ABSTRACT: Purpose: To assess the efficacy of a novel stannous-containing dentifrice in the reduction of dentin hypersensitivity when compared to a marketed positive control dentifrice. Methods: An 8-week, single-center, randomized, parallel group, two-treatment, double-blind clinical study was conducted in a generally healthy adult population with moderate thermal and tactile dentin hypersensitivity. A total of 60 adults were enrolled into the study. Participants were stratified at baseline by age, gender, and cold air sensitivity scores, and randomly assigned to either an experimental stannous-containing sodium fluoride dentifrice or a marketed potassium nitrate positive control. Brushing was supervised on site after baseline and Week 4 examinations. All other product usage was unsupervised. Subjects brushed 2 minutes twice daily. At baseline, Week 4 and Week 8, efficacy outcomes were assessed for tactile sensitivity via the Yeaple Probe, and for thermal sensitivity with air-blast/Schiff Air Index. Results: Fifty-eight subjects completed all evaluations. Both the experimental stannous-containing and positive control dentifrices provided significant (P<0.05) reductions in both tactile and thermal dentin hypersensitivity compared to baseline at both Weeks 4 and 8. There were no significant differences in Yeaple Probe or Schiff Air Index results between the dentifrices with either efficacy measurement at Week 4 and Week 8 (P≥ 0.5375). (Am J Dent 2010;23 Sp Is B:17B-21B).

CLINICAL SIGNIFICANCE: A novel stannous-containing dentifrice provided comparable reductions in dentin hypersensitivity to a marketed positive control, with the advantage of offering multiple therapeutic benefits in a single formulation.

Introduction

Afflicting perhaps 15% of the adult population worldwide,1,2 and possibly up to 57% in some regions,2,3 dentin hypersensitivity is a frequent patient malady, most commonly affecting the premolar and canine facial surfaces. The etiology of tooth sensitivity can stem from multiple sources, such as chemical erosion, traumatic oral hygiene and periodontal disease. The resulting gingival recession, enamel loss, or root surface denudation that exposes the dentin tubules leads to the transient pain and discomfort elicited by tactile, thermal, or osmotic stimuli.5

First-line treatment for dentin hypersensitivity sufferers often includes an over-the-counter desensitizing dentifrice, typically incorporating either potassium nitrate or stannous fluoride as the key active ingredient.6 Brännström’s widely-accepted hydrodynamic theory asserts that tooth sensitivity is caused by the provocation of rapid fluid movement in the tubules, which stimulates nerve terminals following exposure to a stimulus.6,7 By occluding the dentin tubules via precipitation of the stannous ions and thus blocking the nerve stimulus response,8 stannous-containing products have been clinically proven in multiple trials to reduce hypersensitivity.9-13 Potassium nitrate products have also been shown to improve tooth sensitivity in many clinical studies,14-17 with the mechanism of action reported to occur through disruption of the nerve synapses.18,19

The well-documented success of stannous fluoride as a desensitizing agent was somewhat marred by the association with extrinsic staining and suboptimal esthetics in its initial period of use.20 In the last few years, reformulated, stabilized stannous-containing product introductions have overcome these barriers to patient acceptance.12,13 A unique experimental dentifrice containing sodium fluoride (1450 ppm F”) as the active ingredient and a stannous source (stannous chloride as a key excipient) has recently been developed, and these two agents combine intraorally during toothbrushing to form a bioavailable stannous-fluoride complex. The formula utilizes polychelation technology to prevent stain and stabilize the stannous-fluoride complex.21

As reported elsewhere in this issue,22 well-controlled clinical research has shown that the extrinsic staining profile of this novel experimental stannous-containing dentifrice is not different from that of a marketed non-staining triclosan dentifrice.

The 8-week clinical trial reported here was conducted to determine the desensitizing efficacy of the novel experimental stannous-containing dentifrice in comparison to a 5% potassium nitrate-containing positive control dentifrice.

Materials and Methods

This 8-week, single-center, randomized, parallel group, two-treatment, double-blind clinical study was conducted in Xian, China in 2009. An institutional review board, Clinical Research Center IRB, reviewed and approved the study protocol and the consent form prior to the start of the trial. The recruited study population included generally healthy adults at least 18 years of age who presented with baseline moderate tactile and thermal sensitivity on at least two canine and/or premolar teeth, and who met all other inclusion and exclusion criteria (Table 1).

After providing written informed consent at the baseline visit, enrolled subjects were stratified on age, gender and baseline cold air sensitivity score, and randomly assigned to
either: (1) the experimental dentifrice (1450 ppm F- sodium fluoride as active ingredient; stannous chloride as a key excipient); or (2) the positive control dentifrice Crest Sensitivity Protectiona (Crest SP) - 5% potassium nitrate (KNO₃) within fluoride as active ingredient; stannous chloride as a key excipient: (1) the experimental dentifrice (1450 ppm F- sodium fluoride as active ingredient; stannous chloride as a key excipient); or (2) the positive control dentifrice Crest Sensitivity Protectiona (Crest SP) - 5% potassium nitrate (KNO₃) within fluoride as active ingredient; stannous chloride as a key excipient.

Inclusion criteria

- Generally healthy adults between 18 and 65 years of age.
- Moderate dentin hypersensitivity, as defined by a baseline Yeaple Probe score of 10 grams and a Schiff Air Score > 1.0 on at least two premolar/canine teeth in separate quadrants.
- Study teeth have signs of facial/cervical erosion, abrasion, and/or gingival recession.
- Agreement to refrain from taking analgesics, antihistamines or anti-inflammatory drugs within 48 hours prior to all evaluations.

Exclusion criteria

- Self-reported pregnant or nursing females.
- Chronic disease which is associated with intermittent episodes of constant daily pain, e.g., arthritis.
- Current use of a desensitizing dentifrice.
- Known allergy to commercial dental products or cosmetics.
- Anticonvulsants, sedatives, tranquilizers, or other mood-altering drugs taken daily.
- Participation in a desensitizing dentifrice clinical study within the previous 2 months.
- Teeth: 1) with severe gingivitis at the mid-radicular site; or 2) with deep, defective, or facial restorations, full crowns, extensive caries, or cracked enamel; or 3) used as abutments for fixed or removable partial dentures; or 4) which have been periodontally surgicated within the previous 6 months, or scaled/root planed within the past 3 months; or cleaned via dental prophlaxis within the previous 2 weeks.

For the purpose of blinding, test dentifrices were packaged in identically-appearing white tubes. The randomization sequence was prepared by the Clinical Supplies Logistics Department. Each subject received two tubes of their assigned dentifrice from site personnel along with a Crest soft toothbrush, a timer, and an instruction sheet, all packaged in a subject kit labeled with the study number, product number and relevant required cautionary/usage information. Home use instructions directed participants to pre-wet the toothbrush, cover the length of the brush head with the assigned dentifrice, and brush all surfaces of the teeth for 2 minutes – using the timer provided – before expectorating or diluting with water. Brushing was to occur twice daily (morning and evening) for the duration of the 8-week study period. A monitored, on-site brushing was also performed at the baseline and Week 4 visits under the supervision of clinical site personnel.

At both subject recall examination visits, subjects were questioned to determine protocol adherence and continuing study eligibility (Table 1), including the postponement of elective dentistry and dental prophylaxis prior to study completion, and use of any mouthrinses or dentifrices other than those assigned.

A trained clinical grader conducted both of the efficacy evaluations at each subject visit. The examiner was blinded to subjects’ test dentifrice assignments and was not given access to the areas dedicated to product assignment and/or supervised brushing. Product efficacy was evaluated via two different parameters – mechanical (tactile) and thermal sensitivity – using separate measures. At baseline, tactile sensitivity was assessed first with a pre-calibrated Yeaple Probe (Model 200A Yeaple Electronic Force Sensing Probeh) set to 10 grams of force. Testing began at 10 grams of force and increased by 10 grams up to a maximum of 50 grams as applicable. Each successive challenge increased until a “yes” subject response of discomfort occurred, and then the challenge was repeated. If a second ”yes” was not obtained, the force setting was increased to the next 10 gram increment and continued until a setting elicited two consecutive ”yes” responses; this was recorded as the threshold response. If no sensitivity was present up to 50 grams, the value “> 50g” was the threshold.

After the Yeaple Probe examination, the clinical grader assessed thermal sensitivity. Teeth anterior to the first molars received a 1-second application of cold air delivered from a standard dental unit syringe at a pressure of 40-60 psi and temperature of 70°F ± 5°F. The presence or absence of discomfort in response to the air blast was documented according to the Schiff Air Indexes as follows:

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 responds 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.

At the Week 4 and Week 8 visits, subjects were re-tested for tactile and thermal tooth sensitivity.

To compare treatment differences between the dentifrices and the change from baseline for each group, statistical data analyses were carried out on the average of the two most sensitive teeth selected from baseline. Treatment differences were assessed separately at Weeks 4 and 8. All pairwise comparisons were two-sided at the 0.05 level of significance. At least 24 subjects per group completing the study ensured at least 80% power to detect a difference of 0.6 on the Schiff scale and a difference of 10 on the Yeaple scale between the treatment groups with a common standard deviation of 0.7 (Schiff) and 12 (Yeaple), in two-sided testing at a 0.05 significance level. Considering the possible subject drop out, up to 30 subjects were recruited for each group (up to 60 subjects in the study).

**Results**

Sixty subjects enrolled in the trial at baseline. Two subjects withdrew prior to the Week 8 visit, and thus 58 participants – 30 in the experimental stannous-containing den-
The results of the Yeaple Probe tactile evaluations are shown in Table 3 and Fig. 1. The baseline sensitivity score was 10 grams for all study subjects. At Week 4, the mean sensitivity score was 18.4 for the experimental stannous-containing dentifrice group and 18.8 for the positive control group, which was an increase of 83.9% and 87.9% from baseline respectively, demonstrating statistically significant improvements in tactile sensitivity compared with baseline for both dentifrices (P<0.05). These improvements were not statistically different (P=0.8978) between test groups.

At Week 8 (Table 3, Fig. 1), there were additional gains in tactile sensitivity reduction for both dentifrice groups, with mean Yeaple Probe scores of 25.3 and 25.4 for the experimental dentifrice and positive control groups, representing an increase of 153% and 154% from baseline respectively. The difference of 0.1 between the test dentifrices was not statistically significant (P=0.9949).

Schiff Air Index results are presented in Table 4 and Fig. 2, representing thermal sensitivity changes at Weeks 4 and 8 following the air-blast evaluation. At baseline, the two dentifrice groups were balanced (P=0.7274): the experimental stannous containing dentifrice group had a mean score of 2.26, while the mean for the positive control group was 2.29. After 4 weeks of twice daily dentifrice use, the adjusted 4-week means were 1.43 and 1.47 for the experimental stannous-containing and positive control groups, respectively, which were percent reductions of 36.5% and 36.0% from baseline. The difference between the two groups was not statistically different (P=0.7787).

**Table 3. Tactile sensitivity (Yeaple Probe) results: Week 4 and Week 8 - evaluable subjects.**

<table>
<thead>
<tr>
<th>Week</th>
<th>Experimental</th>
<th>Crest SP</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stannous (n=31) 10.00 18.4 (2.19)</td>
<td></td>
<td>0.8978</td>
</tr>
<tr>
<td></td>
<td>Crest SP (n=29) 10.00 18.8 (2.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 8</strong></td>
<td>Experimental</td>
<td>Stannous (n=30) 10.00 25.3 (2.55)</td>
<td>0.9949</td>
</tr>
<tr>
<td></td>
<td>Crest SP (n=28) 10.00 25.4 (2.64)</td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 4. Thermal sensitivity (Schiff Air Index) results: Week 4 and Week 8 - evaluable subjects.**

<table>
<thead>
<tr>
<th>Week</th>
<th>Experimental</th>
<th>Crest SP</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stannous (n=31) 2.26 (0.36) 1.43 (0.08)</td>
<td></td>
<td>0.7787</td>
</tr>
<tr>
<td></td>
<td>Crest SP (n=29) 2.29 (0.41) 1.47 (0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 8</strong></td>
<td>Experimental</td>
<td>Stannous (n=30) 2.26 (0.36) 0.80 (0.14)</td>
<td>0.5375</td>
</tr>
<tr>
<td></td>
<td>Crest SP (n=28) 2.29 (0.41) 0.92 (0.14)</td>
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</tbody>
</table>

The study population was predominately female (93%), and ranged in age from 22 to 56 years (mean 40.5 years). There were no significant differences in the baseline demographic characteristics between the dentifrice test groups (P≥0.05).

The results of the Yeaple Probe tactile evaluations were no statistically significant differences in mean adjusted tactile sensitivity scores between the experimental stannous-containing dentifrice and the positive control dentifrice groups at either time point, as measured by the Yeaple Probe.
Week 8 Schiff Air Index results (Table 4, Fig. 2) were consistent with Week 4 findings, again showing no significant difference between the experimental dentifrice and the positive control in thermal sensitivity reduction ($P=0.5375$). Brushing with either test dentifrice for 8 weeks resulted in further sensitivity reductions on average beyond Week 4 improvements: the adjusted 8-week mean scores were 0.80 for the experimental dentifrice and 0.92 for the positive control which were reductions of 64.4% and 59.7% from baseline, respectively.

Both test dentifrices were well-tolerated, with no reported adverse events.

**Discussion**

This randomized, double-blind, placebo-controlled clinical trial measured dentin hypersensitivity over 8 weeks when subjects brushed twice daily with either an experimental stannous-containing dentifrice, or a marketed 5.0% potassium nitrate positive control toothpaste. Study eligibility and entrance criteria (Table 1) were rigorous to minimize potential bias. Further, two well-accepted efficacy measurements – the Yeaple Probe for tactile assessment and the Schiff Air Index for thermal measurement – were included.

The subject population, with a mean age of 40.6 years and a disproportionate percentage of females, is consistent with tooth sensitivity prevalence surveys, which have indicated that on average, sufferers are more likely to be female and the peak occurrence is between 30 and 40 years of age.

The study results indicated that both the novel stannous-containing and marketed positive control dentifrices significantly ($P<0.05$) reduced dentin hypersensitivity (both tactile and thermal) compared to baseline in this subject population at 4 and 8 weeks of use. Comparing the two dentifrices revealed their highly similar benefits: by either efficacy measure, there were no statistically significant differences between the experimental and positive control dentifrices at either Week 4 or Week 8. The marked agreement between the two distinct effectiveness measurements convincingly demonstrated that the experimental stannous-containing dentifrice was comparable in effectiveness to a marketed product with known benefits in lessening tooth sensitivity in this study.

While a negative control was not included in this trial, potassium nitrate formulations are used as the only control dentifrice in many clinical trials. Furthermore, a separate clinical research has demonstrated statistically significant benefits for the stannous-containing dentifrice relative to a negative control sodium fluoride dentifrice.

The tactile and thermal desensitizing benefits produced by both dentifrices at Week 4 had increased by the final evaluation. Yeaple Probe scores (Table 3, Fig. 1) were roughly 1.5-fold higher in both test groups at Week 8 compared with Week 4. The incremental improvements realized by subjects brushing with either dentifrice suggests that subject compliance with product use instructions in both groups was high, and also supports longer term use of desensitizing dentifrices for maximum benefits.

A 2002 global survey of 11,000 adults found that 48% of tooth sensitivity sufferers had consulted a dentist for help, highlighting the need for professionals to stay informed about the relative merits of available desensitizing products and their supporting research. The results of this trial suggest that a new stannous-containing sodium fluoride dentifrice was as effective as a marketed potassium nitrate dentifrice in relieving hypersensitivity pain. Importantly, this new multi-benefit dentifrice goes beyond the traditional single-benefit desensitizing product offerings by targeting other additional oral/dental needs, as outlined elsewhere in this special issue.

Dentin hypersensitivity sufferers may have co-existing oral health issues; e.g., one estimate indicates 60-98% of those with periodontal disease have tooth sensitivity. Patients seeking a multi-benefit dentifrice with desirable esthetics and stain-fighting effectiveness that combines significant desensitizing ability will likely find new options such as the stannous-containing dentifrice in this trial very appealing.

**References**

15. Schiff T, Dotson M, Cohen S, De Vizio W, McCool J, Volpe A. Efficacy of...


