Anticalculus Efficacy and Safety of a Stabilized Stannous Fluoride/Sodium Hexametaphosphate Dentifrice

Abstract: The purpose of this study was to assess the anticalculus efficacy and long-term safety of a new stannous fluoride dentifrice containing sodium hexametaphosphate. This trial was a randomized, double-blind, parallel-group, 6-month study where, after a prophylaxis, subjects brushed twice daily with either a stabilized 0.454% stannous fluoride/13% sodium hexametaphosphate dentifrice (Crest® Pro-Health) or a marketed multibenefit triclosan/copolymer control dentifrice. Study subjects were known to form supragingival calculus and had previously demonstrated the ability to form at least 1.5 mm using the Volpe-Manhold Calculus Index over a 2-month pretest period. Comparisons between treatments for anticalculus efficacy were performed using analysis of covariance. Eighty subjects were randomized into one of two treatment groups after stratification on gender and baseline calculus scores and then monitored for calculus formation, soft tissue tolerance, and extrinsic stain. The mean calculus score for the stannous fluoride/sodium hexametaphosphate group was statistically significantly lower than that of the triclosan/copolymer group at both months 3 and 6 (P < .01). At month 3, the stannous fluoride/sodium hexametaphosphate group had an adjusted mean 54% lower than that of the triclosan/copolymer group. At month 6, the stannous fluoride/sodium hexametaphosphate group had an adjusted mean 56% lower than that of the triclosan/copolymer group. Both dentifrices were well tolerated and neither dentifrice group developed appreciable extrinsic stain over the 6-month trial period. Overall, the stannous fluoride/sodium hexametaphosphate dentifrice had superior anticalculus efficacy relative to the marketed triclosan/copolymer control and a comparable soft tissue safety and extrinsic stain profile.

Dentifrices containing calcium phosphate–mineralization inhibitors have been shown to be highly effective in reducing the amount of calculus that forms between dental prophylaxes. Dental prophylaxis is required to remove calculus. Preventing supragingival calculus formation is worthwhile for several reasons, including easier dental scaling at routine office visits and better hygiene for patients between professional cleanings. Calcium phosphate–mineralization inhibitors are believed to control calculus by slowing the rate and extent of calcium-phosphate mineralization within dental plaque, thereby increasing the length of time during which deposits can be removed in normal oral hygiene. Dentifrices containing mineralization inhibitors also have been shown to

Learning Objectives

After reading this article, the reader should be able to:

• explain a common clinical methodology used to evaluate tartar-control dentifrices.

• discuss the mechanism by which sodium hexametaphosphate inhibits calculus.

• describe the benefits of a novel, stabilized stannous fluoride/sodium hexametaphosphate dentifrice for controlling calculus.

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provide efficacy in reducing the scaling effort required during prophylaxis to rid the teeth of hardened concretions.\(^5\)

The mineralization inhibitors used in tartar-control toothpastes provide variable activity, depending on both the strength and duration of their actions within dental plaque. The clinical actions of pyrophosphate, a common mineralization inhibitor found in the majority of tartar-control toothpastes, are affected by hydrolysis reactions resulting from plaque and salivary enzymes at mineral surfaces.\(^9\) These hydrolysis reactions break down the chemically active pyrophosphate into inactive orthophosphate molecules. Polymeric phosphates may show improved efficacy as they resist complete deactivation. Moreover, the degradation products (shorter-chain polyphosphates) maintain activity.

Sodium hexametaphosphate, which is also called polypyrophosphate (with monomeric orthophosphate chain lengths greater than 3), requires formulation in low-water environments to ensure hydrolytic stability for the shelf-life of the product.\(^10\) Previously, a dual-phase sodium hexametaphosphate formulation was tested, and it demonstrated 19% better calculus efficacy relative to a sodium fluoride control.\(^11\) New advances in formulation development have allowed both the fluoride source and sodium hexametaphosphate to be present in a single-phase dentifrice. This article reports the findings from testing this new formulation, a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice for anticalculus efficacy. The study design and examination methods (using the Volpe-Manhold criteria)\(^i\) were purposely chosen to replicate the calculus trials conducted for another multibenefit dentifrice. (Triclosan/copolymer has demonstrated benefits that range from 23% to 36% vs placebo in 3 long-term clinical studies; 2 of the studies were 3 months long\(^12,13\) and the other was 6 months long.\(^14\)) The dual-phase sodium hexametaphosphate dentifrice was shown to be superior for anticalculus efficacy when compared with the triclosan/copolymer dentifrice.\(^11\)

**Methods**

**Design**

This 6-month, randomized and controlled, double-blind, parallel-group, clinical trial assessed the anticalculus efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice vs a marketed, multibenefit tartar-control dentifrice (Colgate® Total\(^6\)®) in subjects who previously demonstrated the ability to rapidly form calculus. Generally healthy adults were enrolled and given a prophylaxis, then for the 6-month test period they brushed unsupervised twice daily with their randomly assigned dentifrice. Calculus formation, extrinsic stain, and safety outcomes were evaluated at 3 months and again at the end of the test period.

A total of 81 adult volunteers were enrolled. These subjects had previously demonstrated the ability to form at least 1.5 mm of calculus on the lingual surfaces of the mandibular anterior teeth in an 8-week pretest phase after receiving a prophylaxis under controlled conditions. One subject withdrew voluntarily at the baseline visit before receiving treatment. Subjects with poor general or dental health, fewer than six mandibular anterior teeth, sensitivity to tartar-control toothpastes, fixed orthodontic appliances or dental implants in the mandibular anterior region, any condition requiring antibiotic premedication before dental procedures, chlorhexidine use, or other factors that may have affected the ability to measure calculus were excluded from participation.

Before study initiation, the protocol was approved by the University of the Pacific Institutional Review Board, and informed consent was obtained from all volunteers. Participants qualified for inclusion to the study presented at the clinical site for calculus and oral soft tissue assessments at baseline. Then, subjects were given a prophylaxis and subsequently stratified on gender and baseline calculus scores. Within strata, subjects were randomized to one of the two treatment groups.

At months 3 and 6, the participants returned for calculus evaluations to assess test-product effectiveness, as well as oral soft tissue examinations to evaluate safety outcomes. In addition, extrinsic stain levels were assessed at both 3 and 6 months to determine whether there was any stain accumulation during the use of the test dentifrices.

**Clinical Evaluations**

The Volpe-Manhold Index (V-MI) was used to measure the calculus present on the lingual surfaces of the lower six anterior teeth.\(^15\) After drying the teeth with a stream of air, a standard periodontal probe was placed on the most infe-

\(^a\)The Colgate-Palmolive Company, New York, NY 10022; 800-338-8388
rior border of visible calculus and measurements were obtained in three planes in 0.5-mm increments. A score of zero denoted that there was no calculus present at a measurable site. The V-MI was calculated for each subject by summing the millimeter scores over all of the sites graded.

Test-product safety was assessed at both months 3 and 6 via oral soft tissue examinations encompassing the gingiva (free and attached), hard and soft palate, oropharynx and uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal and mucolabial folds, lips, and perioral area. Any abnormalities that were not present at study inception or which exacerbated during test-product use were classified as adverse events and monitored to resolution.

Stain accumulation was quantified at months 3 and 6 using the Lobene method. With this index, the intensity and extent (area) of stain on the 12 anterior test teeth were measured by dividing the facial surfaces of each tooth into two regions: gingival and body. Single intensity and area scores for each subject at each visit were obtained by averaging the values across all graded teeth. Additionally, a composite score was derived by summing all intensity scores multiplied by area scores and then dividing by all sites graded.

Test Products
Study subjects were assigned to 1 of 2 dentifrice groups: stabilized 0.454% stannous fluoride/13% sodium hexametaphosphate (Crest® Pro-Health®) or a marketed control containing 0.30% triclosan, 0.243% sodium fluoride, and 2% Gantrez copolymer (Colgate® Total®). To ensure blinding, all test dentifrices were overpackaged in identical test kits with a toothbrush (Oral-B® P-40®), a 60-second timer, and written instructions. Subjects were told to brush all teeth with their assigned dentifrice, using the toothbrush provided, in their usual manner for 60 seconds twice daily for the 6-month treatment period. Product use was unsupervised.

Statistical Analyses
Analysis of covariance (ANCOVA), using treatment as a factor and baseline V-MI score as the covariate, was used to assess treatment differences separately at months 3 and 6. Subgroup analyses also were performed using the ANCOVA model. These three subgroups were defined by categorizing baseline (preprophy) calculus levels using the tertiles of the distribution (high, medium, and low). All comparisons were 2-sided at the 0.05 level of significance. Adverse events were summarized by treatment and type. Descriptive statistics were used to describe the Lobene stain scores at months 3 and 6.

Results
A total of 80 subjects received the test product; all were evaluable and included in the analyses at months 3 and 6. There were 31 women and 49 men in the study. The mean age was 27.5

### Table 1—Baseline Demographic Characteristics

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Triclosan/Copolymer (n = 40)</th>
<th>Stannous Fluoride/SHMP (n = 40)</th>
<th>Overall (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>16 (40%)</td>
<td>15 (37%)</td>
<td>31 (39%)</td>
</tr>
<tr>
<td>Men</td>
<td>24 (60%)</td>
<td>25 (63%)</td>
<td>49 (61%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>10 (25%)</td>
<td>9 (23%)</td>
<td>19 (24%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>29 (73%)</td>
<td>30 (75%)</td>
<td>59 (74%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.4 (4.5)</td>
<td>27.6 (5)</td>
<td>27.5 (4.7)</td>
</tr>
<tr>
<td>Minimum–Maximum</td>
<td>19–37</td>
<td>23–45</td>
<td>19–45</td>
</tr>
</tbody>
</table>

* n = number of subjects in each treatment group.
+ Number and percent of subjects in each category.
SHMP = sodium hexametaphosphate; SD = standard deviation.
years. The population was 74% Caucasian, 24% African American, and 2% Hispanic. The individual treatment groups were generally well balanced with respect to all demographic parameters (Table 1).

**Calculus**

Table 2 presents the results of V-MI examinations for all evaluable subjects at months 3 and 6. The treatment by baseline score interaction was not statistically significant at either time point and was, therefore, excluded from all statistical models. The mean calculus score for the stannous fluoride/sodium hexametaphosphate group was statistically significantly lower than that of the triclosan/copolymer group, at both months 3 and 6 ($P < .0001$). At month 3, the stannous fluoride/sodium hexametaphosphate group had a covariance adjusted mean 54% lower than that of the triclosan/copolymer group. At month 6, the stannous fluoride/sodium hexametaphosphate group had an adjusted mean 56% lower than that of the triclosan/copolymer group (Figure 1).

For all subgroup analyses (high-, medium-, and low-calculus-forming subjects) the mean calculus score for the stannous fluoride/sodium hexametaphosphate group was statistically significantly lower than that of the triclosan/copolymer group at both months 3 and 6 ($P < .01$). For high-calculus-forming subjects (those with baseline V-MI scores of > 16 mm), the stannous fluoride/sodium hexametaphosphate group had an adjusted mean 47% lower than that of the triclosan/copolymer group for both months 3 and 6. For medium-calculus-forming subjects (those with baseline V-MI scores between 13 mm and up to 16 mm), the stannous fluoride/sodium hexametaphosphate group had adjusted means 57% lower than that of the triclosan/copolymer group for both months 3 and 6. For low-calculus-forming subjects (those with baseline V-MI scores of < 13 mm), the stannous fluoride/sodium hexametaphosphate group had adjusted means 59% and 66% lower than that of the triclosan/copolymer group for months 3 and 6, respectively.

**Stain**

At months 3 and 6, extrinsic stain formation was measured on the facial surfaces of the anterior teeth so as not to confound the calculus measurements being made on the lingual surfaces of the teeth. These surfaces also represent the greatest noticeability to the dental patient. The month-3 Lobene composite mean was 0.0 for each of the stannous fluoride/sodium hexametaphosphate and triclosan/copolymer treatment groups, while the month-6 Lobene composite mean scores were 0.02 and 0.0 for the stannous fluoride/sodium hexametaphosphate and triclosan/copolymer groups, respectively.

**Safety**

The two test dentifrices were well tolerated, with the randomized study population experiencing no adverse events during the course of the clinical trial.

**Discussion**

This 6-month, randomized, parallel-group study was conducted to evaluate the anticalculus efficacy and safety of a stannous fluoride/sodium hexametaphosphate dentifrice compared to a marketed, multibenefit (including tartar control) triclosan/copolymer dentifrice (Colgate® Total®). The design employed is widely accepted for demonstrating anticalculus efficacy of tartar-control dentifrices.\(^6,7,10\)\(^{15}\) The statistically significant 56% reduction in calculus

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### Table 2—Volpe-Manhold Index Analysis of Covariance Means Adjusted for Baseline Values

<table>
<thead>
<tr>
<th>Time/Treatment</th>
<th>n(^a)</th>
<th>Baseline Mean (mm)</th>
<th>Covariance Adjusted Mean (SE)(^b) (mm)</th>
<th>$P$ value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month 3 (Mean SE = 14.2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triclosan/copolymer</td>
<td>40</td>
<td>15.88</td>
<td>11.74 (0.60)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Stannous fluoride/SHMP</td>
<td>40</td>
<td>16.66</td>
<td>5.41 (0.60)</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6 (Mean SE = 25.6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triclosan/copolymer</td>
<td>40</td>
<td>15.88</td>
<td>15.79 (0.80)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Stannous fluoride/SHMP</td>
<td>40</td>
<td>16.66</td>
<td>6.92 (0.80)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) n = number of subjects used in analyses.

\(^b\) Means adjusted for baseline values.

\(^c\) All comparisons are 2-sided at the 0.05 level of significance.

SE = standard error; SHMP = sodium hexametaphosphate.
accumulation observed in this trial for the stannous fluoride/sodium hexametaphosphate dentifrice over 6 months ($P < .0001$) provides clear evidence of superiority to the marketed control, multibenefit dentifrice. The study results agree with what has been reported previously on the anticalculus efficacy of sodium hexametaphosphate relative to triclosan/copolymer. The benefits for inhibiting calculus formation are consistent across the range of calculus severity noted in the test population. Regardless of whether the subjects were low-, medium-, or high-calculus formers, they derived a significant anticalculus benefit from the stannous fluoride/sodium hexametaphosphate dentifrice.

Previously, there has been documentation of extrinsic dental stain formation after stannous fluoride dentifrice use. The staining mechanism appears to be multifactorial and depends on chromogens encountered in daily habits and practices (such as cigarette smoking and coffee or tea consumption), oral hygiene status, thickened dental pellicle, and oxidation reactions whereby stannous reduces chromogens and sulfur-rich pellicle proteins to precipitate stain on teeth surfaces. The stain-prevention and stain-removal properties of sodium hexametaphosphate have been discussed elsewhere.

It is important to point out that the stannous fluoride/sodium hexametaphosphate formulation has significantly improved the esthetics of this stannous fluoride–containing toothpaste consistent with the observation that no subjects were lost to treatment during the study. Over 6 months of use, there was little stain accumulation with either of the dentifrices tested in this population.

Overall, the stannous fluoride/sodium hexametaphosphate dentifrice exhibited superior calculus inhibition and a comparable stain and safety profile compared to the marketed triclosan/copolymer control.

**Disclosure**

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**Acknowledgments**

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**References**