The efficacy and safety of a 10% carbamide peroxide bleaching gel

Bruce A. Matis, DDS, MSD*/Michael A. Cochran, DDS, MSD**/George Eckert, MAS***/Timothy J. Carlson, DDS, MSD*

Objective: A 6-month, double-blind study was undertaken to assess the efficacy and safety of a 10% carbamide peroxide gel designed for at-home tooth bleaching.

Method and materials: Sixty patients were randomized into two equal subgroups balanced by age, gender, and oral health status. Shade guide measurements, color transparency photographs, and colorimeter readings were taken and evaluated at baseline and 1, 2, 3, 6, 12, and 24 weeks. The active phase of treatment lasted 14 days.

Results: At 22 weeks postbleaching (week 24 of the study), patients receiving the active agent had a 14.1 rank order difference in the shade guide from baseline, and 66% had a clinically observable color change as determined by photographic assessment. They also had a measurable, statistically significant color change from baseline to 6 months of treatment. The tooth color of maxillary incisors stabilized at week 6 and maxillary canines at week 12. The mean color change lost from weeks 2 to 24 was 45% (in ΔE*). Transient tissue and tooth sensitivity, noted in some patients, resolved after treatment was completed.

Conclusion: The product tested is an effective and safe tooth-whitening agent. (Quintessence Int 1998; 29:555–563)

Key words: carbamide peroxide, colorimeter, sensitivity, tooth bleaching

Clinical relevance

An observable color change was maintained in the maxillary anterior teeth of 66% of patients 22 weeks postbleaching. Sensitivities that occurred during treatment were transient.

Vital bleaching has become the most frequently used treatment modality for improving the esthetic appearance of teeth. Christensen has said, "It is perhaps the most behavior-changing procedure in dentistry." It is therefore imperative to determine which bleaching agents are effective and safe.

The purpose of this clinical study was to determine the efficacy and safety of Opalescence Whitening Gel (Ultradent Products) by comparing it with a placebo control (identical formulation without carbamide peroxide) in patients of similar age, gender, and oral hygiene status using a double-blind design. The study also attempted to identify any change in color for a 22-week period following treatment.

The American Dental Association introduced guidelines for the acceptance of peroxide-containing products in 1994. This study used three of the four methods recommended for measuring changes in the lightness of teeth.

Method and materials

Patient selection

Sixty of 244 patients who presented for initial screening were selected for the study. The patients were screened to eliminate any individuals with soft or hard tissue pathoses (excluding small carious lesions and mild gingivitis). The patients were required to have all six maxillary anterior teeth, with no more than one sixth of the facial surface restored, and to be non-smokers.
A Loe and Silness Gingival Index (GI) was scored and recorded at six sites around each tooth. Patients with a mean GI of greater than 1 were excluded because of the potential for inflammation to rapidly deactivate peroxide compounds.

A color match of the maxillary anterior teeth was determined and recorded using the Trubyte Bioform Color-Ordered shade guide (Dentsply). The initial color match of all six teeth was required to be B54 or darker, which is the same as shade A3 on the Vita Lumin shade guide (Vita Zahnfabrik). The Vita shade guide has 18 shades and the Trubyte shade guide has 24 shades.

Patients who met the basic criteria at the screening appointment and agreed to participate were informed that they would need to return for an initial dental prophylaxis and again at baseline, 1, 2, 3, 6, 12, and 24 weeks for treatment and evaluations. Sixty patients signed the consent form and agreed to return at the required intervals. Two maxillary alginate impressions were made and casts were poured. Patients were then given an appointment for a complete dental prophylaxis to be completed by licensed hygienists at a minimum of 2 weeks before the baseline evaluation.

### Group assignment

The active and placebo groups were balanced according to three criteria—gender, age, and oral hygiene status. Age was grouped as younger than 35 years of age and 35 years or older. The GI value was used to determine oral hygiene status, and the groups were divided into less than 0.5 GI and 0.5 to 1.0 GI. A dental assistant was responsible for group balancing, so that the evaluators would continue to be blind as to which treatment group each patient was assigned (Table 1).

The following measurement values were determined before either the placebo or the active agent was given to the patient at baseline: Gingival Index, shade guide, and colorimeter. Color slides (Elite 100 Ectachrome, Kodak) were also made of the teeth to be whitened. At each subsequent appointment, the above-mentioned values were determined and photographs were taken.

### Observations and/or measurements to determine efficacy

Each of the evaluations was conducted in one operatory, which had color-corrected overhead fluorescent lighting. The area between the middle and incisal thirds of the tooth gingivo-occlusally was selected for shade guide matching and colorimeter measurement.

#### Shade guide

Color ranking with the shade guide was performed by the principal investigator and recorded by a chairside assistant. The observation that some teeth were lighter or darker than the 1 to 24 rankings available in the shade guide required the addition of one more division to each end of the ordered scale in this study. A tooth that was lighter than the lightest shade in the shade guide received a relative ranking of 0, and a tooth that was darker than the darkest shade in the shade guide received a relative ranking of 25.

#### Photographs

At each appointment, 35-mm color slides were made of the six maxillary and mandibular anterior teeth, end to end. The camera (Model N8008s, Nikon) was equipped with a data back to record the patient number and week number on each slide. A 105-mm Macro lens with electronic flash and AC Adapter (Lester Dine) was used to optimize the consistency of flash. The focal length was marked on the camera lens to maintain consistent magnification at each evaluation.

A numbering scale was established for color change of the slides: 0 = no change; 1 = slight or distinguishable change; 2 = moderate or pronounced change; 3 = large or dramatic change. A "slight" change was distinguishable with careful evaluation but was not consid-
Fig 1 The Chroma Meter cone attachment is inserted into the maxillary arch splint to ensure that the same tooth area is evaluated on a repeated basis.

Fig 2 The CIELAB measures the $L^*$ value, which is shown as the vertical axis of white to black; the $a^*$ value, which is the red to green spectrum; and the $b^*$ value, which is the yellow to blue spectrum.

ied clinically observable. “Moderate” and “large” changes were to be clinically observable. A pre-evaluation calibration, consisting of selected cases representing typical color change responses, was conducted to standardize the evaluators.

The evaluators were two faculty members of the Department of Restorative Dentistry who have had considerable experience as evaluators in clinical research projects, particularly of color assessment. The pre-evaluation calibration slides were from one patient, who was not involved in the study. The slides were projected to an image of 3.0 x 4.5 feet. Each evaluator determined independently the color relationship of the maxillary anterior teeth to the mandibular anterior teeth. Because of the possibility that the maxillary arch might be lighter at baseline, the evaluators were then shown both baseline and 24-week evaluation slides side by side to verify their observations. Following independent evaluation, the examiners were required to reach consensus.

Colorimeter. A Chroma Meter colorimeter (Model CR-121, Minolta) with a detachable and sterilizable cone was used in this study. It has been accepted by many researchers as a standard for tooth color measurements and has demonstrated good repeatability when properly repositioned. To ensure proper repositioning, the Eichhold Coupling System, which uses Pindex dual-pin precision attachments (Coltene/Whaledent), was used. The female pin is embedded in the maxillary splint, which is inserted over the maxillary arch, and the male pin is attached to the cone, which fits over the colorimeter nose cone (Fig 1). The Eichhold Coupling System has demonstrated repeatable measurements. Each tooth was measured three times in nonconsecutive order.

The Chroma Meter measures $L^*$, $a^*$, and $b^*$ color space. This system of color space was defined by the Commission Internationale de l’Eclairage in 1976 and is referred to as CIELAB. In color space, $L^*$ indicates lightness and $a^*$ and $b^*$ represent chromaticity coordinates. A positive $a^*$ value indicates the red direction, a negative $a^*$ value the green direction, a positive $b^*$ value the yellow direction, and a negative $b^*$ value the blue direction (Fig 2). $\Delta E^*$ is accepted as the difference in color value, which is determined by including each of the three parameters:

$$\Delta E^* = \sqrt{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2}$$

Gingival Index

The Löe and Silness Gingival Index consists of placing the tip of a periodontal screening and recording probe 1 mm in sulcus depth and moving it laterally around the cervical collar of each tooth. Each tooth is scored at six sites. A mean score was determined for each patient at each evaluation. The GI index scoring is 0 = pink, healthy tissue; 1 = red color, but no bleeding on probing; 2 = delayed bleeding on probing; 3 = spontaneous bleeding on probing.

Patient sensitivity

Each patient was given a diary for daily entries. They were asked to record any unusual occurrences, to note date, time, and duration during the treatment and including the following week. Sensitivity was measured in three areas: the gingiva, the teeth, and the gastrointestinal system. Severity was measured on a scale of 1 to 5: 1 = no sensitivity; 2 = slight sensitivity; 3 = moderate sensitivity; 4 = considerable sensitivity; 5 = severe sensitivity.

The diaries were used by the patients to fill out the sensitivity review form.
Statistical methodology

One-way analysis of variance (ANOVA) was used to determine if patients receiving the active and placebo treatments had significantly different mean GI at baseline. One-way analysis of covariance models, with baseline GI as the covariate, were used to compare patients receiving the active and placebo treatments for differences in GI at the follow-up examinations.

Repeated-measures ANOVA models were used to compare patients receiving the active and placebo treatments for differences in baseline and follow-up colorimeter and shade guide measurements. All models included treatment group as a nonrepeated factor and tooth as a repeated factor, and the models for follow-up comparisons also included examination as a repeated factor. Multiple comparisons were made using Tukey’s method at a 95% overall confidence level.

The agreement between evaluators’ slide-assessed color change ratings was measured using kappa and weighted kappa statistics. Kappa measures exact agreement between the evaluators, and weighted kappa uses the ordered nature of the ratings to weight the seriousness of the disagreement by the closeness of the ratings. Mantel-Haenszel chi-square tests for ordered data were used to compare the patients receiving the active and placebo treatments for differences in the consensus slide-assessed color changes and maximum gingival, tooth, and gastrointestinal sensitivity.

Results

Measurements at baseline

Although the colorimeter efficacy variable is $E^*$, no reference measurements are available to compute $E^*$ at the baseline examination. Therefore the individual components of $E^* - L^*$, $a^*$, and $b^*$ were individually compared for differences at the baseline examination. Patients receiving the active treatment had a significantly lower ($P = .046$) mean $L^*$ value than did patients receiving the placebo treatment. Patients receiving the active and placebo treatments did not have significantly different $a^*$, $b^*$, shade guide ranked order, or GI.

Efficacy

Shade guide. Those patients receiving the active agent had a mean reduction from baseline of 14.5 ranked units of shade the first week and 17.5 ranked units of shade the second week. The overall shade of the active subgroup was 12.2 ranked units lighter than that of the placebo group at the end of 24 weeks (Fig 3). Patients receiving the active treatment had a significantly greater change in ranked order ($P = .0001$).

Photographs. Agreement between the evaluators’ color change ratings was substantial ($\kappa = 0.61$; weighted $\kappa = 0.75$). After 2 weeks of bleaching, the analysis of photographs revealed that 27 (90%) of the patients using the active agent showed an easily observable (moderate or large) change. Only one patient in the placebo group had a moderate change. Twenty-nine patients in the placebo group (97%) had no or slight change noticeable, whereas only three individuals in the active group had no or slight change.

Four weeks after cessation of bleaching (week 6), 19 (63%) of 30 patients, and 22 weeks after bleaching (week 24), 19 (66%) of 29 patients using the active agent showed an easily observable change. Patients receiving the active treatment had significantly more color change than did patients receiving the placebo treatment ($P = .001$).
The evaluators’ consensus data are presented in Table 2. One slide was not gradable at the 6-week evaluation and one patient withdrew from the study, because of moving, after the 12-week evaluation appointment; therefore only 59 sets of color transparencies were evaluated at weeks 6 and 24.

Colorimeter. The CIELAB $\Delta E^*$ after 2 weeks of bleaching on the canines, lateral incisors, and central incisors was 13.0, 9.6, and 8.6 $E^*$ units, respectively. At week 6, the $\Delta E^*$ values of the canines, lateral incisors, and central incisors were 7.0, 5.1, and 5.1 $E^*$ units, respectively. At week 24, the $\Delta E^*$ values of the canines, lateral incisors, and central incisors were 6.2, 4.9, and 5.0 $E^*$ units, respectively (Fig 4). Patients receiving the active treatment had significantly more change in mean $\Delta E^*$ ($P = .0001$).

To examine how much color change was lost by various weeks, the change between week 2 and each examination period was computed, and those numbers were divided by the change between baseline and week 2. From the endpoint of the active treatment to week 24, $\Delta E^*$ lost 29%, 44%, 42%, and 45% at weeks 3, 6, 12, and 24, respectively (Table 3). The mean $\Delta E^*$ values at weeks 6, 12, and 24 were not significantly different from each other ($P > .05$).

Gingival Index

Patients receiving the active and placebo treatments had significantly different GI values only at the 3-week examination, during which the patients receiving the active treatment had significantly higher GI values than those receiving the placebo treatment.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>None</th>
<th>Slight</th>
<th>Moderate</th>
<th>Large</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color change immediately postbleaching (week 2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>14 (47%)</td>
<td>13 (43%)</td>
<td>30</td>
</tr>
<tr>
<td>Placebo</td>
<td>21 (70%)</td>
<td>8 (27%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>10</td>
<td>15</td>
<td>13</td>
<td>60</td>
</tr>
<tr>
<td><strong>Color change at 4 weeks postbleaching</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>0 (0%)</td>
<td>10 (34%)</td>
<td>13 (45%)</td>
<td>6 (21%)</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>18 (60%)</td>
<td>11 (37%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>21</td>
<td>14</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td><strong>Color change at 22 weeks postbleaching</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>4 (14%)</td>
<td>6 (21%)</td>
<td>14 (48%)</td>
<td>5 (17%)</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>19 (63%)</td>
<td>9 (30%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>15</td>
<td>16</td>
<td>5</td>
<td>59</td>
</tr>
</tbody>
</table>
than did the patients receiving the placebo treatment ($P = .01$) (Fig 5).

**Patient sensitivity**

All patients, except one, turned in their diaries. Sixty-six percent of the patients made daily entries. Patients receiving the active treatment reported a significantly higher level of maximum gingival ($P = .0001$) and tooth ($P = .001$) sensitivity than did patients receiving the placebo treatment. Patients receiving the active and placebo treatments did not report significantly different levels of maximum gastrointestinal sensitivity ($P = .427$) (Table 4). The sensitivity in all categories returned to normal soon after product discontinuance.

### TABLE 3 Color change lost post-bleaching*

<table>
<thead>
<tr>
<th>Value</th>
<th>1 wk</th>
<th>4 wk</th>
<th>10 wk</th>
<th>22 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L^*$</td>
<td>38%</td>
<td>55%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>$a'$</td>
<td>20%</td>
<td>26%</td>
<td>3%</td>
<td>-12%</td>
</tr>
<tr>
<td>$b'$</td>
<td>20%</td>
<td>33%</td>
<td>31%</td>
<td>33%</td>
</tr>
<tr>
<td>$\Delta E^*$</td>
<td>29%</td>
<td>44%</td>
<td>42%</td>
<td>45%</td>
</tr>
</tbody>
</table>

*1 wk post-bleaching = week 3 of study; 4 wk = week 6 of study; 10 wk = week 12 of study; 22 wk = week 24 of study.

### TABLE 4 Maximum sensitivity recorded by patients for placebo and active agents

<table>
<thead>
<tr>
<th></th>
<th>None (%)</th>
<th>Slight (%)</th>
<th>Moderate (%)</th>
<th>Considerable (%)</th>
<th>Severe (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gingival sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>6 (21)</td>
<td>10 (35)</td>
<td>7 (24)</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>23 (79)</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>30</td>
</tr>
<tr>
<td><strong>Tooth sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>13 (45)</td>
<td>3 (10)</td>
<td>8 (28)</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>24 (80)</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>30</td>
</tr>
<tr>
<td><strong>Gastrointestinal sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>25 (66)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>28 (53)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>30</td>
</tr>
</tbody>
</table>
Discussion

Many studies have reported the use of the Vita Lumin shade guide, which has 18 different shades available. Although the manufacturer has listed the values from highest to lowest, there is disagreement in the literature on their proper order. The American Dental Association has guidelines that state the shade guides should be objectively measured to determine their order. We elected to use the Trubyte Bioform Color-Ordered shade guide because it has 24 shade units with manufacturer-established value, chroma, and hue values provided, as recommended by the American Dental Association.

The manufacturer inscribes all color equivalents to the Vita Lumin shade guide on the handles of the Trubyte Bioform Color-Ordered shades. No attempt was made to determine correlation of the two shade guide color equivalents. The shade B54 in the Trubyte shade guide, which was the minimum value necessary to join this study, equates to shade A3 in the Vita shade guide. Shade B54 is ranked number 10 in the lightest to darkest shade order in the shade guide.

One shade was added to each end of the shade guide to represent teeth that were darker or lighter than the available choices. The use of the additional shades did not affect the results of the shade analysis at 6 months.

One of the five patients who received the active agent and was assessed to have a large color change at each of the evaluations is shown in Figs 6a to 6e. The use of color slides has not been reported in other studies. They
were found to have a high level of discrimination when determining observable color changes in this study. According to the interpretation of kappa presented by Landis and Koch, the agreement between the evaluators was substantial. Neither evaluator examined any of the patients during the active phase of the study.

The colorimeter was the only objective way used to determine color change. The color change, as represented by ΔE°, was calculated at each examination interval using the CIELAB system. The central incisors lost only 0.2%, the lateral incisors lost only 2.4%, and the canines lost only 6.1% of the color value in this study (Fig 7) between week 6 and week 24. The week 6 and week 24 ΔE° values were not significantly different (P > .05) for central or lateral incisors. The 1-month posttreatment (week 6) whitening appeared to be an accurate indication of the retention of color in the maxillary anterior incisor teeth at week 24. Color can therefore be considered stabilized by 4 weeks posttreatment in the incisor teeth and by 10 weeks posttreatment in the canine teeth in this 24-week study.

The Gingival Index appeared to improve in both the active and the placebo groups. This phenomenon has also been reported in another whitening study. This is likely due to the patients’ increased awareness of their teeth during the study, their embarrassment when they discovered that they had inflammation in their soft tissues, and from the knowledge that they would need to return for further evaluations of their soft tissues.

Patients in both groups reported gingival, tooth, and gastrointestinal sensitivities. Sources of sensitivities, other than the active agent, include mechanical pressure of the tray, the glycine base in the product, the inherent patient sensitivity to change, etc. None of the patients requested sodium fluoride gel, which they knew was available to them, to reduce the sensitivities.

Conclusions

The product used in this study is an effective and physiologically acceptable tooth-whitening agent. Initial color regression occurred within the first month for incisors, and within 10 weeks for canines, but neither regressed back to baseline for the duration of this 6-month study.

Acknowledgments

We wish to acknowledge review and approval of our protocol by the Institutional Review Board of the Indiana University Purdue University Indianapolis campus. This study was supported by a grant from Ultradent Products.

References


