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Continuing Education

An Integrated Clinical Summary: Professional Tooth Bleaching Using 14% Hydrogen Peroxide Whitening Strips

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Continuing Education Units: 1 hour

This continuing education course is intended for general dentists, dental hygienists and dental assistants. Various advances in vital bleaching continue to expand the number of treatment options available to patients. A unique bleaching strip with 14% hydrogen peroxide (Crest® Whitestrips® Supreme) was introduced in 2003. This advanced system carries a thinner but more concentrated gel on each strip. The combination of a higher concentration gel with lowered gel volume translates to improved whitening without adversely affecting oral soft tissue tolerability and irritation. This course provides an integrated review of comparative clinical trials evaluating the whitening response and safety of this vital bleaching system.

Overview

Various advances in vital bleaching continue to expand the number of treatment options available to patients, particularly in the area of at-home whitening. The development of bleaching strips represented a new paradigm in the delivery of peroxide. The efficacy and safety of bleaching strip systems delivering up to 6.5% hydrogen peroxide has been established in numerous randomized clinical trials. In 2003, an innovative bleaching strip with 14% hydrogen peroxide (Crest® Whitestrips® Supreme) was introduced. This advanced system carries a thinner but more concentrated gel on each strip, resulting in a relatively similar total amount of peroxide as compared to other strip systems. This 2-variable change, higher concentration gel with lowered gel volume translates to improved whitening without adversely affecting oral soft tissue tolerability and irritation. This course provides an integrated review of 9 comparative clinical trials evaluating the whitening response (six trials) and safety (nine trials) of this novel vital bleaching system.

Learning Objectives

Upon the completion of this course, the dental professional will be able to:

- Describe the benefits of the whitening strip delivery system
- List common adverse events associated with tooth whitening
- Understand the relationship between peroxide concentration and whitening efficacy
- Understand the relationship between peroxide dose and soft tissue tolerability
- Discuss integrated clinical findings for a 14% hydrogen peroxide strip
- Describe integrated safety results for a 14% hydrogen peroxide strip

Course Contents

- Introduction
- Clinical Plan
- Results - Study Population
- Results - Effectiveness
- Results - Safety
- Discussion
- Conclusions
- Course Test
- References
- About the Authors

Introduction

The past decade has been characterized by various advances in vital bleaching, especially with the advent of new in-office options for immediate care and the emerging popularity of the direct-to-consumer systems. Such is the case with the whitening strip – an innovative bleaching system that uses a flexible polyethylene strip to deliver a hydrogen peroxide bleaching gel to the anterior dentition.[1] This "trayless" delivery system is reported to offer advantages with respect to controlled peroxide dose, contact time, and ease-of-use compared to other delivery systems.[2]

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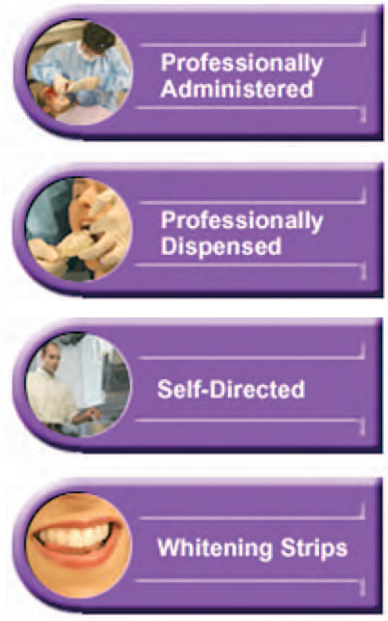
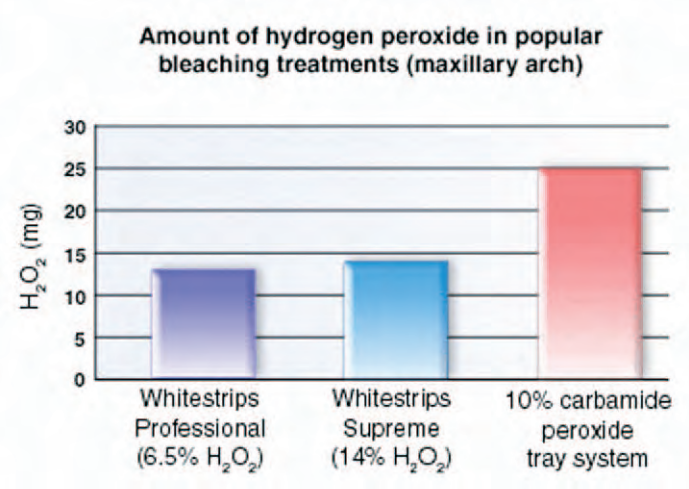


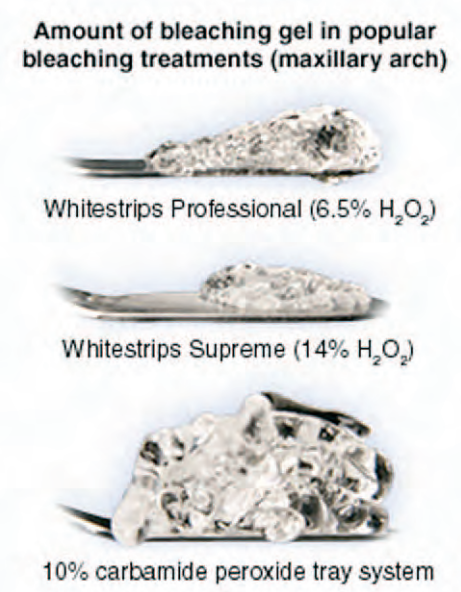
Evidence of the safe and efficacious use of the strip bleaching systems has been established in a series of randomized clinical trials relative to various marketed or experimental controls in studies involving different populations and time points.[3-16] Use of whitening strips was well-tolerated, with transient tooth sensitivity and minor oral irritation representing the most prominent side effects. The majority of events were mild in severity. In one integrated summary of 13 whitening strip clinical studies, only 1% of subjects who used strips discontinued treatment early because of tooth sensitivity or oral irritation.[3]

In composite, the published clinical data on whitening strips represents one of the most comprehensive bodies of research on vital bleaching in the literature. The trials were conducted at various sites by different investigators using several study designs and measurement methods. This extensive clinical research program evaluated whitening strip effectiveness and safety across a broad range of populations, formulations, and usage conditions. Since the mid-year 2000 introduction of Crest® Whitestrips®, there are already over 150 abstracts and publications on the clinical and preclinical effectiveness and safety of strip-based vital bleaching.

Go to http://www.dentalcare.com/soap/cws/ for Crest Whitestrips Product Research

Following the launch of strips containing 6% and 6.5% hydrogen peroxide, an innovative bleaching strip was developed with 14% hydrogen peroxide (Crest® Whitestrips® Supreme). Packaged in a 3-week kit, this system is reported to represent a unique option for professional at-home tooth whitening that does not require custom tray fabrication. While this system has a higher concentration of hydrogen peroxide relative to the marketed Crest® Professional Whitestrips® (14% versus 6.5%), the total amount of hydrogen peroxide is approximately the same. A maxillary strip from the Crest Whitestrips Supreme system carries half the amount of bleaching gel as Crest Professional Whitestrips with 14% hydrogen peroxide, or 1.4 mg per cm of hydrogen peroxide.[17] For comparison, each maxillary strip from the Crest Professional Whitestrips system has 6.5% hydrogen peroxide in twice the amount of gel, delivering 1.3 mg per cm of hydrogen peroxide.





The primary advantage of the 14% hydrogen peroxide strip versus the 6.5% hydrogen peroxide strip is theorized to be more effective whitening. With this higher concentration strip, peroxide molecules interact with and diffuse through enamel more efficiently following diffusion principles.[18] This increased diffusion is believed to contribute to better peroxide availability within the tooth, especially at the level of the dentinoenamel junction, where acquired chromagenic material is oxidized through normal chemical processes, resulting in whiter teeth. However, the same mechanism that promotes whitening could plausibly affect oral soft tissue response. There is considerable practical evidence of this with the higher concentration, in-office whitening systems, where treatment is typically preceded by the application of a barrier (such as a rubber dam or other device) to limit contact of the peroxide gel with gingival tissues during bleaching. To limit such effects, the gel layer on the new concentrated strips was reduced, leaving the total amount of peroxide exposure for the two professional strips essentially unchanged.

Go to the online Continuing Education to view an animation that illustrates the impact of a higher concentration of hydrogen peroxide. (There is no audio for this animation.)

Using the strip as a barrier, application of the thin concentrated gel is reported to yield extended peroxide residency on teeth for up to 1-hour, with only limited oral soft tissue exposure.[19] The intraoral peroxide degradation profile demonstrated rapid peroxide degradation from the thin gel on gingiva. After 5 minutes, the mean gingival peroxide concentration fell to 0.4%, which is less than one-thirtieth of the starting concentration on strips. This differed from the peroxide recovered from teeth where there was a 20-40-fold higher concentration compared to gingiva. This peroxide degradation profile provides the basis for a higher concentration, thin gel system for improved whitening without additional oral irritation. Following this kinetic model, a series of studies were conducted to evaluate clinical response with the thin 14% hydrogen peroxide gel pre-dispensed on a flexible whitening strip.

Clinical Plan

Nine randomized clinical trials were conducted at different clinical sites to evaluate the 14% hydrogen peroxide strip relative to various experimental controls. The research was conducted with independent institutional review and informed consent in accordance with the appropriate national and international guidelines for human research and standard operating procedures. Study design, clinical methods, and performance criteria were consistent with the preceding extensive research on whitening strips. Each study was under the direction of a qualified investigator with considerable clinical trials experience in the area of vital bleaching.

Examples of Products Tested

Each clinical trial was designed to address a specific research question. (A brief description of the study design and objectives for each trial is listed below.) Experimental controls, either a positive control professional at-home bleaching system or placebo, were selected to meet each study's specific needs.

1. Randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy, safety, and tolerability of 14% hydrogen peroxide strips with extended 6-weeks use.
2. Randomized and controlled, examiner-blind, clinical trial to evaluate the whitening efficacy and safety of 14% hydrogen peroxide strips among teenagers relative to one of the lower concentration (10% carbamide peroxide), tray-based positive controls that had previously earned the American Dental Association (ADA) "Seal of Acceptance."
3. Randomized, double-blind, placebo controlled clinical trial to evaluate the color stability and safety of 14% hydrogen peroxide strips over a 3-month post-treatment monitoring period.
4. Randomized and controlled, examiner-blind, clinical trial to evaluate the whitening efficacy and safety of 14% hydrogen peroxide strips relative to an intermediate concentration (16% carbamide peroxide), tray-based positive control.
5. Randomized, examiner-blind, crossover study conducted among individuals who had a history of tooth sensitivity and/or oral irritation

during a previous vital bleaching clinical trial to evaluate the safety and tolerability of 14% hydrogen peroxide strips relative to a 6.5% hydrogen peroxide strip-based positive control.

6. Randomized, examiner-blind clinical trial to evaluate the whitening efficacy and safety of 14% hydrogen peroxide strips relative to one of the higher concentration (9.5% hydrogen peroxide) tray-based positive controls.
7. Randomized and controlled, examiner-blind clinical trial to evaluate the comparative safety and tolerability of 14% hydrogen peroxide strips relative to one of the higher concentration (20% carbamide peroxide), tray-based positive controls.
8. Randomized, double-blind, placebo-controlled clinical trial to compare shade change and safety of 3-week, twice daily use of 14% hydrogen peroxide strips to placebo.
9. Randomized and controlled, examiner-blind clinical trial to evaluate the comparative safety and tolerability of 14% hydrogen peroxide strips relative to one of the higher concentration (30% carbamide peroxide), tray-based positive controls.

The research was conducted at 7 different academic or clinical research settings. This combination of sites and researchers was desired to obtain the broadest possible perspective on clinical response to the novel bleaching strip.

Each clinical study had an experimental control (Table 1). Three trials were placebo-controlled. These double-blind trials allowed for the direct assessment of causality with respect to safety endpoints. Five studies used one of the popular custom tray-based vital bleaching systems dispensed by professionals for at-home whitening as a positive experimental control. One sensitivity study used Crest Professional Whitestrips as the positive experimental control. Such controls allow for the direct comparison of the novel 14% strip relative to marketed controls that are regularly used in dental practice. Because professional systems differ

Table 1. Study Description.

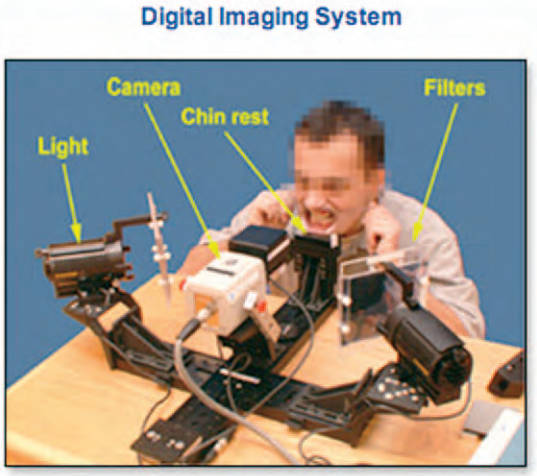
Study	N[a]	Treatment Description	Treatment Regimen
1	39	Crest Whitestrips Supreme Placebo Strips	30 min BID, 6 weeks
2	60	Crest Whitestrips Supreme Opalescence 10%	30 min BID, 2-3 weeks/arch Overnight, 2-3 weeks/arch
3	50	Crest Whitestrips Supreme Placebo Strip	30 min BID, 3 weeks
4	69	Crest Whitestrips Supreme Nite White Excel3 16%	30 min BID, 3 weeks 2-4 hours QD-BID, 10 days
5	18[b]	Crest Whitestrips Supreme Crest Prof. Whitestrips	30 min BID, 1 week
6	39	Crest Whitestrips Supreme Day White 9.5%	30 min BID, 3 weeks 30 min BID, 9 days
7	60	Crest Whitestrips Supreme Opalescence 20% F	30 min BID, 3 weeks Overnight, 14 days
8	29	Crest Whitestrips Supreme Placebo Strip	30 min BID, 3 weeks
9	44	Crest Whitestrips Supreme Rembrandt XTRA Comfort	30 min BID, 3 weeks 30 min BID, 10 days

[a]Total number of treated subjects.
[b]Crossover study, 16 subjects used both products.

with respect to peroxide source, formulation, and concentration, we selected various marketed controls and regimens to provide perspective on the comparative response versus a range of peroxide concentrations and sources. Four of these studies specifically evaluated the 14% hydrogen peroxide bleaching strip relative to the highest peroxide concentration systems marketed by leading manufacturers for at-home use at the time of testing (Crest Professional Whitestrips, Day White 9.5%, Opalescence 20% F, Rembrandt XTRA Comfort 30%).

In composite the research evaluated normal and extended use of 14% hydrogen peroxide bleaching strips as well as post-treatment status. Efficacy and safety measurements were collected in accordance with standard methods used in numerous preceding whitening clinical trials.[3] Tooth color efficacy was measured in five trials (Studies 1, 2, 3, 4, and 6 above) using a standard, objective method involving archival-quality digital images collected from the anterior dentition. Safety was measured by treatment-blinded examination of the oral soft and hard tissues, along with subject interview to assess the presence or absence of symptoms (tooth sensitivity and oral irritation) that may have occurred at any time during treatment. The nature of any adverse events, along with information relating to onset, severity, and duration, were recorded along with examiner-assigned causality according to pharmaceutical industry research standards. For analysis, all adverse events were classified using the standard COSTART coding nomenclature. In one study, safety was assessed by the absence of irreversible side effects associated with use of the test product, including notably, assessment of the effect of treatment on gingivitis and plaque.

In the integrated analysis, individual subject outcomes were pooled into three categories to provide a general framework to assess the clinical response of the novel strips: experimental strips (Crest Whitestrips Supreme), positive controls (6 peroxide-containing professional at-home tray or strip systems), or placebo strips (no peroxide). Effectiveness was compared between categories using a general linear model (for tooth color) or analysis of covariance (for tooth shade) adjusting for starting color/shade and/or study effects, as



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appropriate. All between-category testing was two-sided ($p < 0.05$).

Results - Study Population

The composite research involved 348 adult volunteers who provided informed consent, and 60 teenagers, for whom both parental informed consent and child assent was obtained. By treatment, there were a total of 212 subjects who used the 14% bleaching strips, 152 who used one of the positive bleaching controls, and 60 who used placebo strips.

One study (Table 1, #5) was a crossover design, where subjects used both 14% hydrogen peroxide strips and a positive control. Overall, the population exhibited considerable diversity with respect to age, gender, and ethnicity (Table 2). Subjects ranged from 12-72 years of age. Both genders were well-represented. Treatment groups were balanced overall with respect to demographic parameters.

Results - Effectiveness

The primary efficacy endpoint in 5 comparative studies (Table 1, #1, 2, 3, 4, and 6) was reduction in yellowness (Δb^*), which has been previously reported to represent the most perceptually relevant color measurement in vital bleaching clinical trials.[9] The pooled sample included 110 subjects assigned to 14% hydrogen peroxide strips over a 2-6 week usage period. Response was approximately normally distributed with 69% of subjects experiencing between 2-5 units

Table 2. Demographic Characteristics by Group – Nine Randomized Controlled Trials.

Baseline Characteristic/ Statistic	14% H_2O_2 Strips (n = 212)	Positive Controls (n = 152)	Placebo Strips (n = 60)
Age (Years)			
Mean (SD)	33.8 (13.85)	33.1 (13.74)	35.7 (14.18)
Min - Max	12 - 70	12 - 72	18 - 66
Sex			
Female	134 (63.2%)	94 (61.8%)	35 (58.3%)
Male	78 (36.8%)	58 (38.2%)	25 (41.7%)
Ethnicity			
American Indian	0 (0.0%)	1 (0.7%)	0 (0.0%)
Asian	9 (4.2%)	3 (2.0%)	2 (3.3%)
Black	22 (10.4%)	17 (11.2%)	6 (10.0%)
White	146 (68.9%)	104 (68.4%)	35 (58.3%)
Hispanic	21 (9.9%)	22 (14.5%)	8 (13.3%)
Indian Subcontinent	10 (4.7%)	3 (2.0%)	4 (6.7%)
Multi-racial	4 (1.9%)	2 (1.3%)	5 (8.3%)

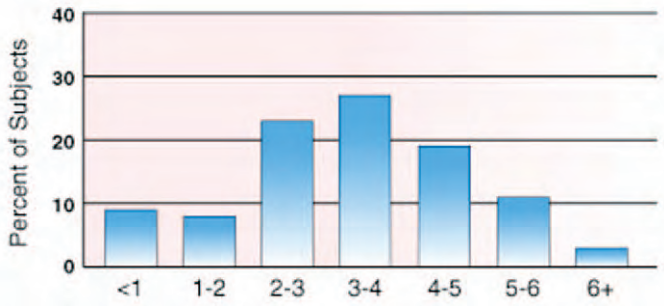

Figure 1. Mean Reduction in Yellowness by Subject 14% hydrogen peroxide strips, Five Clinical Trials.

improvement in Δb*. Approximately 83% of subjects in the pooled 14% bleaching strip group experienced a 2-unit or greater improvement in Δb*, while 60% experienced at least a 3-unit or greater improvement in Δb* (Figure 1).

The comparative research evaluated the pooled color response of 14% hydrogen peroxide strips, the positive controls, and placebo (Table 3). Relative to baseline, the pooled 14% strip group exhibited a highly significant ($p<0.0001$) reduction in yellowness. Mean (SD) Δb* was -3.31 (1.597). There was a similar, highly significant color improvement for other individual (ΔL* and Δa*) and composite (ΔE* and ΔW*) color parameters. Color response in the pooled placebo group was not significantly different ($p>0.60$) from "zero" as evidenced by a mean (SD) Δb* of 0.04 (0.490). Relative to placebo, the pooled 14% strip group exhibited highly significant ($p<0.0001$) improvements in all individual and composite color parameters. Overall, the pooled positive control group had a highly significant ($p<0.0001$) reduction in yellowness, and improvement in other color parameters. Mean (SD) Δb* in this combined group was -2.21 (1.311). Relative to

Table 3. Color or Shade Mean (SD) Change from Baseline – Evaluable Subjects, Six Clinical Trials.

Measurement / Endpoint	14% H_2O_2 Strips	Positive Controls	Placebo Strips
Color	N = 110	N = 77	N = 37
Δb*	-3.31 (1.597)	-2.21 (1.311)	0.04 (0.490)
ΔL*	2.84 (1.384)	2.45 (1.123)	0.02 (0.574)
Δa*	-0.97 (0.681)	-0.84 (0.580)	0.00 (0.309)
ΔW*	-4.27 (1.935)	-3.35 (1.531)	0.00 (0.505)
ΔE*	4.60 (1.917)	3.53 (1.557)	0.73 (0.343)
Shade	N = 13		N = 15
ΔShade (4 Teeth)	-8.01 (2.379)		-0.76 (2.134)
ΔShade (6 Teeth)	-8.51 (1.925)		-1.04 (1.892)

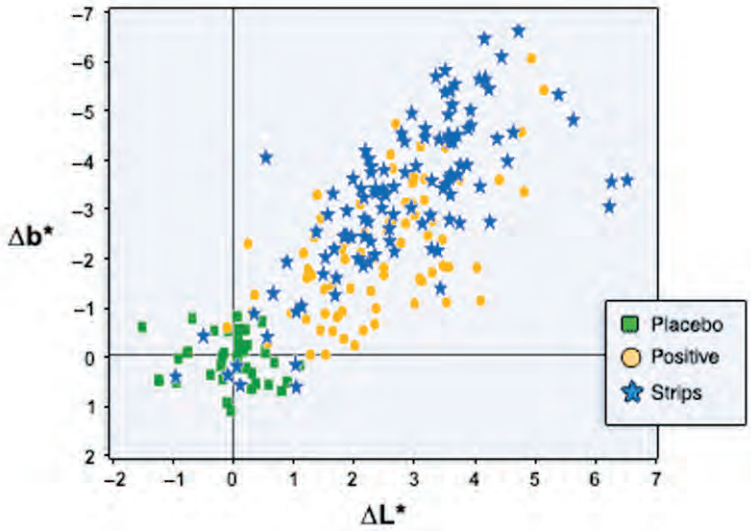

Figure 2. Individual Subject Color Response: Strips, Positive Controls, and Placebo Controls.

the pooled positive controls, the 14% hydrogen peroxide group exhibited significant ($p<0.05$) improvement in the individual parameters b* and ΔL* as well as the composite parameters ΔE* and ΔW*.

Results - Effectiveness

The scatterplot of two-parameter whitening (Δb* versus ΔL*) illustrated the individual whitening response with the strips, and the positive and placebo controls (Figure 2). Most of the placebo subjects clustered generally around zero for Δb* and ΔL. In contrast the overwhelming majority of subjects using one of the peroxide-containing products (strips or trays) experienced two parameter (b* & L*) improvements in tooth color with treatment. While there was considerable variability in whitening response, the 14% hydrogen peroxide group experienced the greatest absolute two-parameter improvement compared to the pooled positive control products or placebo.

One study (Table 1, #8) used tooth shade as an endpoint with shade change measured on the 6 maxillary anterior teeth. After three weeks of treatment, 96% of incisors in the 14% strip group exhibited at least a 2-shade improvement. Similar results were observed for the incisors and cuspids, where 97% of those teeth exhibited at least a 2-shade improvement.

In this shade study clinical response in the 14% strip group was approximately normally distributed, with 69% of subjects experiencing a

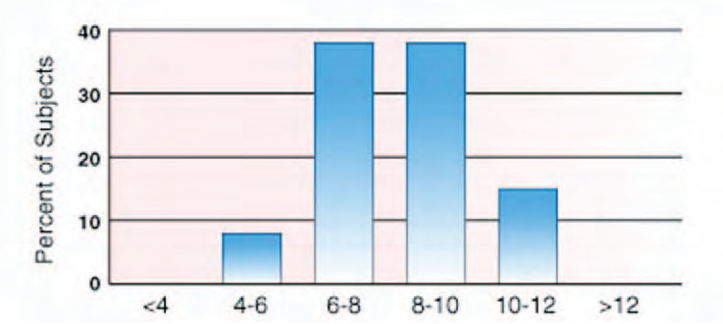

Figure 3. Mean Shade Improvement by Subject 14% hydrogen peroxide strips.

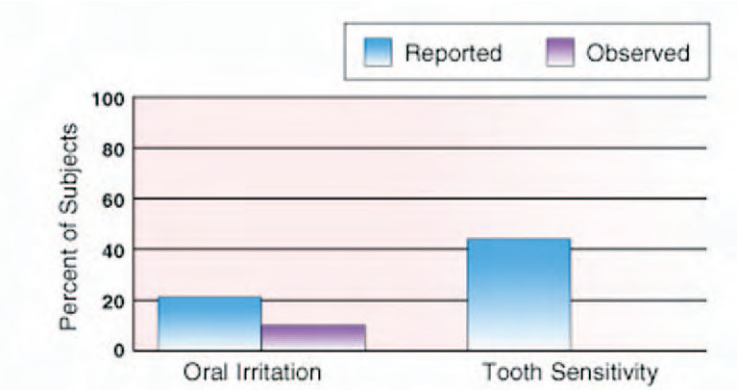

Figure 4. Oral Irritation and Tooth Sensitivity 14% hydrogen peroxide strips, All Studies.

7-10 shade improvement. All subjects (100%) averaged at least a 4-shade improvement, while approximately 92% of subjects in the pooled 14% strip group experienced a 6-unit or greater shade improvement (Figure 3).

Compared to baseline, the 14% hydrogen peroxide strip group exhibited a highly significant ($p<0.0001$) reduction in shade at end-of-treatment. Mean (SD) shade change was -8.0 (2.38) for the 4 maxillary incisor teeth and -8.5 (1.93) for the 6 maxillary anterior teeth (Table 3). In contrast, the placebo group exhibited no more than a 1-shade change on average. Treatments differed significantly ($p<0.0001$) with respect to shade change after 3 weeks.

Results - Safety

Tooth sensitivity and oral irritation were specifically monitored in each study at each time point, because these two events have been widely recognized as the most common adverse events with vital bleaching. Overall, 43% of strip users reported tooth sensitivity and 23% reported oral irritation (Figure 4). Clinically detected oral irritation was less common. For these events, study results demonstrated use of 14% hydrogen peroxide strips was well tolerated both in the absolute and relative to the other professional at-home systems tested in this research (Table 4).

Overall, there were a total of 132 subjects in the pooled 14% strip group (62% of the population) with at least one adverse event (related or unrelated to treatment) during the evaluation period (Table 5). The 14% strip users had on average less than one (0.91) adverse event of any type or causal relationship. Among subjects with adverse events, the total number of reports was limited. The 132 subjects in the 14% strip group with an adverse event averaged 1.46 adverse events, slightly more than one report per affected subject.

The majority (83%) of adverse events in the 14% bleaching strip group were “mild” in severity. Only 2% of events in the pooled 14% strip group were classified as “severe,” a proportion that was similar to or less than that observed among the positive control or placebo groups (Figure 5).

Table 4. Possible or Probable Treatment Related Oral Irritation or Tooth Sensitivity – All Subjects Treated, Nine Clinical Trials.

Adverse Event Source / Classification	14% H_2O_2 Strips (N = 212) Subject # (%)	Positive Controls (N = 152) Subject # (%)	Placebo Strips (N = 60) Subject # (%)
Self Reported			
Oral Irritation	48 (22.6)	51 (33.6)	2 (3.3)
Tooth Sensitivity	91 (42.9)	50 (32.9)	0 (0)
Oral Irritation and Tooth Sensitivity	22 (10.4)	20 (13.2)	0 (0)
Oral Irritation or Tooth Sensitivity	117 (55.2)	81 (53.3)	2 (3.3)
Examiner Observed			
Oral Irritation	24 (11.3)	34 (22.4)	0 (0)

Table 5. Summary of Adverse Events – All Subjects Treated, Nine Clinical Trials.

	14% H_2O_2 Strips (N = 212)		Positive Controls (N = 152)		Placebo Strips (N = 60)	
	Subject # (%)	AEs # (%)	Subject # (%)	AEs # (%)	Subject # (%)	AEs # (%)
Serious AEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild AEs	121 (57)	161 (83)	73 (48)	101 (73)	3 (5)	4 (67)
Moderate AEs	21 (10)	28 (15)	27 (18)	32 (23)	0 (0)	0 (0)
Severe AEs	3 (1)	4 (2)	4 (3)	5 (4)	1 (2)	2 (33)
Not Related	2 (1)	2 (1)	3 (2)	3 (2)	0 (0)	0 (0)
Doubtful Related	7 (3)	7 (4)	3 (2)	3 (2)	3 (5)	3 (50)
Possibly Related	32 (15)	34 (18)	19 (13)	19 (14)	0 (0)	0 (0)
Probably Related	102 (48)	150 (78)	77 (51)	113 (82)	2 (3)	3 (50)
TOTAL	132 (62)	193 (100)	90 (59)	138 (100)	4 (7)	6 (100)
# AEs / N	0.91		0.91		0.1	
# AEs / N AEs	1.46		1.53		1.5	

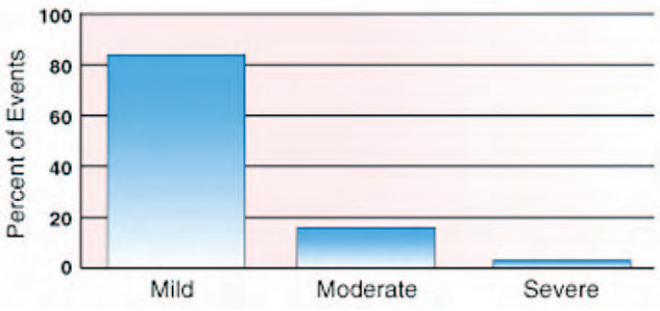

Figure 5. Adverse Event Severity by Causality 14% hydrogen peroxide strips, All studies.

There were no serious adverse events (according to the FDA definition) in any of the trials. Across all studies, only 8 subjects discontinued treatment early because of an adverse event that was possibly or probably related to treatment. By treatment group, the "for cause" drops included 4 subjects (2% of the group) assigned to 14% bleaching strips, 3 subjects (2% of the group) assigned to a positive control, and 1 subject (2% of the group) assigned to placebo.

The most common adverse events for 14% strips were tooth sensitivity and oral irritation. These accounted for 93% of all adverse events

Example of transient finger whitening

Resolution of whitening

(causal and non-causal) in the pooled 14% strip group. The most common extraoral adverse event was finger "whitening or tingling" reported for 8 subjects in the 14% strip group (4% of that population). This mild and transient effect sometimes occurred immediately following strip application. Clinical manifestations were generally mild, and similar to that seen following topical application of common bottled 3% hydrogen peroxide. Resolution was within a few minutes to an hour without intervention.

Across all studies, there was only one unusual adverse event – oral leukoplakia seen on examination following use of one of the positive controls – that likely existed pre-treatment. There were no reports of nausea, gastric distress, or other extraoral adverse events in the 14% hydrogen peroxide strip group except for temporary finger "whitening." Importantly, the research showed no evidence of increased severity with extended use of 14% strips for up to 6 weeks.

In one comparative study periodontal health was assessed using standard methods for measuring gingivitis (GI) and plaque (PII). Overall, the strip groups had lower mean gingivitis and plaque scores after treatment (Figure 6). Increased plaque and/or gingivitis may provide evidence of oral irritation or other treatment-related adverse events (such as new found tooth sensitivity) that interrupt normal oral hygiene. This research showed no evidence of additional plaque or gingivitis after 3 weeks of treatment with 14% hydrogen peroxide strips, since periodontal health improved in the absolute. The placebo response was generally similar, and there were no significant between-group differences in gingivitis or plaque at any post-baseline time point. As such, the research fails to demonstrate any significant adverse effect of the hydrogen peroxide in higher concentration strips on periodontal health.

Discussion

Crest Whitestrips Supreme, a thin 14% hydrogen peroxide whitening strip, represents an innovative approach for professional at-home vital bleaching. Characterized as a two-variable change (increased peroxide concentration in the bleaching gel, decreased amount of gel), this 14% hydrogen peroxide strip carries a relatively similar total amount of peroxide compared to other strip systems.[17] A total of 9 comparative clinical trials were conducted initially to evaluate clinical response of this novel vital bleaching system.

The integrated results showed Crest Whitestrips Supreme to be both effective (using tooth color or tooth shade as endpoints) and well-tolerated overall. With respect to tooth color, the integrated research demonstrated significant improvements in the individual color parameters (Δb^* and ΔL^*) as well as composite endpoints (ΔE^* and ΔW^*) for the 14% hydrogen peroxide strip. With respect to shade change, twice daily use of the

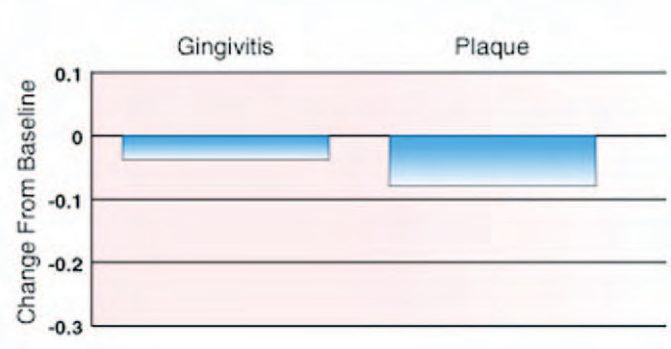

Figure 6. Mean Change in Gingivitis & Plaque with Treatment 14% hydrogen peroxide strips.

Subject treated with 14% H_2O_2 strips (maxillary arch only) for 3 weeks.
Photo courtesy of Dr. Ingvar Magnusson, University of Florida.

thin concentrated strips resulted in a mean 8-unit shade change after 3 weeks. Results from these studies demonstrate the clinical effectiveness of 14% hydrogen peroxide bleaching strips is robust and not confined to a single measurement method.

Across all studies, tooth sensitivity and oral irritation represented the most common adverse events with the 14% hydrogen peroxide strips. Like the preceding research on professional at-home vital bleaching with trays or strips, these events were generally mild in severity, and resolved fully during or after treatment.[3,14,21,22] Also like preceding tray and strip research, there was no evidence of any short-term adverse effects on periodontal health, with gingivitis and plaque scores directionally lower at the end-of-treatment with the 14% hydrogen peroxide strip.[23-25] With respect to oral safety and tolerability, the composite research provided no evidence of unexpected or atypical findings for the high concentration whitening strips. Based on this research, use of a low, uniform amount of a higher peroxide concentration gel resulted in a generally similar oral adverse event profile to that seen with other professional at-home vital bleaching systems at lower peroxide concentrations. While extraoral events were infrequent and unremarkable, there was one new finding associated with the higher concentration strip system. Approximately 4% of subjects in the 14% hydrogen peroxide group reported some minor and transient post-application finger whitening, proximate to the time of application. The clinical meaningfulness of both the oral and non-oral findings is low given the similar 2% "for cause" dropout rate in the strip, positive control, and placebo groups.

The integrated research showed generally better efficacy and tolerability for the 14% hydrogen peroxide strips compared to marketed positive bleaching controls. Individual patient responses varied, as demonstrated in the scatterplot on change in yellowness (Δb^*) versus lightness (ΔL^*). While both the strip and positive control clusters differed from "zero" and placebo (evidence of absolute and relative whitening for these peroxide-containing products), whitening response in the strip group was better overall. The best individual patient responses for Δb^* and ΔL^* were seen among strip users, with these categories differing significantly ($p<0.05$) with respect to mean color change for Δb^*, ΔL^*, ΔE^*, and ΔW^*. Relative to the other professional whitening systems, the higher concentration strips exhibited similar or better tolerability (tooth sensitivity, oral irritation, examiner-assessed severity, and overall adverse event rates).

What are the advantages of an integrated review? While the randomized clinical trial remains the "gold standard" of research, systematic review and meta-analysis of the outcomes from many trials has long been recognized as providing even a higher level of evidence for use in clinical decision making.[26] Limitations in this approach, including publication bias, inconsistent reporting, differences in methodologies or populations, and other factors, have been previously described with respect to the dental clinical trials literature.[24,27] The meta-analysis reported herein, which used original source data from all evaluable subjects in all trials, has fewer limitations. The integrated review, an inclusive assessment of over 200 subjects age 12-70 years, evaluated use of the 14% hydrogen peroxide strips for periods of up to 6 weeks at 7 different clinical sites.

Pooling results from several trials, in addition to increasing sample size, assures greater diversity among the study population and investigators.

The data set was particularly rich in that it includes both placebo and positive controlled studies. The former double-blind placebo trials allowed for the direct assessment of causality, while the latter allowed assessment of relative performance versus products already familiar to many clinicians.[28] Nonetheless, caution must be taken when interpreting results even from an integrated analysis like this one. Comparative response, especially versus the positive controls, must be an informed one given the dissimilar nature of the various products in that category. For example, professionally-directed, at-home bleaching encompasses a wide range of treatment times (ranging from a few minutes each day to overnight use) and durations (ranging from episodic use over a few days to continuous use over a period of months).[29] The clinical research summarized herein covered only a portion of these possible combinations, starting first with placebo-control and then moving up through selected higher concentration positive controls. These integrated results substantiate the clinical effectiveness and safety of this novel professional at-home whitening system in the absolute, and relative to contemporary marketed controls.

Conclusions

- Nine randomized and controlled clinical trials were conducted under the direction of qualified, independent investigators explicitly for the purposes of evaluating Crest Whitestrips Supreme in a diverse population.
- Crest Whitestrips Supreme effectiveness was demonstrated in multiple clinical trials by multiple examiners using different efficacy endpoints (color and shade) both in the absolute and when compared to placebo or the pooled professional at-home bleaching controls.
- Tooth sensitivity and oral irritation, the common adverse events with Crest Whitestrips Supreme use, were generally mild in severity, and resolved during or after treatment.
- Crest Whitestrips Supreme was generally similar to or better than popular, marketed tray-based whitening systems with respect to tolerability (tooth sensitivity, oral irritation, examiner-assessed severity, and overall adverse event rates).

For more information on Crest Whitestrips Supreme or to make a purchase, go to http://www.dentalcare.com/soap/products/index_whitestrips.htm

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to www.dentalcare.com and find this course in the Continuing Education section.

1. Compared to other delivery systems, "trayless" bleaching strips offer advantages of:

a. Controlled peroxide dose
b. Ease-of-use
c. Contact time
d. All of the above

2. Although the concentration of 14% hydrogen peroxide strip is higher than 6.5% hydrogen peroxide strips, both strips deliver approximately the same amount of _____.

a. Bleaching gel
b. Whitening
c. Peroxide
d. None of the above

3. The majority (83%) of adverse events in the 14% bleaching strip group were _____ in severity.

a. Mild
b. Moderate
c. Severe

4. In the study using shade guides, _____% of incisors in the 14% strip group showed at least a 2-shade improvement after 3 weeks.

a. 50%
b. 72%
c. 89%
d. 96%

5. The composite research involved 212 subjects who used the 14% whitening strips, 152 who used a positive control and 60 who used placebo strips.

a. True
b. False

6. Using objective efficacy endpoints, a negative change in b* represents:

a. An increase in lightness
b. An increase in yellowness
c. A reduction in yellowness
d. A reduction in lightness

7. The nine clinical trials included in the integrated summary were conducted at _____ different sites.

a. Two
b. Three
c. Five
d. Seven

8. Relative to baseline, the pooled 14% hydrogen peroxide strip group showed _____ reduction in yellowness.

a. No
b. A significant (p=0.05)
c. A highly significant (p< 0.0001)
d. A slight

9. The most common adverse events for 14% strips were _____.

a. Tooth sensitivity
b. Oral irritation
c. Both A and B
d. Neither A nor B

10. Relative to the marketed positive bleaching controls, the 14% hydrogen peroxide strips showed generally _____ efficacy and tolerability.

a. Better
b. Worse
c. Similar
d. None of the above

11. Compared to the 6.5% hydrogen peroxide strips, the 14% hydrogen peroxide strip:

a. Has half the beaching gel level
b. Has a higher peroxide concentration
c. Delivers a similar amount of peroxide
d. All of the above

12. The pooled population exhibited little diversity in terms of age, gender and ethnicity.

a. True
b. False

13. There were ___ serious adverse events, according to the FDA definition, in any of the trials.

a. No
b. 3
c. Five
d. More than 10

14. Compared to the randomized clinical trial, a systematic review of outcomes from many trials has been recognized as providing _____ evidence for use in clinical decision making.

a. The same level of
b. A higher level of
c. A lower level of
d. Irrelevant

15. The effectiveness of the 14% hydrogen peroxide strips Crest Whitestrips Supreme was demonstrated in multiple clinical trials by multiple examiners using one efficacy endpoint.

a. True
b. False

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