Placebo-Controlled Clinical Trial Evaluating 9.5% Hydrogen Peroxide High-Adhesion Whitening Strips

James F. Simon, DDS, MEd Llewellyn Powell, DMD, MSHCE Scott Hollis, DDS

The University of Tennessee Health Science Center College of Dentistry
Memphis, TN, USA

Mary Kay Anastasia, BA Robert W. Gerlach, DDS, MPH Svetlana Farrell, DDS, PhD

The Procter & Gamble Company
Mason, OH, USA

Abstract

- **Objective**: To evaluate the effectiveness and tolerability of an experimental 9.5% hydrogen peroxide whitening strip relative to a placebo control over a three-week period.
- **Methods**: In this parallel-design, double-blind clinical trial, 54 adult volunteers were randomized to an experimental 9.5% hydrogen peroxide whitening strip or placebo strip balancing for age and baseline tooth color, and received treatment. Strips were worn on the maxillary arch 30 minutes daily for 20 days. Efficacy was measured objectively as L*a*b* color change from digital images at Days 4, 7, 15, and 21.
- **Results**: As early as Day 4 and at all subsequent visits, the 9.5% strip group experienced significant ($p < 0.004$) color improvement relative to placebo for b* and L* color parameters. The amount of color improvement increased with continuing peroxide strip use. Mean ± SE between-group differences in Δb^* were –0.6 ± 0.16, –0.8 ± 0.15, –1.6 ± 0.19, and –1.9 ± 0.20 at Days 4, 7, 15, and 21, respectively. Similar results were noted for ΔL^*. Minor tooth sensitivity was the most common adverse event, as reported by 12% of subjects in the 9.5% strip group and 11% of subjects in the placebo group. No subjects discontinued treatment due to an adverse event.
- **Conclusion**: This placebo-controlled clinical trial demonstrated that an experimental 9.5% hydrogen peroxide strip yielded significant tooth whitening relative to a placebo strip as early as after three days of product use.

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Introduction

Research on the use of peroxides for tooth whitening has gained in prominence over the past several years, in part because of the popularity of this common esthetic procedure. Many techniques have been reported to be effective. In one literature review, treatment factors like peroxide concentration and contact time, and patient factors like age and color, have been identified as impacting on the clinical response.[1] Initial research with custom trays established effectiveness under various conditions of use, with safety concerns primarily limited to the common occurrence of oral irritation and tooth sensitivity during the period of active treatment.[2] In clinical studies involving excessive starting shades, most subjects experienced measured improvement with extended treatment, and most were satisfied with the short- and long-term response.[3,4] Throughout the 1990s, whitening laboratory and clinical research focused on the overall response or time-to-response, via higher peroxide concentrations in custom trays for at-home use or direct application of up to 35% hydrogen peroxide.[5,6]

In 2000, a whitening system was introduced using a flexible polyethylene strip coated to deliver a peroxide bleaching gel. This novel approach, which represented the first prominent easy-to-use system, eliminated the need for custom-fabricated trays and professional adjustment, but still allowed a comfortable, close-fitting device for at-home application.[7] Numerous clinical trials demonstrated the safety and efficacy of the initial whitening strips at 5–6% hydrogen peroxide concentrations.[8,9] Follow-up research extended treatment options to include higher concentrations of up to 14% hydrogen peroxide.[10] By carrying a very thin bleaching gel, these strips enabled the use of concentrations comparable to some in-office systems, but at a much lower amount compared to various professional applications. Inclusive integrated analysis showed that high-peroxide concentration strips demonstrated generally better whitening efficacy and comparable or better tolerability compared to various marketed professional controls.[11]

Recent developments involve the use of high-adhesive gel technology for strip-based whitening. This new polymeric gel combination was designed with adhesive and cohesive properties that improve fit, allow extended wear time, and make clean removal possible. New clinical research was conducted to evaluate the effectiveness and tolerability of high-adhesion whitening strips.

Materials and Methods

A randomized, parallel, placebo-controlled clinical trial was conducted to evaluate the safety and tooth-whitening efficacy of tooth whitening strips containing 9.5% hydrogen peroxide over a 21-day period. The protocol, consent, and recruitment were reviewed and approved by the University of Tennessee at Memphis Institutional Review Board for a study targeting generally healthy volunteers, ages 18 to 65 years, who desired tooth

whitening. Subjects were recruited who had at least four gradable maxillary anterior teeth with tooth shades of A2 or darker to help preclude individuals who may have undergone tooth whitening. In addition, subjects were excluded from the study if they had extensive restorative dentistry or orthodontic devices, severe or atypical intrinsic staining, or current tooth sensitivity.

At baseline, written informed consent and a medical history were obtained, an oral examination was conducted, and starting tooth color was measured by digital imaging. Enrolled subjects were then randomly assigned to either the 9.5% hydrogen peroxide strips (Crest Whitestrips® Advanced Seal, The Procter & Gamble Company, Cincinnati, OH, USA) or the placebo strips, balancing the two treatment groups for subject age and tooth color. Subjects were dispensed a total of 20 maxillary strips along with one soft toothbrush and an anticavity dentifrice (Crest® Cavity Protection Toothpaste, The Procter & Gamble Company, Cincinnati, OH, USA). Both the peroxide and placebo strips were similar in appearance and packaging, and were dispensed in blank white foil pouches. The first application was supervised, after which subjects were instructed to apply the assigned strips on the maxillary arch for 30 minutes, once daily, for 20 days. In addition, subjects were instructed not to apply the test product in the morning prior to any study visit.

Effectiveness was assessed from standardized digital images taken at baseline and on Days 4, 7, 15, and 21. At each of these visits, the subject's position was fixed with a chin rest, and images were taken with a photographic system consisting of a high-resolution digital camera (KY-F75U CCD, JVC, Wayne, NJ, USA) equipped with a 25 mm lens and linear polarizer to permit cross-polarized light. Two 150 watt lights, located on each side of the camera, provided illumination. Images were recorded on a personal computer that was calibrated versus color standards each day prior to use, and hourly during use. Tooth color scores were calculated for the anterior facial surfaces of the six maxillary anterior teeth using a standard color scale and analytical methods.[12] Using this approach, tooth whitening was represented by a negative Δb^* (reduced yellowness) and positive ΔL^* (increased lightness). Safety was evaluated from clinical examinations and interviews to detect tooth sensitivity or irritation that may have occurred during treatment. Positive findings from these examinations were classified as to type, duration, severity, and relationship to test product use.

Summary statistics (*i.e.*, means, standard deviations, frequencies, etc.) of the demographic characteristics and digital imaging color measurements were calculated for each group and visit. Between-group effectiveness comparisons used analysis of covariance, with baseline color and age as covariates. Safety data were summarized over time by treatment group, and groups were compared on occurrence of tooth sensitivity and oral irritation using Fischer's Exact Test. All efficacy and safety comparisons used a two-tailed 5% level of significance.

Results

The study population consisted of 54 adults, including 26 who were randomized to the peroxide group and 28 to the placebo group. Mean (SD) age was 36.6 (11.16) years, and groups were balanced ($p > 0.57$) with respect to demographic parameters (Table I). While there was considerable range in baseline values, groups were well-balanced ($p > 0.87$), differing only at the first decimal point on mean b*and L* (Table II). Prior to analysis, a total of four subjects (three in the placebo group and one in the peroxide group) were considered non-evaluable because of protocol violations or early withdrawal. All other data were included in the analyses.

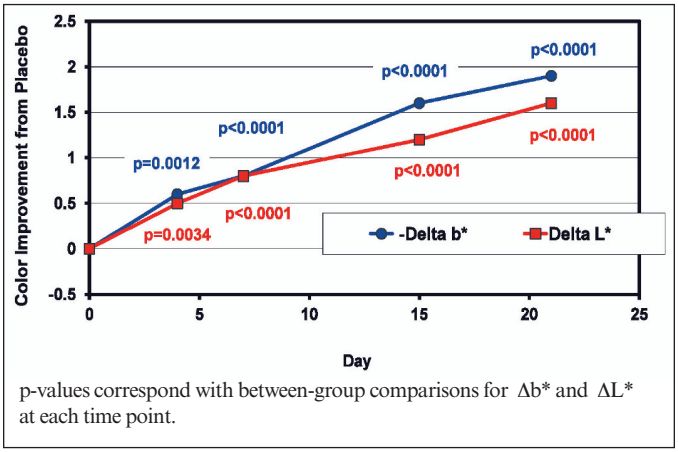
Table I
Baseline Demographic Characteristics
Evaluable Subjects

Baseline Characteristic/ Statistic	Peroxide (N=26)	Placebo (N=28)	Overall (N=54)	Two-sided p-values
Age (Years)				
Mean (SD)	37.2 (11.20)	36.1 (11.30)	36.6 (11.16)	0.73
Min.-Max.	23 – 61	19 – 60	19 – 61	
Sex				
Female	17 (65.4%)	17 (60.7%)	34 (63.0%)	0.78
Male	9 (34.6%)	11 (39.3%)	20 (37.0%)	
Race				
Non-White	12 (46.2%)	13 (46.4%)	25 (46.3%)	0.57
White	14 (53.8%)	15 (53.6%)	29 (53.7%)	

Table II
Baseline Color Value, Maxillary Arch
Evaluable Subjects

Color/ Treatment	N	Mean (SD)	p-values
b*			
Peroxide Strip	26	16.35 (2.143)	0.87
Placebo Strip	28	16.44 (2.071)	
L*			
Peroxide Strip	26	73.16 (2.717)	0.89
Placebo Strip	28	73.05 (3.213)	

Between-group comparisons showed greater color improvement in the peroxide group versus the placebo control. This was evident beginning at Day 4 for Δb^* and ΔL^*, and continuing throughout the 21-day study (Figure 1). The amount of color



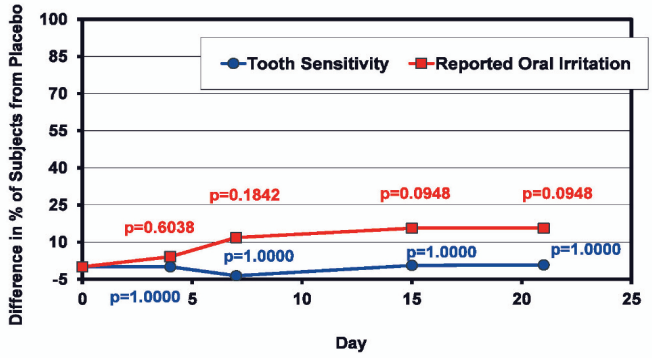
p-values correspond with between-group comparisons for Δb^* and ΔL^* at each time point.

Figure 1. *Efficacy outcomes for the strip group, mean color improvement ($-\Delta b^*$, $+\Delta L^*$) from placebo.*

improvement increased with continuing peroxide strip use. Mean ± SE between-group differences in Δb^* were –0.6 ± 0.16, –0.8 ± 0.15, –1.6 ± 0.19, and –1.9 ± 0.20 at Days 4, 7, 15, and

21, respectively. Similar results were noted for ΔL* with an end of treatment (Day 21) mean (SE) between group difference of 1.6 (0.21). Results were generally similar for Δa* (a minor parameter for vital bleaching) with respect to direction and significance, and are not reported herein for brevity. Groups differed significantly ($p < 0.02$) on whitening for all color parameters at all study visits.

Adverse events were observed and reported in both the peroxide and placebo groups, with oral irritation and tooth sensitivity representing the most common findings. At Day 4, three subjects (two in the peroxide group and one in the placebo group) reported oral irritation. No subjects reported tooth sensitivity at this initial time point. Between-group comparisons showed that groups did not differ significantly ($p > 0.09$) on occurrence of tooth sensitivity or oral irritation at any study visit (Figure 2). Overall, adverse events were generally mild in severity and transient in duration, and occurrence did not contribute to modification or early discontinuation of assigned strip use.



p-values correspond with between-group comparison for occurrence of tooth sensitivity or oral irritation at each time point.

Figure 2. *Safety outcomes for the strip group, difference from placebo, cumulative occurrence.*

Discussion

This randomized, parallel-design, double-blind, placebo-controlled clinical trial demonstrated significant whitening improvement following the use of novel, high-adhesive 9.5% hydrogen peroxide whitening strips. This whitening effect was evident at the first post-treatment evaluation (after three strips) for all color parameters measured in the study. Previous research on whitening strips has shown treatment duration to be positively associated with whitening response.[13] Effects of treatment time on response were similarly evident in this new placebo-controlled trial, with between-group differences approximately three times greater at Day 21 compared to Day 4. Use of this high-adhesion gel resulted in an early color change that improved with continued use throughout the three-week evaluation.

Importantly, extended use of the new peroxide-containing whitening strips did not contribute to any appreciable increase in adverse event occurrence with continued use, and between-group comparisons failed to show any significant safety differences versus placebo. This is noteworthy, because the adhesive gel in these new whitening strips, which is believed to improve retention, could potentially increase hydrogen peroxide contact with the adjacent gingiva. Continued use at irritated sites could theoretically exacerbate local oral irritation. Only five subjects in the 9.5% hydrogen peroxide strip group reported oral irritation at any time during the 21-day evaluation, and no subjects discontinued use early due to treatment-related adverse events. In this study, repeated use of a highly adhesive, low total dose peroxide gel in direct contact with the gingival tissue did not contribute to any meaningful persistent oral soft tissue irritation. Of note, both the comparative whitening and safety outcomes were generally similar to previous placebo-controlled trials using a similar number of strips and peroxide concentrations, but with less adhesive peroxide whitening gels.[14,15]

In conclusion, this placebo-controlled clinical trial demonstrated that an experimental 9.5% hydrogen peroxide strip yields significant tooth whitening when used once daily for three days. Response improved with continued treatment, as evidenced by a significant reduction in yellowness and increase in lightness relative to placebo over a 20-day usage period. Treatment was well tolerated. Side effects were mild, and no subjects discontinued study treatment because of adverse effects. Overall, this clinical research provides evidence of initial and cumulative tooth whitening after use of high-adhesive 9.5% hydrogen peroxide whitening strips.

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For correspondence with the authors of this paper, contact Dr. Svetlana Farrell – farrell.s.2@pg.com.

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