Special Issue Article

Post-prophylaxis gingivitis prevention with two-step stannous fluoride dentifrice plus whitening gel sequence or chlorhexidine gluconate mouthrinse

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Abstract: Purpose: To assess use of a two-step dentifrice/gel sequence versus chlorhexidine gluconate mouthrinse on gingivitis prevention after dental prophylaxis. **Methods:** A 12-week, randomized controlled trial was conducted to compare the effectiveness and safety of a two-step dentifrice/gel sequence to a positive control in healthy adults with established gingivitis. After informed consent, gingivitis and stain levels were assessed by clinical examination. Eligible subjects received a dental prophylaxis and were randomly assigned to twice daily unsupervised use of either (1) two-step oral hygiene sequence: 0.454% stannous fluoride dentifrice followed by 3.0% hydrogen peroxide whitening gel for the test group; or (2) 0.12% chlorhexidine gluconate oral rinse and 0.76% sodium monofluorophosphate dentifrice for the control group. Clinical measurements of gingivitis bleeding sites and tooth stain area/intensity were collected after 4, 8 and 12 weeks use, while safety was assessed via clinical examination and oral status interview of the subjects. **Results:** A total of 44 subjects were enrolled and 35 completed the 12-week study. At baseline, bleeding sites ranged from 10-33. After prophylaxis and assigned treatment, both groups exhibited significant ($P \leq 0.0001$) reductions in bleeding sites. Responses were directionally better in the two-step sequence at all post-baseline timepoints, with groups differing significantly ($P < 0.05$) at Week 8. Tooth stain measurements demonstrated that the two-step dentifrice/gel sequence did not contribute to any significant ($P > 0.13$) stain accumulation. In contrast, stain accumulation was evident ($P < 0.003$) in the chlorhexidine group beginning at the Week 4 visit. Adverse events were more common in the positive control, and contributed to early termination. (*Am J Dent* 2018;31:18A-23A).

Clinical significance: Twice daily use of a two-step stannous fluoride dentifrice and peroxide whitening gel sequence after prophylaxis provided comparable or superior gingivitis benefits to chlorhexidine gluconate rinse without the concomitant side effect of staining.

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Introduction

Gingivitis, an inflammation of the gingival tissues without loss of connective tissue attachment, is a highly prevalent oral health disease.[1] It is reported to affect four out of five adults globally,[2] and approximately 90% of American adults have signs of gingivitis of at least mild severity.[3]

Dental plaque plays a prominent etiological role in gingivitis onset.[4] The resulting localized inflammatory response manifests as gingival redness, swelling, and bleeding.[5] Dental prophylaxis and daily oral hygiene represent the most common approaches to treat and prevent gingivitis. Both professional and at-home treatment may be supplemented by the use of antimicrobial agents, including triclosan, stannous fluoride, essential oils or cetylpyridinium chloride, which have been reported to yield antigingivitis effects when delivered via dentifrices or mouthrinses.[6-8]

One of the most recognized antimicrobials is chlorhexidine, which has been studied for at least 50 years and has proven effectiveness. One of the most common approaches is as a prescription-based 0.12% chlorhexidine gluconate rinse. Clinical research has established effectiveness to improve and maintain gingival health following clinical intervention.[9,10] A systematic review[11] of six clinical trials of more than 6 months duration found a weighted mean plaque index percentage decrease of 40% and a gingivitis index reduction of 28% with chlorhexidine. Another systematic review[12] of 18 gingivitis prevention trials of at least 4 weeks duration reported that chlorhexidine provided 33% greater plaque reduction and 27% greater gingivitis prevention than did control agents. As such, chlorhexidine rinses are widely recognized as the "gold standard" for care, however their use is associated with undesirable side effects that can impact patient compliance and clinical effectiveness. While some adverse events are uncommon, two are prominent: extrinsic tooth staining and altered taste sensation. Extrinsic tooth staining has been shown to manifest after as little as 3 days of chlorhexidine usage in digital colorimeter research.[13] Altered taste sensation has been reported, especially with longer term use.[14] Each of these can substantially hinder patient compliance, and thereby minimize the utility of chlorhexidine, particularly longer-term use.[15,16]

Plaque accumulation after prophylaxis and subsequent gingivitis has contributed to interest in oral care products with the effectiveness of chlorhexidine but without the problematic staining. One such product is a novel daily two-step dentifrice/gel sequence. Step 1 is a dentifrice containing stannous fluoride, a well-studied antimicrobial agent with anticaries, antiplaque, antigingivitis, and sensitivity reduction efficacy.[17-22] Step 2 utilizes a hydrogen peroxide whitening gel. In the current 12-week investigation, this novel, over-the-counter, two-step 0.454% stannous fluoride dentifrice/3% hydrogen peroxide whitening gel sequence, (marketed as Crest Pro-Health [HD][a] or Oral-B [HD],[a] depending on the region), was compared to a control regimen of a 0.12% chlorhexidine mouthrinse and 0.76%

Table 1. Baseline subject characteristics (randomized subjects).

	Two-Step Sequence	Chlorhexidine	Overall	P-value
Demographic parameter	N=21	N=23	N=44	
Mean Age, years (SD)	34.3 (10.53)	38.0 (12.49)	36.3 (11.62)	0.2892[a]
Age Range, years	19-62	20-65	19-65	
Female (n, %)	12 (57%)	14 (61%)	26 (59%)	1.0000[b]
Male (n, %)	9 (43%)	9 (39%)	18 (41%)	
Asian Indian (n, %)	1 (5%)	0 (0%)	1 (2%)	0.3434[b]
Asian Oriental (n, %)	1 (5%)	1 (4%)	2 (5%)	
Black (n, %)	5 (24%)	7 (30%)	12 (27%)	
Caucasian (n, %)	10 (48%)	6 (26%)	16 (36%)	
Hispanic (n, %)	4 (19%)	9 (39%)	13 (30%)	
Gingivitis/Stain parameters				
Number of Bleeding sites (mean, SD)	16.57 (6.01)	17.13 (7.21)	16.86 (6.60)	0.7826[a]
Lobene Composite Stain Score (mean, SD)	0.11 (0.27)	0.16 (0.40)	0.14 (0.34)	0.5952[a]

SD = standard deviation; n = number of subjects; % = percentage.
[a] Two-sided ANOVA for the treatment comparison.
[b] Two-sided Fisher's exact test for the treatment comparison.

sodium monofluorophosphate dentifrice in order to assess their relative effectiveness for gingival health maintenance and esthetics, in subjects with pre-existing mild-to-moderate gingivitis.

Materials and Methods

A 12-week randomized controlled clinical trial was conducted to compare post-prophylaxis effectiveness and safety of an experimental oral hygiene regimen versus a positive control. Institutional review and approval was obtained from Nova Southeastern University Institutional Review Board (NSUIRB No. 06301425Exp.). The study was conducted in compliance with the International Conference on Harmonization's Good Clinical Practice Consolidated Guidelines. All subjects provided written, informed consent. Eligibility was limited to generally healthy adults 18 years of age or older with at least 16 gradable teeth, and presenting with a minimum of 10 bleeding sites at baseline. Subjects with severe periodontal disease, active treatment for periodontitis, fixed facial or lingual orthodontic appliances, or antibiotic use within 2 weeks of baseline were excluded. Up to 50 subjects were targeted for enrollment based on non-inferiority testing for the experimental group versus control, and the 12-week time frame was selected to assess the longer-term durability of health effects after prophylaxis.

At baseline, a thorough medical history was obtained for each subject and a comprehensive clinical examination of the oral and perioral regions, including the hard and soft tissues, was conducted. Following the oral examination, extrinsic tooth stain was measured using the Lobene Stain Index and gingivitis was measured using the Löe-Silness Gingivitis Index.[23,24] Subjects who met all entrance criteria received a thorough dental prophylaxis from a dental hygienist within approximately 7-10 days of baseline. Subjects were then stratified by age, gender, number of bleeding sites, and stain levels, and assigned randomly to either the test group (twice-daily brushing with 0.454% stannous fluoride dentifrice followed by 3.0% hydrogen peroxide whitening gel[a]) or to the positive-control group (twice-daily brushing with 0.76% sodium monofluorophosphate dentifrice, Colgate Cavity Protection,[b] and twice-daily rinsing with 0.12% chlorhexidine oral rinse, Peridex[c]). Both groups were provided with a soft, flat-trim manual toothbrush (Oral-B Indicator[a]) and a timer in test kit boxes that were identical in appearance for blinding purposes. All subjects were instructed to use the study products in place of their usual oral hygiene products for the duration of the study.

Those assigned to the test group were instructed to brush twice daily. First, they were to brush for 1 minute with the Step 1 stannous fluoride dentifrice and then to expectorate without rinsing. They were instructed to next brush with the Step 2 hydrogen peroxide gel for 1 additional minute. After brushing with the Step 2 gel, subjects were to expectorate, and then rinse with tap water. Subjects assigned to the control group were instructed to brush in their customary manner twice daily with the provided sodium monofluorophosphate dentifrice, followed by rinsing with 15 mL of undiluted chlorhexidine oral rinse for 30 seconds using the provided dosing cups.

Subjects were recalled after 4, 8 and 12 weeks of unsupervised product use. At each visit, continuance criteria were assessed, safety was assessed by interview and examination, and gingivitis and tooth stain were measured by clinical examination by a trained, qualified dentist who was blind to treatment assignment. Gingivitis was measured at up to 168 sites (maximum 28 teeth) using mild marginal stimulation with a periodontal probe and recorded using the Löe-Silness Gingivitis Index ranging from 0 to 3.[24] Bleeding sites were derived from individual site scores (GI≥ 2) to yield a practice-relevant dichotomous endpoint of gingival health.

The primary endpoint for oral esthetics was visible extrinsic tooth stain, evaluated on the facial and lingual surfaces of the 12 gradable maxillary and mandibular anterior teeth and quantified using the Lobene Stain Index.[23] Each gradable surface was divided into the gingival and body regions. The gingival region was designated as an approximately 2 mm-wide band along the free margin of the gingiva, while the body region was designated as the remaining tooth surface. Extrinsic stain was assessed within each region in terms of both area and intensity, which were quantified using standard four-point scales. In addition to the efficacy and safety assessments, intra-

Table 2. Number of bleeding sites efficacy results[a] – Evaluable subjects.

	Adjusted mean (SE)	Treatment difference (SE)	% Change versus chlorhexidine[b]	P-value; 95% CI of the treatment difference
Week 4				
Two-Step Sequence (n=20)	7.447 (0.779)	2.431 (1.543)	24.6%	0.1246
Chlorhexidine (n=16)	9.878 (1.328)			(-0.708, 5.570)
Week 8				
Two-Step Sequence (n=19)	4.715 (0.697)	3.486 (1.617)	42.5%	0.0385
Chlorhexidine (n=17)	8.201 (1.458)			(0.196, 6.775)
Week 12				
Two-Step Sequence (n=19)	3.840 (0.551)	0.475 (0.884)	11.0%	0.5946
Chlorhexidine (n=16)	4.315 (0.690)			(-1.326, 2.277)

SE = standard error; % = percentage; CI = confidence interval; n = number of subjects.
[a] Via two-sided ANCOVA, where model included baseline and treatment as fixed effect(s), and unequal variances were modeled for each treatment group.
[b] Percent change versus chlorhexidine = 100 × [(chlorhexidine minus two-step sequence)/chlorhexidine].

Table 3. Lobene Composite Stain Index efficacy results[a] – Evaluable subjects.

	Adjusted mean (SE)	Treatment difference (SE)	% Change versus chlorhexidine[b]	P-value
Week 4				
Two-Step Sequence (n=20)	0.103 (0.068)	1.749 (0.429)	94.4%	0.0003
Chlorhexidine (n=16)	1.853 (0.423)			
Week 8				
Two-Step Sequence (n=19)	0.059 (0.043)	2.405 (0.583)	97.6%	0.0002
Chlorhexidine (n=17)	2.463 (0.581)			
Week 12				
Two-Step Sequence (n=19)	0.130 (0.110)	3.148 (0.624)	96.0%	<0.0001
Chlorhexidine (n=16)	3.278 (0.615)			

SE = standard error; % = percentage; n = number of subjects.
[a] Via two-sided ANOVA, where model included treatment as a fixed effect, and unequal variances were modeled for each treatment group.
[b] Percent change versus chlorhexidine = 100 × [(chlorhexidine minus two-step sequence)/chlorhexidine].

oral clinical photographs were collected at baseline and end-of-treatment.

Summary statistics of the demographic characteristics and measurements were calculated for each treatment group and overall. Gingivitis and stain scores were calculated for each treatment group and visit, and comparisons to baseline were investigated using paired-difference t-tests. The treatment groups were compared using the ANCOVA method with baseline as a covariate. In addition, for gingivitis scores, two-sided 95% confidence intervals were calculated. All comparisons were two-sided at the 0.05 level of significance.

Results

Forty-four subjects were eligible and randomized to treatment, 21 in the two-step dentifrice/gel sequence (test) group, and 23 in the chlorhexidine positive-control group. The enrolled study population ranged from 19 to 65 years in age, with a mean age of 36.3 years, and 59% were female. As seen in Table 1, the adjusted mean number of bleeding sites at baseline was 16.6±6.0 in the test group and 17.1±7.2 in the positive-control group; these values did not differ significantly (P= 0.78). Eight subjects, two from the test group and six from the positive-control group, withdrew on or before Week 12. One subject in the positive-control group had non-evaluable data at Week 12, resulting in 35 subjects completing the trial with fully evaluable data: 16 in the control group and 19 in the test group.

Both the test regimen and the positive-control regimen produced similar reductions in the number of bleeding sites during the study versus baseline, with adjusted means of 7.45, 4.72, and 3.84 bleeding sites for the test group, and 9.88, 8.20, and 4.32 bleeding sites for the control group at Weeks 4, 8, and 12, respectively (P≤ 0.0001 for all comparisons vs. baseline). For between-group comparisons of gingival health outcomes, the two-step sequence provided comparable reductions in gingival bleeding sites to the chlorhexidine group at Weeks 4 and 12 (P≥ 0.12), with a significant difference favoring the two-step sequence at Week 8 (P= 0.04; Table 2).

For Lobene composite stain, there were no significant between-group differences at baseline (P= 0.595). Relative to baseline, the chlorhexidine positive-control group had significant increases in composite, area and intensity stain scores (P< 0.003) whereas there were no significant changes in the two-step dentifrice/gel sequence group (P> 0.12). Between-treatment comparisons showed significantly higher composite, area and intensity stain scores for the chlorhexidine group compared to the two-step dentifrice/gel sequence at Weeks 4, 8 and 12 (P≤ 0.0006; Tables 3-5). Differences in stain scores ranged from 92.1% to 97.6%.

Table 4. Lobene Intensity Stain Index efficacy results[a] – Evaluable subjects.

	Adjusted mean (SE)	Treatment difference (SE)	% Change versus chlorhexidine[b]	P-value
Week 4				
Two-Step Sequence (n=20)	0.066 (0.038)	0.763 (0.180)	92.1%	0.0002
Chlorhexidine (n=16)	0.828 (0.176)			
Week 8				
Two-Step Sequence (n=19)	0.037 (0.029)	1.047 (0.243)	96.6%	0.0001
Chlorhexidine (n=17)	1.084 (0.241)			
Week 12				
Two-Step Sequence (n=19)	0.080 (0.067)	1.404 (0.272)	94.6%	<0.0001
Chlorhexidine (n=16)	1.484 (0.264)			

SE = standard error; % = percentage; n = number of subjects.
[a] Via two-sided ANOVA, where model included treatment as a fixed effect, and unequal variances were modeled for each treatment group.
[b] Percent change versus chlorhexidine = 100 × [(chlorhexidine minus two-step sequence)/chlorhexidine].

Table 5. Lobene Area Stain Index efficacy results[a] – Evaluable subjects.

	Adjusted mean (SE)	Treatment difference (SE)	% Change versus chlorhexidine[b]	P-value
Week 4				
Two-Step Sequence (n=20)	0.035 (0.023)	0.631 (0.167)	94.8%	0.0006
Chlorhexidine (n=16)	0.665 (0.166)			
Week 8				
Two-Step Sequence (n=19)	0.026 (0.019)	0.807 (0.192)	96.8%	0.0002
Chlorhexidine (n=17)	0.833 (0.191)			
Week 12				
Two-Step Sequence (n=19)	0.051 (0.041)	1.046 (0.209)	95.3%	<0.0001
Chlorhexidine (n=16)	1.097 (0.205)			

SE = standard error; % = percentage; n = number of subjects.
[a] Via two-sided ANOVA, where model included treatment as a fixed effect, and unequal variances were modeled for each treatment group.
[b] Percent change versus chlorhexidine = 100 × [(chlorhexidine minus two-step sequence)/chlorhexidine].

There were seven adverse events, one in the test group and six in the positive control group. By type, there was one report of tooth sensitivity in the test group, severity was mild, and this occurrence did not impact participation. The six adverse events recorded in the positive-control group included taste alteration (two), tooth sensitivity (two), xerostomia (one) and tooth staining (one), the latter of which contributed to early discontinuation.

Discussion

The antiplaque/antigingivitis effectiveness of chlorhexidine is well demonstrated, making this agent a gold standard for gingival health maintenance.[9-12,16] Yet, this agent requires a prescription, can result in taste alteration,[14,15] and tends to promote tooth staining requiring removal by a dental professional.[12,13,15] These barriers to patient acceptance often limit its use to short-term periods. Stannous fluoride, the active antimicrobial agent in the two-step dentifrice/gel sequence, has demonstrated statistically significant reductions in plaque accumulation and gingival bleeding in numerous published clinical trials.[11,17-22] In this head-to-head investigation, both chlorhexidine and the two-step sequence produced significant reductions in the number of bleeding sites relative to baseline at all time-points (P≤ 0.0001). At Week 12, each treatment had reduced the approximate mean number of bleeding sites from 17 to 4, a significant and meaningful improvement. Importantly, while the study design was planned to assess non-inferiority for the experimental product, measured bleeding site responses were directionally better with the two-step dentifrice/gel sequence compared to chlorhexidine at Week 4 and Week 12, and treatments differed significantly (P= 0.04) at Week 8 favoring the two-step group.

While both groups had significant reductions in gingivitis, esthetic responses differed. Stain accumulation was evident in the chlorhexidine group beginning at the first post-prophylaxis visit (Week 4) and continuing through study completion (Week 12). In contrast, there was no evidence of stain accumulation in the two-step group. As measured, stain accumulation was essentially zero (with the median change in composite stain accumulation of 0.0 after 4, 8 and 12 weeks of test product use), irrespective of the habits and practices of study subjects after prophylaxis. Groups differed significantly (P≤ 0.0006) on stain accumulation at each post-baseline timepoint favoring the two-step group (Figure). Of note, these tooth stain accumulation differences were easily visible with intraoral images as early as Week 4 of this study.

The two-step sequence was well tolerated in this study, producing beneficial effects for gingival health without important adverse safety outcomes. Only one subject in the two-

Figure. Example of stain accumulation with the chlorhexidine positive-control regimen (left) versus the two-step dentifrice/gel sequence regimen (right).

step sequence group reported an adverse event (mild tooth sensitivity), which did not affect participation. Adverse events were more common in the positive control group, and were typical of those previously reported in studies involving chlorhexidine rinses.[12,15] One subject in the positive-control group discontinued the study due to tooth staining.

The gingivitis prevention model used in this study (prophylaxis followed by treatment) was selected due to its applicability to the practice setting, and limited to 3 months post-prophylaxis due to concerns about stain accumulation without intervention in the chlorhexidine group. Results from this 12-week prevention study demonstrated that use of the two-step stannous fluoride dentifrice/hydrogen peroxide whitening gel sequence provided similar or better antigingivitis benefits to chlorhexidine gluconate rinse without attendant stain accumulation. As such, it likely represents a viable, non-prescription alternative for longer term use in practice to manage gingivitis between recall visits.

a. Procter & Gamble, Cincinnati, OH, USA. Two-step product marketed as Crest Pro-Health [HD] or Oral-B [HD], depending on the region.
b. Colgate-Palmolive Company, New York, NY, USA.
c. 3M ESPE, St. Paul, MN, USA.

Acknowledgements: To Jillian Lokere, MS and Shelly Campbell, RDH, MPH for assistance with manuscript development.

Disclosure statement: Dr. Garcia-Godoy and Mr. Rothrock declared no conflict of interest. Dr. Gurich, Ms. Anastasia and Dr. Gerlach are employees of Procter & Gamble. This research was sponsored by The Procter & Gamble Company.

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