Randomized controlled trial evaluating concurrent gingivitis and stain effects of a two-step dentifrice/gel sequence

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Abstract: Purpose: A randomized controlled trial was conducted to evaluate the clinical efficacy of a two-step dentifrice/whitening gel oral hygiene sequence on natural gingivitis and extrinsic stain. **Methods:** The population consisted of healthy adults with clinical evidence of gingivitis and extrinsic stain. Consent, demographic information and clinical measurements were collected, after which subjects were randomized to treatment. Eligible subjects were dispensed blinded test kits containing over-labeled two-step 0.454% SnF_2 dentifrice then 3% H_2O_2 whitening gel sequence or a regular 0.76% NaMFP dentifrice control (Colgate Cavity Protection), plus a regular soft manual toothbrush and instructions for use. Efficacy was assessed blind-to-treatment using the Gingivitis Bleeding Index (GBI) measured whole-mouth and the composite Lobene Stain Index (LSI) measured on the anterior dentition. Treatments were compared at Week 1 and Week 3 versus baseline for ΔGBI and ΔLSI using a two-sided 5% level of significance. **Results:** A total of 61 subjects with a mean (SD) age of 33.4 (12.0) years were enrolled. Overall baseline means (SD) were 0.16 (0.05) for GBI and 1.30 (0.94) for LSI. After 1 week, only the two-step 0.454% SnF_2 dentifrice then 3% H_2O_2 whitening gel sequence demonstrated significant ($P< 0.0001$) reductions in both gingivitis and stain. Adjusted means for the changes with the dentifrice/gel sequence and control were –0.055 and –0.001 for ΔGBI, and –0.619 and –0.095 for ΔLSI, with groups differing significantly ($P< 0.0001$) on gingivitis and stain improvement. Outcomes at Week 3 were generally similar, with groups differing on bleeding and stain. Treatments were generally well-tolerated. (*Am J Dent* 2018;31:13A-17A).

Clinical significance: In a randomized controlled trial, use of a two-step 0.454% SnF_2 dentifrice then 3% H_2O_2 whitening gel sequence yielded concurrent improvements in gingivitis and stain compared to regular oral hygiene.

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Introduction

The role of daily oral hygiene in plaque control and cleaning is well-established. Unfortunately, home care techniques are often imperfect, and the visible effects of poor plaque control on oral health have been recognized for at least 50 years as the rapid onset and increased severity of local gingivitis.[1] Prevalence is common despite routine home care. Approximately one-half of US adults have gingival bleeding, and some populations exhibit disproportionately higher gingivitis levels.[2,3]

At-home care can be enhanced by the use of topical antimicrobials, and extensive research has demonstrated anti-gingivitis effects for up to 6 months with at-home daily use.[4,5] Despite this effectiveness, there is long-standing recognition of tradeoffs between health and esthetics with topical antimicrobial treatments, the most common of which is development of extrinsic tooth stain. Research[5-10] conducted over several decades has shown the potential for different rinses and dentifrices with therapeutic actives such as cetylpyridinium chloride, stannous fluoride, essential oils and others to contribute to tooth staining. Various mechanisms have been suggested, depending on the antimicrobial agent in question.[11] A multi-factorial etiology including contributions from dietary chromogens is likely, as staining potential varies widely between individuals.

Chlorhexidine plausibly represents the archetype of 'health versus esthetics' outcomes. Developed as a long-term adjunct for daily oral hygiene, a 0.12% chlorhexidine digluconate rinse has been shown in definitive clinical trials research to significantly reduce plaque and gingivitis over a 6-month period between dental visits.[12] Other effects have been explored, including use of chlorhexidine for microbial control during implant placement, post-surgical periodontal maintenance, and prevention of alveolar osteitis from third molar surgery.[13-15] Despite its original indication for between-recall gingivitis, chlorhexidine is primarily confined to short-term use because of an adverse event profile that includes calculus formation and noteworthy staining, the latter of which may develop within a few days or weeks of use.[16] One illustration of the potential for tooth staining with chlorhexidine is its use in tooth stain induction research models, where antimicrobial-related stain is rapidly formed, in order to study the relative effectiveness of whitening dentifrices on stain prevention and removal.[17,18] While treatment is generally uncomplicated, and antimicrobial staining can be typically managed or prevented using various whitening dentifrices or routine prophylaxis, visible side effects like staining remain an ever-present challenge to compliance, and therefore, to the favorable health responses that may be achieved with many common actives.

Is there a technology with the usage benefits from daily oral hygiene that combines effectiveness and acceptable esthetics (i.e: without extrinsic dental stain)? This question was specifically evaluated using a novel technology that separated oral hygiene into two consecutive steps for the explicit purpose of optimizing health and esthetic benefits. The first step involves brushing for 1 minute with a 0.454% stannous fluoride dentifrice, while the second step follows with brushing for 1 minute with a 3% hydrogen peroxide whitening gel. This easy-to-use sequence maintains brushing time at approximately 2 minutes, with separate, consecutive therapeutic and esthetic steps. Clinical research was conducted to simply assess whether this two-

step sequential oral hygiene yielded concurrent health and esthetic outcomes.

Materials and Methods

A randomized controlled trial was conducted to evaluate the effects of a two-step dentifrice/whitening gel oral hygiene sequence on oral health and esthetics. The research, which was conducted with appropriate human subjects review (U.S.IRB 2013SRG/01) following written informed consent, targeted generally healthy adult volunteers with clinical evidence of naturally-occurring gingivitis and extrinsic stain. Inclusion was limited to adults (18+ years old) with at least six natural anterior teeth, plus evidence of visible extrinsic stain on four anterior teeth, and gingivitis-associated bleeding at 15 sites, while subjects were excluded due to pregnancy, fixed orthodontic appliances or recent antibiotic use. There were three study visits over a 3-week period. After baseline measurements, eligible subjects were randomly assigned to treatment and test products were dispensed. Clinical examinations were conducted after 1 and 3 weeks of assigned product usage to assess both absolute and comparative safety and efficacy of the two-step system and control.

There were two daily oral hygiene treatment groups, the two-step hygiene sequence experimental group and a regular control. Test products were randomly assigned by computer algorithm on a 1:1 ratio in blocks of four, balancing for gingivitis (≤ 24, > 24 bleeding sites) and stain (≤ 0.6, > 0.6 composite LSI). The experimental group received a two-step sequence: 0.454% stannous fluoride dentifrice, then 3% hydrogen peroxide whitening gel,[a] while the control group received a marketed regular anticavity dentifrice[b] with 0.76% sodium monofluorophosphate. These test products were overlabeled to disguise their identities, and since the treatments differed in appearance (two tubes versus one), test products were dispensed in a plain white labeled kit box with a soft manual brush (Oral-B Indicator[a]) and instructions. Instructions specified twice daily use either as sequential 1+1 minute brushing for the experimental group or regular hygiene practices for the control group. First use was independently supervised to maintain blinding, and subsequent use was at-home and unsupervised.

The study assessed concurrent effects of hygiene on oral health, esthetics and safety/tolerability. Each outcome was measured at each visit by a single treatment-blinded examiner using long-standing clinical indices to assess health and esthetics. For oral health, the primary endpoint was gingival bleeding, which was assessed across the whole mouth and quantified using the Gingival Bleeding Index (GBI).[19] This method used mild provocation of the gingival crevice with a periodontal probe at 2 mm depth passed gently circumferentially around each tooth at approximately a 60° angle. After 30 seconds, each tooth site was assessed and bleeding was quantified with respect to absence/presence and severity using a standard 3-point scale. For oral esthetics, the primary endpoint was visible extrinsic tooth stain, which was assessed on the facial and lingual surfaces of the anterior teeth and quantified using the Lobene Stain Index (LSI).[20] With this method, each tooth was divided into gingival and body regions, the former of which represented approximately a 2 mm band along the margin, while the latter represented the remaining tooth surface. Within each region, extrinsic stain was assessed with respect to coverage and intensity and quantified using standard 4-point scales. Safety was assessed by oral examination, and any oral adverse events were coded by severity and causality using standard pharmaceutical research practices.

Table 1. Baseline demographics by group and overall.

Variable	Experimental group (N=30)	Control group (N=31)	Overall (N=61)	P-value
Age in years				
Mean (SD)	33.6 (12.69)	33.3 (11.39)	33.4 (11.95)	0.92
Range	18-64	20-66	18-66	
Gender (N,%)				
Female	17 (57%)	18 (58%)	35 (57%)	0.99
Male	13 (43%)	13 (42%)	26 (43%)	
Ethnicity (N,%)				
Asian	3 (10%)	4 (13%)	7 (11%)	0.43
Black	4 (13%)	9 (29%)	13 (21%)	
Caucasian	10 (33%)	10 (32%)	20 (33%)	
Hispanic	6 (20%)	4 (13%)	10 (16%)	
Multiracial/Other	7 (23%)	4 (13%)	11 (18%)	

Table 2. Baseline gingivitis and stain by group and overall.

Variable	Experimental group (N=30)	Control group (N=31)	Overall (N=61)	P-value
Gingivitis (GBI)				
Mean (SD)	0.17 (0.06)	0.15 (0.04)	0.16 (0.05)	0.22
Bleeding sites (SD)	24.6 (7.31)	23.5 (6.00)	24.1 (6.64)	0.52
Tooth Stain (LSI)				
Composite	1.26 (0.73)	1.34 (1.12)	1.30 (0.94)	0.75
Area	0.59 (0.29)	0.57 (0.38)	0.58 (0.34)	0.89
Intensity	1.08 (0.62)	1.05 (0.62)	1.06 (0.62)	0.82

The principal effectiveness (GBI & LSI) and safety (oral examination & adverse events) data, demographics, and any other measurements were collected by direct entry using a portable computer and transmitted blind to treatment for evaluability and analysis. After evaluability, the database was locked, treatment was assigned, and analysis was conducted following an a priori plan. In brief, demographic data were summarized by treatment and overall. For oral health, whole mouth GBI scores were derived by subject and visit by summing the gradable site-level GBI scores and dividing by the number of gradable sites. For esthetics, mean LSI scores were derived in a similar fashion. Comparisons to baseline were conducted using paired t-tests. Treatment groups were compared using analysis of covariance with baseline, treatment and interactions. Safety data were summarized by treatment and overall. Secondary analyses of the subject-level relationships between health and esthetic outcomes were investigated using Pearson correlations. All comparisons were two-sided with a significance level of 5%.

Results

After screening, informed consent and baseline measurements were obtained from 61 adults. The study population exhibited appreciable diversity in gender, ethnicity and age, the latter of which ranged from 18-66 years (Table 1). For gingivitis, the mean (SD) GBI was 0.16 (0.05), with a mean (SD) 24.1 (6.6) bleeding sites ranging from 15-47. For stain, the mean (SD) LSI composite was 1.3 (0.94), with some subjects exhibiting extensive dark staining. After baseline, randomiza-

Table 3. Week 1 changes in gingivitis and stain levels by group.

Variable	Experimental group N=30	P value	Control group N=31	P-value
Gingivitis (GBI)				
Mean (SD)	-0.06 (0.04)	<0.0001	0.00 (0.03)	0.83
Bleeding Sites (SD)	-8.30 (5.44)	<0.0001	-0.19 (4.69)	0.82
Tooth Stain (LSI)				
Composite	-0.60 (0.58)	<0.0001	-0.09 (0.46)	0.003
Area	-0.26 (0.26)	<0.0001	-0.05 (0.08)	<0.002
Intensity	-0.47 (0.47)	<0.0001	-0.05 (0.14)	<0.04

Table 4. Week 3 changes in gingivitis and stain levels by group.

Variable	Experimental group N=30	P value	Control group N=31	P-value
Gingivitis (GBI)				
Mean (SD)	-0.08 (0.05)	<0.0001	-0.01 (0.05)	0.08
Bleeding Sites (SD)	-10.93 (5.79)	<0.0001	-2.10 (5.70)	0.05
Tooth Stain (LSI)				
Composite	-0.82 (0.61)	<0.0001	-0.31 (0.46)	0.0009
Area	-0.33 (0.17)	<0.0001	-0.13 (0.17)	<0.0003
Intensity	-0.66 (0.48)	<0.0001	-0.16 (0.14)	0.007

tion yielded 30 and 31 subjects assigned to the experimental and control groups, respectively, with groups balanced (P> 0.20) on gingivitis and stain (Table 2). One subject in the experimental group voluntarily withdrew after Week 1. All other subjects completed all visits and were included in the analyses.

Relative to baseline, the two-step group showed improvements in both health and esthetics at Week 1, as evidenced by significant reductions (P< 0.0001) in GBI, bleeding sites, and LSI, with the latter evident for the composite and individual measures of stain area and stain intensity. In contrast, the control group showed no significant (P≥ 0.82) changes in GBI or bleeding sites at Week 1, but did show significant (P< 0.04) reductions in LSI composite, area and intensity. Results were generally consistent at Week 3 (Tables 3, 4).

Comparing treatments, the Week 1 adjusted bleeding sites means (SE) were 15.9 (0.91) and 23.9 (0.86) in the experimental and control groups, respectively. The Week 1 adjusted LSI composite means (SE) were 0.68 (0.08) in the two-step group compared to 1.2 (0.03) in the control. Groups differed significantly (P< 0.0001) on bleeding sites and stain favoring the two-step oral hygiene sequence. At Week 3, the adjusted bleeding site means (SE) were 13.3 (0.96) for the experimental group compared to 21.8 (1.04) for the control, with groups differing significantly (P< 0.0001). Stain showed similar responses, with groups differing significantly (P< 0.0001) on stain removal throughout the 3-week period. For the principal health and esthetic endpoints, this represented 33-39% reductions in bleeding and 44-55% reductions in stain for the stannous fluoride dentifrice plus hydrogen peroxide whitening gel sequence versus control, depending on endpoint and visit (Fig. 1).

There were four adverse events (one per subject), each of which was in the experimental group, and coded as hyperesthesia (two subjects) or gingival irritation (two subjects). Of these, three events were reported during the subject interview, and one (gingival irritation) was observed on examination. Each of these was considered mild in severity, and resolved without discontinuation of assigned treatment.

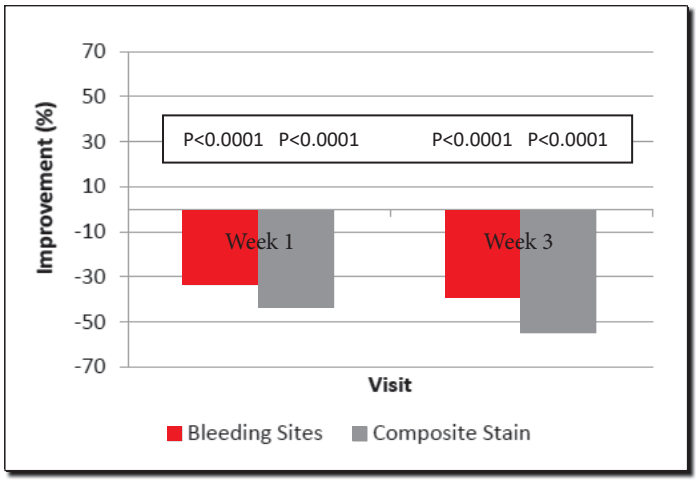

Fig. 1. Comparative improvement (%) for SnF_2/H_2O_2 Sequence vs Control.

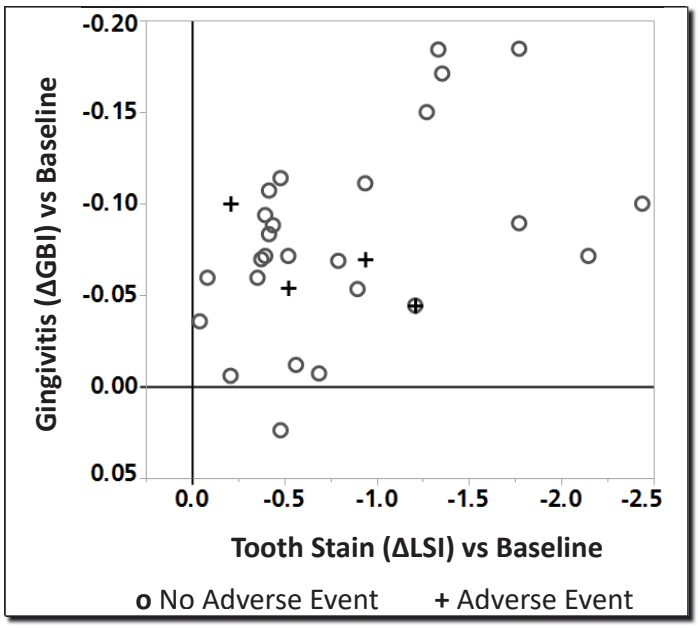

Fig. 2. Change in GBI and LSI by Subject and Event, SnF_2/H_2O_2 Sequence.

Secondary analysis specifically assessed the relationships between the health/esthetic outcomes and the possible impact of adverse events on effectiveness. This analysis compared the Week 3 GBI and LSI composite scores for all subjects (N=30) assigned to the stannous fluoride dentifrice plus hydrogen peroxide whitening gel group. Relative to baseline, there were highly significant (P< 0.0001) reductions in gingivitis (47.1%) and stain (65.1%) after 3 weeks' BID use. Gingivitis and stain responses were correlated (r= 0.42). Overall, 97% of subjects exhibited improvement in gingivitis, 100% exhibited improvements in stain, and 13% had one adverse event. Subjects with adverse events had generally similar mean responses to those without adverse events (Fig. 2). Only one subject (3%) failed to exhibit improvement in both health and esthetics after 3 weeks use of the stannous fluoride dentifrice plus hydrogen peroxide hygiene whitening gel sequence.

Discussion

This new randomized controlled trial directly assessed concurrent health and esthetic outcomes with two-step daily

oral hygiene, as these endpoints were the primary intention behind development of the novel stannous fluoride dentifrice plus hydrogen peroxide gel technology. With this focus, the target population was adult volunteers with evidence of visible gingivitis and extrinsic tooth stain. Eligible subjects were randomly assigned test products, and the health and esthetic outcomes were measured clinically after 1 week to assess initial response and after 3 weeks to assess durability. Results from the research demonstrated that the two-step sequence yielded significant ($P< 0.0001$) concurrent improvements in both gingivitis and stain beginning at the first post-treatment visit (Week 1), and these results were sustained through the second visit (Week 3). Relative to baseline, this represented 35-65% reductions in gingival bleeding and overall tooth stain, with benefits evident across methods and timepoints.

The clinical study compared daily oral hygiene with the novel two-step sequence head-to-head versus a normal hygiene control. Groups were dispensed blinded test products with two or one steps, along with a common manual brush and specific marketed instructions for use. Both groups had measured improvements in gingivitis and stain, though treatments differed with respect to response. At Week 1, use of the two-step sequence yielded a mean 8.30 bleeding site reduction, compared to 0.19 for the control. Stain response was generally similar with a mean reduction of 0.60 for the two-step group, compared to 0.09 for the control. Overall, this represented at least a 6-fold initial concurrent improvement in gingivitis and stain for the population studied in this research. Initial differences persisted, and between-group comparisons demonstrated significant ($P< 0.0001$) reductions in both gingivitis and stain for the stannous fluoride plus hydrogen peroxide group throughout the clinical trial.

There were three endpoints: health measured as gingivitis, esthetics measured as extrinsic stain, and safety measured via adverse events during treatment. Interestingly, each of these endpoints may have brushing implicated in the nominal etiology. Gingivitis is the most obvious of these, with its widespread recognition as an inflammatory response to plaque accumulation usually as a result of inadequate oral hygiene. One long standing research approach (the so-called "experimental gingivitis" model) involves suspension of tooth brushing and subsequent disease induction a few days thereafter.[1] Extrinsic stain has a potentially more complex etiology that includes behavior and diet, tooth brushing and other factors.[21] Like gingivitis, extrinsic stain accumulation can be accelerated by suspending tooth brushing, along with concurrent use of agents like tea or chlorhexidine.[18] Safety is the least obvious endpoint with respect to brushing etiology. Research has implicated tooth brushing in gingival abrasion, though clinical manifestations may be sufficiently modest to necessitate use of disclosing solutions for detection and quantification.[22] Other research[23,24] has suggested a role of brushing frequency, though outcomes are generally ambivalent.

The research has some limitations, given the objective of measuring concurrent gingivitis and stain. Both outcomes are commonly seen in dental practice and/or via population surveys. In research, more than one-half the US population exhibits gingivitis.[2,25] Numerous options exist for quantifying gingivitis, and this research focused on marginal bleeding (measured using GBI) because it has previously been recognized as a simple and reliable indicator of health/disease.[26] In addition to its clinical utility, the GBI index allowed easy quantification of bleeding site numbers (GBI> 0), an important metric of disease extent and severity. Extrinsic stain development has been less studied in population surveys, and its occurrence is less well known. In this study, extrinsic stain was measured on anterior tooth surfaces using a common clinical trials method.[27,28] While meaningful, this approach differed from the "whole mouth" measurements made for gingivitis, so further research would be indicated to assess concurrent stain reduction in the posterior dentition. Other endpoints may have yielded different outcomes. More importantly, the research was confined to subjects with both gingivitis and extrinsic stain. While these are plausibly concurrent conditions, inference from this specific research may be limited to those individuals presenting with both gingival disease and tooth stain. Finally, this research used a multivariable design under labeled usage conditions pertinent to patient care, and other single-variable studies may be indicated to ascertain causality.

Outcomes from this new research support use of the novel two-step dentifrice/gel sequence for daily oral hygiene, given the important immediate and durable health benefits with the absence of stain formation. In fact, there was actual stain reduction relative to both baseline and control evident after just 1 week of at-home use of the sequence. Adverse events with the two-step hygiene were uncommon and minor, and did not negatively affect individual health or esthetic responses. Long term health and well-being implications with two-step oral hygiene are unknown, but potentially important. For the former, consistent gingival bleeding has been implicated with other adverse outcomes, including loss of periodontal attachment, and conceivably, tooth loss.[29] For the latter, new research[30] suggests that treatment may improve oral health quality of life. While such research awaits, daily at-home use of the stannous fluoride plus hydrogen peroxide sequence yielded early, meaningful health effects without esthetic tradeoffs.

a. Marketed as Crest Pro-Health [HD] or Oral-B [HD] depending on the region, The Procter & Gamble Company, Cincinnati, OH, USA.
b. Colgate Cavity Protection, Colgate-Palmolive, New York, NY, USA.

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