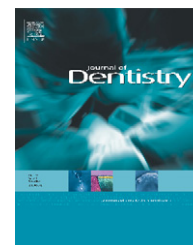


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Placebo-controlled trial evaluating safety with 12-months continuous use of 6% hydrogen peroxide whitening strips

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ABSTRACT

Objective: To assess the safety and tolerability of 6% hydrogen peroxide whitening strips over 12 months. **Methods:** 80 adults were randomly assigned equally to one of two treatments: 6% hydrogen peroxide strips or placebo strips. Strips were worn 5 min daily for 12 months. Safety and tolerability were assessed via oral status interviews and oral examinations at baseline and after 1, 2, 3, 6, 9, and 12 months of use. **Results:** Tooth sensitivity and oral irritation were the two most common adverse events. After 12 months use, tooth sensitivity was reported by 10% of subjects in the 6% strip group with a 95% confidence interval (CI) of (2.8%, 23.7%) and 5% of subjects in the placebo group with a 95% CI of (0.6%, 16.9%). The occurrence of reported oral irritation was 0% in the 6% strip group with a 95% CI of (0%, 8.8%) and 2.5% in the placebo strip group with a 95% CI of (0.1%, 13.2%). The occurrence of observed oral irritation was also similar between groups. The groups did not differ significantly ($p > 0.67$) for the percent of subjects with each type of adverse event. In the 6% strip group, two subjects discontinued product use due to an adverse event (tooth sensitivity) compared to no subjects in the placebo group. Groups did not differ significantly ($p > 0.49$) with respect to this outcome. **Conclusion:** Use of 6% hydrogen peroxide whitening strips over 12 months resulted in a safety profile similar to that seen with placebo strips.

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1. Introduction

The use of peroxides in dentistry is long-standing and extensive, including applications in periodontics, endodontics, and other areas, extending over a century.¹ Oral hygiene applications gained in popularity in the early 1990s, following the advent of a dual-phase peroxide-containing dentifrice.² Around the same time as the dual-phase peroxide dentifrice, “nightguard” vital bleaching was introduced, where a custom bleaching tray was used to deliver a peroxide-containing gel directly to the dentition for tooth whitening.³ Other applications have been forthcoming. Some have been objectively evaluated in randomized controlled trials, including peroxide delivered via mouthrinse, paint-on gels, and other combinations.^{4–6}

Today, there are numerous oral care delivery systems using carbamide or hydrogen peroxide or some other oxidative source. By far, the most prominent use of peroxides in contemporary dentistry involves applications in esthetic dentistry for in-office and/or at-home tooth whitening.⁷ Although treatment may be initiated in-office using various approaches, completion is typically accomplished at-home similar to the original nightguard approach from the late 1980s. Over the past decade, extensive evidence has accumulated on peroxide safety with at-home tooth whitening. For example, a recent review of 25 clinical trials involving 14-day use of peroxides for tooth whitening found tooth sensitivity and oral irritation representing the most common adverse events associated with treatment.⁸ Such events are reported to

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typically resolve during or soon after treatment, often without any special intervention.⁹

While much of the whitening research involved short-term peroxide use and equally short-term evaluation, a few clinical trials have evaluated daily use of peroxides for tooth whitening over periods of months. Typically, these longer duration clinical trials have focused on tetracycline discoloration, which may necessitate extended treatment to secure sufficient whitening.¹⁰ Similar to the short-term clinical trials, tetracycline studies with continuous daily peroxide use over 6-months showed tooth sensitivity and oral irritation to be the most common adverse events, affecting approximately two-thirds of participants.¹¹ Post-treatment evaluations extending over periods of years have failed to show a persistent toxicity associated with tray-based peroxide whitening.^{12,13}

The introduction of easy-to-use whitening strips in 2000 expanded access and short-term use of peroxide for tooth whitening.¹⁴ Randomized controlled trials have reportedly played an important role in the development of this low peroxide dose delivery system.¹⁵ To date, numerous whitening strip clinical studies have been conducted, published and reviewed.^{7,8,16} For example, a recent diverse series of studies evaluated hydrogen peroxide whitening strips used for up to 3 weeks, and then monitored subjects for up to 18-months post-treatment.¹⁷ These studies, conducted at hospitals, dental schools, and private dental practice, demonstrated significant color improvement with whitening strips relative to baseline and/or various controls, without serious adverse events. Mild and transient tooth sensitivity and oral irritation were the most common adverse events, and these findings did not contribute to appreciable “for cause” study dropout. This new clinical study was conducted to further extend the safety evidence for 6% hydrogen peroxide whitening strips under conditions of extended use, in this case, continuous daily treatment over a period of 1 year.

2. Materials and methods

A randomized, placebo-controlled, 1-year clinical trial was conducted to evaluate safety of 6% hydrogen peroxide whitening strips under continuous use conditions. Healthy adults who desired to undergo tooth whitening were recruited for the study. In order to participate in the clinical trial, volunteers had to be at least 18 years of age, with at least 4 unrestored maxillary anterior teeth. Candidates were excluded due to existing tooth sensitivity, regular use of anti-hypersensitivity dentifrices, meaningful malocclusion, fixed maxillary orthodontic appliances or gross neglect of oral hygiene. Because of the long duration of treatment and periodic clinical evaluations, subjects were further advised to delay oral prophylaxis for the first 3 months of the study, scheduling it no less than 30 days prior to the scheduled study visit between months 3 and 12 of the study.

After informed consent, 80 healthy adult volunteers were randomly assigned to one of the two treatment groups: 6% hydrogen peroxide whitening strips (Crest Whitestrips® Daily Multicare™, The Procter & Gamble Company, Cincinnati, OH) or placebo strips containing 0% hydrogen peroxide. Each peroxide strip carried approximately 0.13 gm of a 6% hydrogen

peroxide gel distributed uniformly across the surface, for a total peroxide dose of approximately 9 mg per maxillary strip. Placebo strips were identical, except for the absence of hydrogen peroxide. Test products were dispensed in blinded kits (other than subject number and required contact information) that held 40 identical blank strip pouches containing peroxide or placebo maxillary strips. Subjects were instructed to apply strips to their maxillary anterior teeth for 5 minute daily over a 12-month period. The 5 minute wear time was based on the labeled instructions for Crest Whitestrips Daily Multicare. First product use was supervised. All other use was at-home and unsupervised. Subjects were allowed to use their regular oral hygiene products (toothbrush and toothpaste) during the course of the study.

Product safety was assessed via subject interviews and oral examinations at baseline and after 1, 2, 3, 6, 9 and 12 months of product use. At each visit, subjects were interviewed regarding the presence or absence of oral discomfort. In the event of an adverse reaction its severity was assessed by a subject on a mild-moderate-severe scale. Oral examinations were then conducted by a qualified examiner blinded to treatment. Assessment included visual overall examination of the oral cavity and detailed examination of free and attached gingiva, hard and soft palate, buccal and labial mucosa, tongue, floor of the mouth, oropharynx, lips and perioral area. Subject interviews and oral examinations were conducted in two separate areas to ensure blinding. All relevant reported or observed adverse events were recorded.

Summary statistics (e.g., means, standard deviations, frequencies, etc.) of the demographic characteristics were calculated for each treatment group and overall. Number and percent of subjects with adverse events (oral irritation and tooth sensitivity) were calculated by treatment group. For each treatment group, Clopper-Pearson 95% confidence intervals were calculated for the percent of subjects with adverse events. Fisher's exact test was used to compare occurrence rates between the treatment groups.

3. Results

Study participants ranged in age from 20 to 62 years with an average of 39 years. Females accounted for 72.5% of study population, and 11.3% of the subjects were smokers. The two treatment groups were well-balanced ($p \geq 0.44$) with respect to their demographic parameters and behavioral characteristics (Table 1).

Tooth sensitivity and oral irritation were the two most common adverse events reported during the study. During the 12 months of product use, tooth sensitivity was reported by 5% of subjects in the placebo group with the confidence intervals (CI) of (0.6%, 16.9%) and 10% of subjects in the 6% hydrogen peroxide strip group with the CI of (2.8%, 23.7%). Oral irritation was reported by 2.5% of subjects in the placebo group with the CI of (0.1%, 13.2%) and 0% of subjects in the 6% peroxide strip group with the CI of (0%, 8.8%). The majority of subjects (86%) reported adverse events early, during the first 3 months of the clinical trial (Table 2). Occurrence of oral irritation observed by the examiner was also similar between the treatment groups. Similarly to reported AEs, the majority (79%) of subjects with

Table 1 – Baseline demographic characteristics

	0% H ₂ O ₂ strips (N = 40) ^a	6% H ₂ O ₂ strips (N = 40) ^a	Overall (N = 80) ^a	Two-sided p-value
Age				
Mean	39.7	38.0	38.9	0.44
Min–Max	20–62	21–53	20–62	
Sex ^b				
Female	29 (72.5%)	29 (72.5%)	58 (72.5%)	1.00
Male	11 (27.5%)	11 (27.5%)	22 (27.5%)	
Smokers ^b				
No	34 (85.0%)	37 (92.5%)	71 (88.7%)	0.48
Yes	6 (15.0%)	3 (7.5%)	9 (11.3%)	

^a N = number of subjects in each treatment group and overall.

^b Number (percent) of subjects in each category.

examiner-observed adverse events were seen during the first 3 months of the trial (Table 2). There were no significant ($p > 0.67$) differences between the treatment groups with respect to percent of subjects with each type of adverse event.

The majority of adverse events (97%) were mild in nature. One subject in the 6% peroxide strip group reported moderate tooth sensitivity (3% of total adverse events). There were no serious adverse events in the study. Two subjects (5%) in the 6% peroxide strip group discontinued treatment because of product-related tooth sensitivity. No subjects in the placebo group dropped from the study due to treatment-related adverse events. Treatment groups did not differ significantly

($p > 0.49$) with respect to “for cause” dropout occurrence. All adverse events were transient in nature and resolved during the course of the study.

4. Discussion

There is considerable clinical evidence demonstrating the safety of peroxide-based, at-home tooth whitening, in total, exceeding that found for certain other popular dental procedures.¹⁷ Despite this evidence, some reviewers have questioned safety of such treatments, identifying the need for further and longer term evaluations.⁸ Clinical evidence (often manufacturer sponsored), and practical experience (from the clinician-user) have demonstrated safety under routine conditions of use, while another vested interest (the research community) has taken the common and parochial “more research is needed” position. Which perspective is correct?

A critical evaluation of the presenting evidence suggests both have some merit. On review, most of the published research is confined to relatively few delivery systems (trays or strips), often under conditions of short-term (days to weeks) treatment without long-term follow-up. Now, some clinical trials have evaluated response with 6-months continuous treatment, making peroxide whitening of tetracycline stain a useful model to assess safety associated with chronic peroxide exposure. These studies have generally shown no new adverse events associated with chronic use, other than tooth sensitivity and oral irritation seen in the short-term clinical trials.^{11–13} However, most of the safety reporting, even for tooth sensitivity and oral irritation, is confined to simple occurrence rates, sometimes using indirect comparisons. To date, there are few rigorous statistical comparisons, or placebo-controlled trials, where causality can be directly inferred. We designed this new placebo-controlled trial to directly test long-term clinical safety of a 6% hydrogen peroxide strip and peroxide-casual outcomes associated with continuous daily treatment.

Results from the 12-month study demonstrated that the peroxide strip was remarkably well-tolerated. Adverse event occurrence rates were low in the absolute in the peroxide strip group. Tooth sensitivity represented the most common finding, with 10% of subjects in the peroxide strip group reporting at least one event over 12 months. There were no reports of oral irritation in the peroxide strip group anytime during the study.

Table 2 – Subjects with new adverse events by month

	Reported tooth sensitivity (N/%)	Reported oral irritation (N/%)	Observed oral irritation (N/%)
Month 1			
0% peroxide strip	0 (0)	1 (2.5)	5 (12.5)
6% peroxide strip	1 (2.5)	0 (0)	2 (5.0)
Month 2			
0% peroxide strip	1 (2.5)	0 (0)	1 (2.5)
6% peroxide strip	1 (2.5)	0 (0)	2 (5.0)
Month 3			
0% peroxide strip	1 (2.5)	0 (0)	1 (2.5)
6% peroxide strip	1 (2.5)	0 (0)	4 (10.0)
Month 6			
0% peroxide strip	0 (0)	0 (0)	1 (2.5)
6% peroxide strip	0 (0)	0 (0)	1 (2.5)
Month 9			
0% peroxide strip	0 (0)	0 (0)	1 (2.5)
6% peroxide strip	0 (0)	0 (0)	0 (0)
Month 12			
0% peroxide strip	0 (0)	0 (0)	0 (0)
6% peroxide strip	1 (2.5)	0 (0)	1 (2.5)
Cumulative at 12 month ^a			
0% peroxide strip	2 (5.0)	1 (2.5)	9 (22.5)
6% peroxide strip	4 (10)	0 (0)	10 (25.0)

^a No significant ($p \geq 0.67$) difference for percent of subjects with reported adverse events by type.

In the placebo strip group, 5% of subjects reported tooth sensitivity and 3% reported oral irritation. Similar results were reported for both groups with respect to examiner-observed oral irritation. Groups did not differ significantly ($p > 0.67$) on occurrence of tooth sensitivity or oral irritation.

The 95% confidence intervals for tooth sensitivity occurrence ranged from approximately 3–24%, while oral irritation ranged from 0 to 9%. Even at the upper bounds, these rates are low in the absolute, and lower than those commonly reported with short-term use of tray-based systems.⁹ Adverse events were generally mild in severity, only two subjects (5% of the peroxide strip group) discontinued treatment early due to self-reported tooth sensitivity. Study participation was voluntary and adverse event-related treatment cessation was at the discretion of each subject. Groups did not differ significantly ($p > 0.49$) with respect to “for cause” dropout. Examinations were generally unremarkable throughout the 12-month study, and groups did not differ with respect to clinical signs or adverse findings.

Importantly, the research provided no evidence of cumulative toxicity associated with 12-months continuous strip use. While adverse events were infrequent, neither onset nor severity increased over time. Most subjects experienced adverse events early in the study and most adverse events resolved by the end of the study. We speculate that the low total peroxide dose (approximately 9 mg) and short daily contact time (5 min) with these peroxide strips contributed to the favorable overall adverse event profile seen in this study relative to baseline and placebo. Further research would be indicated to ascertain whether these findings translated to other less controlled delivery systems (such as self-loaded trays), higher peroxide concentrations or longer contact times.

Results from this 12-month continuous use study are consistent with preceding clinical trials with 6% hydrogen peroxide strips. In those studies, where 6% hydrogen peroxide whitening strips were used daily for a few weeks, safety outcomes were primarily limited to minor and transient tooth sensitivity and oral irritation, which typically resolved during treatment.^{18–20} Post-treatment follow-up over periods of up to 18 months has not shown any latent or persistent adverse events after completion of strip use.^{21,22}

5. Conclusion

This new research extended the evidence on daily strip treatment to 12-months continuous use, testing statistically, safety responses versus the placebo control. This may represent one of the longest continuous use studies involving a peroxide-containing, daily use barrier product, where causality may be directly inferred. In this randomized controlled trial, daily use of 6% hydrogen peroxide whitening strips did not result in a causal increase in adverse events over that seen with placebo strips.

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