Comparative Investigation of the Efficacy of Triclosan/Copolymer/Sodium Fluoride and Stannous Fluoride/Sodium Hexametaphosphate/Zinc Lactate Dentifrices for the Control of Established Supragingival Plaque and Gingivitis in a Six-Month Clinical Study

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Abstract

• **Objective:** This double-blind clinical study, conducted at the University of Puerto Rico, San Juan, Puerto Rico, was designed to compare the efficacy of two commercially available dentifrices for the control of supragingival plaque and gingivitis.

• **Methods:** Qualifying adult male and female subjects from the San Juan, Puerto Rico area were randomly assigned to one of two treatment groups: 1) a commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride (Colgate® Total®); and 2) a commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate (Crest® Pro-Health®). All subjects received an oral soft and hard tissue examination, and were dispensed their assigned dentifrice product, along with a soft-bristled adult toothbrush for home use. Subjects were instructed to brush their teeth for one minute, twice daily (morning and evening), using only the dentifrice provided. Examinations for supragingival plaque and gingivitis, and oral soft and hard tissue assessments were repeated after six weeks, three months, and six months of product use.

• **Results:** One-hundred and nine (109) subjects complied with the protocol and completed the six-month examinations. At the six-month examination, both treatment groups exhibited statistically significant reductions from baseline with respect to supragingival plaque and gingivitis scores. Relative to the Crest Pro-Health Toothpaste group, the Colgate Total Toothpaste group exhibited statistically significant reductions in supragingival plaque index scores of 18.5%, 20.7%, and 25.8% after six weeks, three months, and six months of product use, respectively. For gingival index scores, statistically significant reductions of 20.5%, 18.9%, and 17.1% were exhibited after six weeks, three months, and six months of product use, respectively.

• **Conclusion:** The results of this double-blind clinical study support the conclusion that a dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride provides a significant reduction in established supragingival plaque and gingivitis, as compared to a dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate when used over a period of six months.

(J Clin Dent 2010;21[Spec Iss]:117–123)

**Introduction**

Dental plaque-induced gingivitis is inflammation of the gingival tissues characterized by a change in color, texture, and a tendency to bleed upon probing.1,2 Unlike periodontitis, there is no tissue attachment loss to the tooth structure in gingivitis. However, if unattended, gingivitis can lead to periodontitis and, eventually, to tooth loss.3

Epidemiological studies have reported a high prevalence of gingivitis in adult populations in the US, with variations observed in different ethnic groups and gender. According to the US National Survey of Employed Adults conducted in 1985, 47% of men and 39% of women presented bleeding on probing in at least one site.4 An apparent improvement in gingival health in adults has been reported since the First National Survey in Adults conducted in 1960-1962. The prevalence reported in that first study was 85% in men, 79% in women, while years later a prevalence of 50% in adults was reported in the NHANES III (1988-1994). More recently, Dye, et al. concluded that data from NHANES III and NHANES 1999–2004 indicates that periodontitis has declined across nearly all major groups in the US.5,6 Findings from the NHANES7 revealed that Hispanics in the US had a higher prevalence of gingivitis than Caucasian adults in the US.

The scientific literature supports that the accumulation of dental plaque, or what is commonly referred to now as the oral
biofilm, in susceptible hosts is associated with gingivitis and periodontitis, considering it a cause and effect relationship. Plaque or biofilm formation is a process that consists of a formation of the acquired pellicle on the tooth surface. There is then the initial adhesion and attachment of gram positive bacteria, followed by microbial colonization by gram negative anaerobic bacteria. This leads to an organized and structured biofilm. Bacterial plaque is the primary cause of gingivitis in conjunction with other predisposing factors, such as tobacco, calculus, and orthodontic therapy, among others.

Therefore, therapy for gingivitis should be directed primarily at the reduction of oral bacteria and calcified and non-calcified deposits. Optimal oral hygiene, brushing twice daily, and flossing as recommended by the ADA, all contribute to good oral health. However, a large percentage of the population is unable to adequately clean their teeth. In a clinical study, more than 66% of subjects who stated that they brushed their teeth twice a day presented with dental plaque. Several factors, such as the brushing technique, duration of brushing, and failure to remove plaque from interproximal areas of posterior teeth and lingual areas, affect and impede mechanical plaque removal.

The high prevalence of gingivitis reported in the US and other parts of the world and its possible development into periodontitis, combined with the evidence from clinical studies showing the difficulties encountered in adequately removing dental plaque, and the recent evidence relating periodontal disease and atherosclerotic disease, all support the use of chemotherapeutic agents in dental products for plaque control.

Chemotherapeutic agents with antibacterial properties, such as triclosan, have been added to fluoride-containing toothpastes to reduce plaque and gingivitis. Triclosan is a nonionic, bisphenolic germicidal agent. It has low toxicity, a broad spectrum of activity, and is effective against both gram positive and gram negative bacteria. Colgate® Total® Toothpaste (Colgate-Palmolive Co., New York, NY, USA) also contains the copolymer, PVM/MA (polyvinylmethylethether/maleic acid), which, when combined with the triclosan, ensures the delivery and retention of triclosan to hard and soft tissues. The combination of 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride, Colgate Total Toothpaste, has been tested in clinical studies and shown to significantly reduce plaque and gingivitis.

The objective of this six-month randomized clinical trial was to compare the efficacy of a dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride to a dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate for the control of established supragingival plaque and gingivitis.

Materials and Methods

This clinical study, conducted at the School of Dental Medicine of the University of Puerto Rico in San Juan, Puerto Rico, employed a double-blind, randomized, two-treatment, parallel-group design. Adult male and female subjects from the San Juan area were enrolled into the study based upon the following criteria:

- Subjects had to be between the ages of 21 and 70, in generally good health, and possess a minimum of 20 uncrowned permanent natural teeth (excluding third molars).
-Subjects needed to be available for the duration of the study, and to sign an Informed Consent form.
- Subjects were required to present, at baseline, a mean Loe-Silness Gingival Index score of at least 1.0, and a mean plaque index score of 1.5 or greater, as determined by the Turesky modification of the Quigley-Hein Plaque Index.
- Subjects were excluded from the study if they had orthodontic bands, presence of partial dentures, tumors of the soft or hard tissues of the oral cavity, advanced periodontal disease (purulent exudates, tooth mobility, and/or extensive loss of periodontal attachment or alveolar bone), or individuals who participated in any other clinical study or who had used antibiotics any time within one month preceding the study were excluded from participation.
- Subjects who received a dental prophylaxis within two weeks prior to the baseline examination, or subjects with existing medical conditions or conditions which precluded them from not eating and drinking for periods up to four hours, or who were taking any medications that might interfere with the study outcome were also excluded from the study.

Prospective study subjects reported to the clinical facility having refrained from all oral hygiene procedures for 12 hours, and having refrained from eating, drinking, or smoking for four hours prior to their examination. All prospective subjects who met the inclusion/exclusion criteria received a baseline plaque and gingivitis examination, along with an oral soft and hard tissue assessment.

Qualifying subjects were randomly assigned to one of the two study treatments:

1. A commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride (Colgate Total Toothpaste).
2. A commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate (Crest® Pro-Health® Toothpaste, Procter & Gamble Co., Cincinnati, OH, USA).

Following their assignment to a study group, all subjects were provided with their assigned dentifrice and an adult soft-bristled toothbrush for home use. All dentifrice products were supplied in their original packaging and overwrapped with a white label to mask the product’s identity. Subjects were instructed to brush their teeth for one minute, twice daily (morning and evening), using only the dentifrice and toothbrush provided, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no restrictions regarding diet or smoking habits during the course of the study.

Subjects returned to the clinical facility for plaque and gingivitis examinations and oral soft and hard tissue assessments after six weeks, three months, and six months of product use. All examinations were performed by the same dental examiner using the same procedures as employed at baseline. Training and standardization sessions were conducted before the beginning of...
the study’s data collection visits at the University of Puerto Rico School of Dental Medicine. The dental examiner and a back-up examiner were trained and standardized on the plaque and gingivitis indices employed in the study by a periodontist who served as the reference examiner. At the six-week, three-month, and six-month examinations, in addition to visual examinations by the dental examiner, subjects were also interviewed to determine if they experienced any adverse events during the study period.

Clinical Scoring Procedures

Plaque Assessment. Plaque was scored according to the Turesky modification of the Quigley-Hein Plaque Index. Each tooth was divided into six surfaces, three facial and three lingual, as follows: 1) mesio-facial; 2) mid-facial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) disto-lingual. Third molars and those teeth with cervical restorations or prosthetic crowns were excluded from the scoring procedure. Plaque was disclosed and scored on each tooth surface according to the following criteria:

0 = No plaque.
1 = Separate flecks of plaque at the cervical margin of the tooth.
2 = A thin, continuous band of plaque (up to 1 mm) at the cervical margin of the tooth.
3 = A band of plaque wider than 1 mm, but covering less than 1/3 of the crown of the tooth.
4 = Plaque covering at least 1/3, but less than 2/3 of the crown of the tooth.
5 = Plaque covering 2/3 or more of the crown of the tooth.

Whole-mouth mean scores were obtained by averaging the values obtained over all scoreable surfaces in the mouth.

Gingivitis Assessment. Gingivitis was scored according to the Löe-Silness Gingival Index. Each tooth was divided into six surfaces, three facial and three lingual, as follows: 1) mesio-facial; 2) mid-facial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) disto-lingual. Third molars and those teeth with cervical restorations or prosthetic crowns were excluded from the scoring procedure. The gingiva adjacent to each tooth surface was scored as follows:

0 = Absence of inflammation.
1 = Mild inflammation: slight change in color and little change in texture.
2 = Moderate inflammation: moderate glazing, redness, edema, hypertrophy. Tendency to bleed upon probing.
3 = Severe inflammation: marked redness and hypertrophy. Tendency to spontaneous bleeding.

Whole-mouth mean scores were obtained by averaging the values obtained over all scoreable surfaces in the mouth.

Oral Soft and Hard Tissue Assessments. The dental examiner visually examined the oral cavity and peri-oral area using a dental light and dental mirror. This examination included an assessment of the soft and hard palate, gingival mucosa, buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsilar and pharyngeal areas of the mouth.

Adverse Events. Adverse events were obtained from an interview with the subject and a dental examination by the investigator.

Statistical Methods

Statistical analyses were performed separately for the gingival index and plaque index. Comparisons of the treatment groups with respect to baseline plaque and gingivitis scores, as well as for age, were performed using analyses of variance (ANOVA). Comparisons between the treatment groups with respect to gender were performed using chi-square tests. Within-treatment comparisons of the plaque and gingivitis scores obtained at the six-week, three-month, and six-month examinations versus baseline were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted plaque and gingivitis scores at the six-week, three-month, and six-month examinations were performed using analyses of covariance (ANCOVA). All statistical tests of hypothesis were two sided, and employed a level of significance of $\alpha = 0.05$.

Results

Of the one-hundred and twenty-one (121) subjects who entered the study, 109 subjects (90.1%) complied with the protocol and completed the six-month examination. The subjects who did not complete the study were discontinued for reasons unrelated to the use of the study treatments. A summary of the age and gender of the study population who completed the six-month examination is presented in Table I. The treatment groups did not differ significantly with respect to either of these characteristics. Throughout the study, no adverse effects on the soft or hard tissues of the oral cavity were observed by the examiner or reported by the participants when questioned.

Table I

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Subjects</th>
<th>Age</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Colgate Total Toothpaste$^1$</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Crest Pro-Health Toothpaste$^2$</td>
<td>14</td>
<td>41</td>
</tr>
</tbody>
</table>

$^1$A commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride.

$^2$A commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate.

Baseline Data

Table II presents a summary of the plaque index and gingival index scores measured at the baseline examination for those subjects who completed the six-month examinations. For plaque index, the mean baseline scores were 3.16 for the Colgate Total Toothpaste group, and 3.19 for the Crest Pro-Health Toothpaste group. For gingival index, the mean baseline scores were 2.17 for the Colgate Total Toothpaste group, and 2.18 for the Crest Pro-Health Toothpaste group. No statistically significant difference was indicated between the treatment groups with respect to plaque or gingival index scores at baseline.

Six-Week Data

Plaque Index. Table III presents a summary of the plaque index scores measured after six weeks of product use. The mean six-week plaque index scores were 2.12 for the Colgate Total Toothpaste group, and 2.60 for the Crest Pro-Health...
Toothpaste group. The mean percent reductions from baseline for Colgate Total Toothpaste group, and 1.76 for the Crest Pro-Health index scores measured after six weeks of product use.

The mean three-month gingival index scores were 1.95 for the Colgate Total Toothpaste group, and 2.46 for the Crest Pro-Health Toothpaste group. The mean percent reductions from baseline were 35.5% for the Colgate Total Toothpaste group, and 19.3% for the Crest Pro-Health Toothpaste group, both of which were statistically significant.

Relative to the Crest Pro-Health Toothpaste group, the Colgate Total Toothpaste group exhibited a statistically significant 20.5% reduction in gingival index scores after six weeks of product use.

Table II
Summary of the Baseline Löe-Silness Gingival Index Scores and Quigley-Hein Plaque Index Scores for Subjects Who Completed the Six-Month Clinical Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>n</th>
<th>Baseline Summary (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Index</td>
<td>Colgate Total Toothpaste</td>
<td>54</td>
<td>3.16 ± 0.64</td>
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<tr>
<td></td>
<td>Crest Pro-Health Toothpaste</td>
<td>55</td>
<td>3.19 ± 0.56</td>
</tr>
<tr>
<td>Gingival Index</td>
<td>Colgate Total Toothpaste</td>
<td>54</td>
<td>2.17 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>Crest Pro-Health Toothpaste</td>
<td>55</td>
<td>2.18 ± 0.40</td>
</tr>
</tbody>
</table>

1A commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride.
2A commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate.
3No statistically significant difference was indicated between the two treatment groups at baseline with respect to either the Plaque Index or Gingival Index.

Table III
Summary of the Six-Week Plaque Index Scores for Subjects Who Completed the Six-Month Clinical Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Six-Week Summary (Mean ± SD)</th>
<th>Within-Treatment Analysis</th>
<th>Between-Treatment Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percent Reduction ¹</td>
<td>Sig. ¹</td>
</tr>
<tr>
<td>Colgate Total Toothpaste</td>
<td>54</td>
<td>2.12 ± 0.51</td>
<td>32.9%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Crest Pro-Health Toothpaste</td>
<td>55</td>
<td>2.60 ± 0.57</td>
<td>18.5%</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

1A commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride.
2A commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate.
3Percent reduction exhibited by the six-week mean relative to the baseline mean. A positive value indicates a lower plaque score at the six-week examination.
4Significance of paired t-test comparing the baseline and six-week examinations.
5Difference between six-week means expressed as a percentage of the six-week mean for Crest Pro-Health Toothpaste. A positive value indicates a lower gingivitis score for Colgate Total Toothpaste than for Crest Pro-Health Toothpaste.
6Significance of post-ANOVA comparison of baseline-adjusted means.

Table IV
Summary of the Six-Week Gingival Index Scores for Subjects Who Completed the Six-Month Clinical Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Six-Week Summary (Mean ± SD)</th>
<th>Within-Treatment Analysis</th>
<th>Between-Treatment Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percent Reduction ¹</td>
<td>Sig. ¹</td>
</tr>
<tr>
<td>Colgate Total Toothpaste</td>
<td>54</td>
<td>1.40 ± 0.24</td>
<td>35.5%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Crest Pro-Health Toothpaste</td>
<td>55</td>
<td>1.76 ± 0.24</td>
<td>19.3%</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

1A commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride.
2A commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate.
3Percent reduction exhibited by the six-week mean relative to the baseline mean. A positive value indicates a lower gingivitis score at the six-week examination.
4Significance of paired t-test comparing the baseline and six-week examinations.
5Difference between six-week means expressed as a percentage of the six-week mean for Crest Pro-Health Toothpaste. A positive value indicates a lower gingivitis score for Colgate Total Toothpaste than for Crest Pro-Health Toothpaste.
6Significance of post-ANOVA comparison of baseline-adjusted means.
Relative to the Crest Pro-Health Toothpaste group, the Colgate Total Toothpaste group exhibited a statistically significant 18.9% reduction in gingival index scores after three months of product use.

### Six-Month Data

#### Plaque Index

Table VII presents a summary of the plaque index scores measured after six months of product use.

The mean six-month plaque index scores were 1.75 for the Colgate Total Toothpaste group, and 2.36 for the Crest Pro-Health Toothpaste group. The mean percent reductions from baseline were 44.6% for the Colgate Total Toothpaste group, and 26.0% for the Crest Pro-Health Toothpaste group, both of which were statistically significant.

Relative to the Crest Pro-Health Toothpaste group, the Colgate Total Toothpaste group exhibited a statistically significant 25.8% reduction in plaque index scores after six months of product use.

#### Gingival Index

Table VIII presents a summary of the gingival index scores measured after six months of product use.

The mean six-month gingival index scores were 1.16 for the Colgate Total Toothpaste group, and 1.40 for the Crest Pro-Health Toothpaste group. The mean percent reductions from baseline were 46.5% for the Colgate Total Toothpaste group, and 35.8% for the Crest Pro-Health Toothpaste group, both of which were statistically significant.

Relative to the Crest Pro-Health Toothpaste group, the Colgate Total Toothpaste group exhibited a statistically significant 17.1% reduction in gingival index scores after six months of product use.

No significant adverse events were reported or observed during this study.
The present randomized clinical trial compared the efficacy of two commercially available dentifrices in the control of established supragingival plaque and gingivitis. This study provided a six-week, three-month, and six-month whole-mouth evaluation of the plaque and gingivitis efficacy of a dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride (Colgate Total Toothpaste), and a dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate (Crest Pro-Health Toothpaste) when used for one minute, twice daily.

Toothpastes containing the combination of 0.3% triclosan/2.0% copolymer/0.243% sodium fluoride, have been clinically proven in numerous studies to significantly reduce plaque and gingivitis. In addition, antimicrobial tests have also been employed to evaluate the effects of oral hygiene products. Haraszthy, et al. assessed the antimicrobial efficacy of commercial dentifrices containing fluoride, stannous fluoride, and triclosan/copolymer/fluoride on the microorganisms frequently present in the oral cavity, and demonstrated that the dentifrice containing the triclosan/copolymer/fluoride (Colgate Total) resulted in a significantly higher inhibition of bacterial growth as compared to both the stannous fluoride (Crest Pro-Health) and the sodium fluoride dentifrices (p < 0.00005). According to Haraszthy, et al. “Colgate Total had a substantially greater effect on gram negative pathogens (including Aggregatibacter actinomycetemcomitans, E. corrodens, and F. Nucleatum), gram positive organisms, such as streptococci, oral yeast, such as Candida albicans, and non-oral bacteria, including staphylococci and bacillus spp.”

In the present study, subjects assigned to both the Colgate Total Toothpaste group and the Crest Pro-Health Toothpaste group exhibited statistically significant reductions from baseline with respect to supragingival plaque and gingivitis scores at the six-week, three-month, and six-month examinations.

Relative to the Crest Pro-Health Toothpaste group, the Colgate Total Toothpaste group exhibited statistically significant reductions in supragingival plaque index scores of 18.5%, 20.7%, and 25.8% after six weeks, three months, and six months of product use, respectively. For gingival index scores, statistically significant reductions of 20.5%, 18.9%, and 17.1% were exhibited after the same time intervals, respectively.

The results of this double-blind clinical study support the conclusion that a dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride provides a significant reduction in established supragingival plaque and gingivitis when used over a period of six months.

Acknowledgment: This study was supported by the Colgate-Palmolive Company.

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References
17. Panagakos FS, Volpe AR, Petrone ME, Devizio W, Davies RM, Proskin

Table VIII
Summary of the Six-Month Gingival Index Scores for Subjects Who Completed the Six-Month Clinical Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Six-Month Summary (Mean ± SD)</th>
<th>Within-Treatment Analysis</th>
<th>Between-Treatment Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Percent Reduction¹</td>
<td>Sig.⁴</td>
<td>Percent Difference⁵</td>
</tr>
<tr>
<td>Colgate Total Toothpaste¹</td>
<td>54</td>
<td>1.16 ± 0.29</td>
<td>46.5% p &lt; 0.05</td>
<td>17.1% p &lt; 0.05</td>
</tr>
<tr>
<td>Crest Pro-Health Toothpaste²</td>
<td>55</td>
<td>1.40 ± 0.28</td>
<td>35.8% p &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

¹A commercially available dentifrice containing 0.3% triclosan, 2.0% PVM/MA copolymer, and 0.243% sodium fluoride.
²A commercially available dentifrice containing 0.454% stannous fluoride, sodium hexametaphosphate, and zinc lactate.
³Percent reduction exhibited by the six-month mean relative to the baseline mean. A positive value indicates a lower gingivitis score at the six-month examination.
⁴Significance of paired t-test comparing the baseline and six-month examinations.
⁵Difference between six-month means expressed as a percentage of the six-month mean for Crest Pro-Health Toothpaste. A positive value indicates a lower gingivitis score for Colgate Total Toothpaste than for Crest Pro-Health Toothpaste.
⁶Significance of post-ANCOVA comparison of baseline-adjusted means.


