling to minimize potential diurnal pain variability, and blinding to product assignments of both participants and evaluators.

The results of this eight-week clinical study clearly demonstrate that the marketed SnF_2 dentifrice provides statistically significantly superior hypersensitivity relief using two separate symptom outcome parameters after just two weeks of use compared to the NaF/triclosan control toothpaste, and the comparative benefits increased in magnitude versus the control dentifrice with continued use. Notably, twice-daily brushing with Oral-B Pro-Expert dentifrice produces significant sensitivity protection while concurrently providing clinically proven anticaries, antigingivitis, antiplaque, antitartar, antistain, and breath protection benefits.[24]

Acknowledgements: The authors thank Shelly Campbell for her assistance with manuscript preparation, as well as Holly Eynon and Vickie Widmeyer for their involvement in the conduct of the research. The study was supported by Procter & Gamble.

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