Clinical evidence on a unique two-step stannous fluoride dentifrice and whitening gel sequence

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Abstract: Purpose: Recently, a unique two-step product was introduced that includes sequential use of a novel 0.454% stannous fluoride dentifrice followed by a 3% hydrogen peroxide whitening gel. The technology targeted advanced gingival health benefits plus esthetic benefits such as tooth whitening. The two-step sequence has unique brushing instructions to maximize the efficacy of each step; the stannous fluoride dentifrice is used for 1 minute of brushing followed by 1 minute of brushing with the hydrogen peroxide gel. This two-step sequence has been studied in numerous clinical trials over a series of years. This comprehensive program included different populations and sites, endpoints and time points, with responses measured versus different positive and negative research controls. A total of six clinical trials are reported herein. Outcomes from this research program demonstrate the significant gingival health efficacy of the two-step product, providing therapeutic efficacy comparable to chlorhexidine, and its positive impact on plaque, tooth stain and breath odor. (*Am J Dent* 2018;31:4A-6A).

Clinical significance: This unique dentifrice/gel sequence delivers a combination of advanced gingivitis efficacy with significant stain reduction – benefits that will positively impact oral health as well as patient compliance.

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Introduction

The majority of adults (50-90%) have gingival bleeding and inflammation.[1,2] While some individuals appear to have a greater innate susceptibility to gingivitis than others, most cases are the result of inadequate daily plaque removal.[3-6] The dental plaque biofilm is comprised of a broad array of microorganisms, and when allowed to accumulate due to suboptimal oral hygiene, the microbial population becomes increasingly virulent and provokes the inflammatory response that produces the characteristic signs of gingivitis.[5,7]

Treatment, in addition to professional and home care, may necessitate use of topical antimicrobials for plaque control. Chlorhexidine is a well-researched, long-used 'gold standard' antimicrobial for gingival health improvement.[8] As an adjunct to personal oral hygiene efforts, the favored vehicle for chlorhexidine is a 0.12% chlorhexidine gluconate mouthrinse. In a systematic review[9] of 51 clinical studies of at least 4 weeks duration, chlorhexidine mouthrinse in addition to toothbrushing was shown to provide significant reductions in plaque and gingivitis. Unfortunately, patient compliance is often a challenge due to esthetic drawbacks, namely altered taste sensation and the propensity to cause unsightly brown tooth staining requiring professional removal.[9]

Given chlorhexidine's recognition as a highly potent agent to control plaque and gingivitis, the development of a product with comparable efficacy but without chlorhexidine's objectionable taste alteration and stain proclivities would be highly desirable. Leveraging decades of formulation experience with both chemotherapeutic and cosmetic oral care products, Procter & Gamble introduced a novel technology to achieve this goal: a unique two-step system combining the therapeutic efficacy of a novel stannous fluoride dentifrice with the whitening benefits of a hydrogen peroxide gel.

Technology summary

Introduced in North America and China as Crest Pro-Health [HD][a] and Oral-B [HD],[a] respectively, this daily two-step sequential system includes a 0.454% stannous fluoride dentifrice delivering caries protection and plaque/gingivitis control with a 3% hydrogen peroxide gel for tooth whitening (Fig. 1). The dentifrice and gel are separated into two sequential steps, such that the fluoride system is decoupled from the whitening technology to ensure maximum effectiveness.

Fig. 1. Examples of the two-step sequence from the United States, Crest Pro-Health [HD], and China, Oral-B [HD].

Like a regular toothpaste, it is used twice daily (morning and night), however the brushing instructions are novel. First, patients brush for 1 minute with a 0.454% stannous fluoride paste (step 1). After expectorating, but not rinsing, they apply a 3% hydrogen peroxide whitening gel (step 2) to the toothbrush and continue to brush for an additional minute (Fig. 2). The total brushing time is 2 minutes, comparable to the standard recommended time. This technique is not inconvenient, as evidenced by practice reports showing favorable patient and professional satisfaction with daily usage of the system.[10]

The sequence uses stannous fluoride in step 1 for anticaries and antigingivitis properties. Stannous fluoride at 0.454% in a

Fig. 2. Sequential oral hygiene: 0.454% stannous fluoride paste (Step 1) and 3% hydrogen peroxide whitening gel (Step 2).

Table. Summary of clinical results for two-step stannous fluoride dentifrice and hydrogen peroxide whitening gel as reported in this special issue.

Authors	Endpoint	Duration	Control	Outcome
Gerlach & Sagel[17]	Breath Plaque Gingivitis	1 day 3 weeks 11 weeks	SMFP dentifrice (in all 3 studies)	Significant reductions in breath malodor, plaque and gingivitis favoring the two-step group versus the control.
Amini et al[18]	Gingivitis and tooth stain	3 weeks	SMFP dentifrice	The two-step sequence provided concurrent improvements in gingivitis and stain compared to the control.
Garcia-Godoy et al[19]	Gingival bleeding and tooth stain	12 weeks	0.12% chlorhexidine gluconate oral rinse plus toothbrushing with SMFP dentifrice	After prophylaxis, the two-step sequence provided comparable or superior gingivitis benefits to chlorhexidine rinse without staining.
Singh et al[20]	Plaque and saliva flow	6 weeks	SMFP dentifrice	Between-group comparisons for daytime plaque favored the two-step sequence with 41-46% improvements in plaque control. Only the two-step sequence showed increased salivary flow versus baseline.

SMFP = sodium monofluorophosphate.

dentifrice has been shown to inhibit bacterial adhesion and cohesion, reduce bacterial growth, and inhibit acid production.[11] In addition, new research suggests a role in reducing plaque pathogenicity by blocking lipopolysaccharides from inducing processes that contribute to gingivitis.[12] Like chlorhexidine, stannous fluoride dentifrices are highly effective for improving gingival health, but esthetic tradeoffs (e.g., transient extrinsic stain) were noted with early formulations.[13]

Step 2 of the novel sequence, which contains hydrogen peroxide plus an antitartar agent, provides cosmetic benefits. Hydrogen peroxide, which is commonly used in higher concentrations in professionally administered and home-based systems (e.g., whitening strips), has a lengthy history of use for tooth whitening.[14] In addition, it has been shown to be safe for long-term use and well-tolerated in dentifrices.[15] As a chemical whitening agent, hydrogen peroxide acts by disrupting stains through oxidation. Published in vitro and clinical trials have reported on the whitening actions of hydrogen peroxide-containing dentifrices compared to regular dentifrice controls, however proper formulation is critical to ensure effectiveness, typically requiring the isolation of hydrogen peroxide via packaging or other means.[16]

Clinical research

The novel brushing sequence, stannous fluoride dentifrice followed by a hydrogen peroxide whitening gel, was developed based on extensive clinical trials research studying efficacy and safety. These controlled investigations varied in study design, duration, methods, and other factors, and encompassed multiple geographies and diverse subject populations. Six clinical trials are reviewed in this *American Journal of Dentistry* special issue (Table). This supplement includes a unique review of early research on this sequence, followed by three definitive clinical trials on safety and effectiveness relative to different positive and negative experimental controls.

Gerlach & Sagel[17] report on the outcomes of three initial independent randomized and controlled clinical studies which explored the oral health benefits and safety of the new sequential two-step dentifrice and gel system. This feasibility assessment program encompassed research of varying durations and of three distinct clinical endpoints known to be favorably impacted by previous stannous fluoride dentifrice formulations: short-term research evaluating breath malodor; an intermediate-length trial of plaque control; and a longer-term investigation of gingivitis effectiveness. In each trial, the two-step 0.454% stannous fluoride dentifrice and 3% hydrogen peroxide whitening gel system was compared to a regular toothpaste[b] with twice daily usage. Collectively, these pilot trials provided evidence that the new two-step stannous fluoride dentifrice and whitening gel sequence yielded significant antimicrobial effects that were evident almost immediately (malodor), and the sequence sup-

ported a significant intermediate (plaque) and longer-term oral health effect (gingivitis). These results provided validation to proceed with additional research. Importantly, the products were well-tolerated in all of the early trials.

Amini et al[18] report on a clinical trial that specifically evaluated the primary endpoints for the two-step sequence: gingival health and whitening. The study targeted adults with both gingivitis and surface tooth stains at enrollment. Favorable responses in each endpoint were observed after 1 week of product use, and by Week 3, subjects in the two-step group averaged 39% reductions in gingival bleeding and 55% reductions in stain versus the control toothpaste.[b] Notably, 100% of the two-step users had stain reductions compared with baseline, and 97% experienced reductions in gingivitis, all without important adverse safety findings.

Garcia-Godoy et al[19] report on extended usage in a head-to-head clinical trial versus chlorhexidine[c] that models typical clinical practice conditions involving prophylaxis followed by routine monitoring for 3 months. Compared to baseline, both test groups saw significant reductions in bleeding sites at all timepoints, with the two-step group realizing directionally (4 and 12 weeks) or statistically significantly (Week 8) greater gingivitis reductions relative to the chlorhexidine group. Staining was significantly worse in the chlorhexidine group, by 94% as early as Week 4, while the two-step group experienced no significant increase in stain during the course of the trial. With chlorhexidine long considered a benchmark for gingivitis control, these study results are noteworthy in that the two-step stannous fluoride dentifrice and whitening gel provided similar or greater gingival bleeding reductions compared to the chlorhexidine positive control but without the characteristic stain associated with chlorhexidine.

Singh et al[20] share the outcomes of their 6-week clinical trial in a "so-called" vulnerable population: medication-induced xerostomia. This type of hyposalivation, which may impact as many as one-third of medicated individuals, has been reported to increase the risk of oral diseases and conditions associated with increased plaque levels.[21] Using plaque image analysis, results demonstrated that the two-step group provided 41-46% improvements in plaque control relative to the control toothpaste[b] beginning at Week 2 and continuing through Week 6. Safety outcomes were generally favorable, with the daily two-step system yielding an unexpected significant increase in salivary flow versus baseline.

Summary

The data reported in this issue demonstrate meaningful reductions in plaque, gingival bleeding and inflammation from the two-step sequence along with significant improvements in tooth stain and breath odor. Importantly, the gingivitis benefits are comparable to, or better than, the recognized gold-standard chlorhexidine. While clinicians recognize this level of gingival health improvement as foundational to oral health, the significant stain reduction offered by this product may provide the greatest motivation to many patients. Educating patients and assisting them in selecting daily-use oral hygiene products that are backed by solid and consistent research outcomes is an invaluable way to assist patients in meeting both therapeutic and cosmetic needs.

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b. Colgate-Palmolive, New York, NY, USA.
c. 3M ESPE, St. Paul, MN, USA.

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