Clinical Studies - Tooth Whitening

ADA Seal of Acceptance Certification Study for Discus Dental, Inc.
Efficacy of Nite White® Whitening Gel: A Clinical Trial Final Report, March 22, 1997

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PURPOSE

The purpose of this study was to evaluate the clinical efficacy and the duration of the efficacy of Nite White® (NW) 10% carbamide peroxide tooth whitening formulation, marketed by Discus Dental, against placebo. This study followed the guidelines for testing peroxide-containing oral hygiene products which were established by the ADA's Council on Dental Therapeutics. A total of 47 subjects, each with a minimum rating of A3 on the Vita® shade guide (n=24 for placebo group, n=23 for active group) were enrolled in this parallel, double-blinded, two cell, randomized clinical trial. Subjects were directed by this dentist to use the regimen for a minimum of 5 hours every night for two weeks. Subjects were examined at baseline, day 1, day 7, and day 14 during the active phase of the study. There were also 2 follow-up examinations of all subjects at approximately 3 months and 6 months to assess the duration of efficacy. The data from baseline to month 6 is being presented in this abstract. Enamel shade changes, plaque index, gingival index, soft tissue effects, attached gingiva, sensitivity, vitality and adverse events (gingival irritations) were evaluated at all visits. Shade changes were evaluated using both no statistically significant difference between the two groups baseline shade values for teeth # 6, 7, 8, 9, 10, and 11. A statistically significant difference between the two groups was found upon analysis using the Fisher's exact test for the percentage of subjects who experienced at least a 2 value decrease in shade between baseline and two
weeks and between baseline and 6 months. For teeth # 6, 7, 8, 9, 10, and 11, 96% of the subjects in the active group experienced at least a 2 value decrease in shade between baseline and 6 months, while 29% of the subjects in the placebo group experienced a 2 value decrease in shade. There was no statistically significant difference between the placebo and active groups at baseline and day 14 between baseline and 6-months for the measurement of pulpal vitality, gingival index, soft tissue evaluation and attached gingiva. This clinical trial was supported by Discus Dental, Inc.

INTRODUCTION

Simplified procedures for dentist-prescribed, home-administered vital teeth bleaching have heightened the public's interest in cosmetic whitening. A wide range of tooth whitening products, both dentist-dispensed and over-the-counter, has proliferated and flooded the market. Night guard vital bleaching involves a custom mouth guard tray, which is fabricated to keep a peroxide preparation or whitening agent in intimate contact with the tooth surfaces. Dentist-prescribed home teeth-whitening generally involves the use of 10% - 15% carbamide peroxide or 1% - 10% hydrogen peroxide material. Ten percent carbamide peroxide is roughly equivalent to 3% hydrogen peroxide and 7% urea. Hydrogen peroxide is absorbed into the enamel and oxidizes the discolored bodies within the tooth, causing a lightening effect.1-3

The clinical efficacy of these products is variable and depends on the specific formulations. Thicker bleaching materials are retained in the custom tray for longer periods of time. The presence of thickeners such as Carbopol allows for a longer action which seems more advantageous both in material conservation and efficacy. Some concern has been expressed about the drying effects of the glycerin base on the enamel, and taste has been a major deterrent for continued treatment for some groups.

The purpose of this parallel, double-blinded, two cell, randomized clinical study was to evaluate the clinical efficacy and the duration of the efficacy of the tooth whitening formulation, Nite White® marketed by Discus Dental, Inc., against a placebo gel.

MATERIAL AND METHODS

The protocol for this research study and the subject informed consent (IFC) were submitted to the human subject committee at UCLA. Study was commenced, after the IRB approval was obtained. (Attached is a copy of approved informed consent form.)

A total of 50 subjects, each with a minimum rating of A3 on the Vita® shade guide and were enrolled for this double-blinded, parallel, two-cell, randomized clinical trial. The study permitted enrolling a sufficient number of subjects (25) in each of the two groups to enable a minimum of 20 subjects in each group to complete the study.

After the initial screening, the subjects (25 each) were assigned to one of the two groups of the study. In Group one, 25 subjects will be using Nite White® regimen as directed by the manufacturers for minimum of 5 hours every night for 2 weeks. In Group two, 25 subjects will use the placebo regimen 5 hours every night for two weeks. There are also 2 follow-up examinations of all patients at approximately three months and six months after the baseline visit. The patients were accepted based on the following criteria:

Inclusion Criteria
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- Age range between 18 and 65
- Availability of the subject in the area for nine to twelve months
- Minimum of 20 natural teeth including at least 4 molars (excluding third molars)
- Subject must be in good general health
- Subjects need to be clinically diagnosed as not having generalized gingivitis or periodontitis
- At the screening examination, subjects must complete a questionnaire to ensure qualification for participation in the study
- Subjects must agree to not have professional oral prophylaxis or use anti-microbial mouthwashes during the study period
- Subjects must have maxillary anterior enamel shade of at least Vita A-3 shade or darker based on a Vita shade guide arranged in order of value
- Willingness to avoid tobacco, coffee, dark cola, and red wine during the period of the clinical investigation.

Exclusion Criteria

- Systemic medications or disease
- Serious oral pathology (e.g. extensive dental caries, periodontal disease)
- Pregnant or lactating women
- Prophylactic antibiotic coverage for routine dental therapy
- Orthodontic devices or appliances
- Antibiotic drug therapy
- Crowns on maxillary anterior teeth
- Previous bleaching treatment
- Gingival inflammation
- Participation in other clinical or investigational trials
- Extreme tetracycline stains or any stain know to be of tetracycline origin

A stratified, blocked randomization approach were used to assign subjects the whitening agent in which the stratification factors will be age, gender, and oral status.

The product usage was a minimum of 5-6 hours during the night for a period of 14 days. Each subject were assigned a coded test or placebo product and instructed on the product usage according to the manufacturer's directions. Each subject were given a toothpaste (Colgate Tartar Control) and a soft bristled toothbrush (Colgate Classic) to maintain oral hygiene.

Subjects were asked to brush and floss twice daily, after breakfast and before bedtime for at least one minute using their tooth brushing techniques. Subjects were seen after 7 and 14 days of total treatment to evaluate enamel shade change gingival index, soft tissue effects, and concerns of the patient. Shade changes were evaluated using both Vita shade guide and intra-oral photography. Active bleaching was discontinued at the end of 14 treatment days. The log was collected and the patient was told to discontinue the whitening process. Subjects were seen at 3 and 6 months post-treatment to evaluate their perception of the Night Guard Vital Bleaching procedure.

At the screening appointment, maxillary alginate impression (Jeltrate Plusâ ) of the subjects were taken and a stone cast was generated. A bleaching tray was fabricated from the stone cast using a pressure molding machine, having a 0.5 mm facial reservoir on teeth #5-12, and trimmed as described in the manufacturer's instructions. Only the maxillary arch (teeth # 6, 7, 8, 9, 10, and 11) was evaluated for bleaching.
A Stratified, blocked randomization approach was used to assign subjects to the two study groups in which the stratification factors were gender, age, oral health, and shade of teeth. Each subject received an oral prophylaxis at least two weeks prior to the beginning of the active bleaching phase of the study. Subjects were asked to brush and floss twice daily for one minute. At the baseline appointment, which was a minimum of two weeks after the oral prophylaxis, the bleaching guard was delivered and adjusted according to the guidelines provided by Discus Dental, Inc. A baseline enamel shade for teeth #6, 7, 8, 9, 10, and 11 was determined by Vita shade tabs and the results were recorded. Intra-oral color slides were taken to record enamel shade with the appropriate Vita shade tab using Yashica Dental-Eye 2 camera, 1:1 magnification with the Kodak 64 professional grade color transparency film. A color corrected light was used to take picture slides and patients were examined in the same location and at the same time of the day during the period of the study.

Information about the bleaching procedure and written instructions were given to each subjects as well as a daily diary card to record perceived enamel changes, tooth sensitivity irritation, and other comments regarding the study.

Subjects were examined at baseline, Day 1, Day 7, and Day 14 during the active phase of the study to evaluate enamel shade change, gingival index, oral soft tissue, and adverse events. Measurements were also conducted at 3 month and 6 month follow-up visits.

Subjects were instructed to refrain from routine dental treatments to the study investigator. Subjects were told that removal from the study was mandatory if they receive emergency dental treatment that could influence the plaque growth or if loss of antibiotics or antibacterial agents during this study were dropped. Any of the above mentioned scenarios were reported to the study sponsor. Subjects who were excluded from the analysis.

RESULTS

Two product containers were dispensed to subjects. The identity of the products was concealed and neither the subjects nor the investigators had the knowledge of the type of products dispensed to the subjects. Fifty two subjects were randomized to placebo or agent. Of these, 47 subjects completed data collection at 6 months. Since the retention rate of subjects completing the trial was 90%, only efficacy-analyzable analyses were performed. No attempt was made to impute the missing data for the five subjects who were excluded from the analysis.

For the subjects who completed the trial, 24 were randomized to placebo and 23 to agent. Fifty-three percent were Caucasian and 32% were Asian. Forty-seven percent were female. Sixty-four percent had no allergies. The average age of the subjects was 34.4 years (s=10.8yrs) and ranged from 18.5 to 57.1. There was no statistically significant difference in the mean age of the subjects randomized to the two groups (p=0.68) or in length of time between dispensing and return of the product (p=0.43).

For the analysis of shade, descriptive statistics as well as graphs for the placebo and agent groups are provided for the baseline, one-week, two-
week, three-month, and six-month data collection time as well as possible changes between successive time points. These descriptive statistics are given by tooth as well as for the average of the 6 anterior teeth.

The averaged shade value was analyzed using weighted least squares approach for a repeated measures analysis of variance (PROC CATMOD, SAS) which is a more appropriate model than a parametric repeated measure ANOVA since the shade values are ordinal in nature. This approach analyzes the mean response functions and partitions the variation in shade scores among the possible sources of time (baseline, two weeks, and 6 months), treatment group (placebo and active agent), and time by treatment interaction (the pattern of change over time for the two bleaching groups). Contrast within treatments over time and between treatments at baseline, two weeks, and six months were performed within the general linear model using the design matrix from the repeated measures procedure.

There was significant interaction between time and treatment indicating that the change in averaged shade score from baseline to two weeks to six months was not the same in the placebo and active agent groups (p=0.0000). In the placebo group, the averaged shade scores did change significantly over time (p=0.0002). From baseline two weeks, the averaged shade change in the placebo group was statistically significant (p=0.0001) with the mean shade change being 1.7 units. The change from two weeks to 6 months was not statistically different (p=0.25).

For the active agent group, the averaged shade scores also changed significantly over time (p=0.0000). In the active agent group, the baseline averaged shade scores were significantly different from the two-week and 6-month scores (p=0.0000 and 0.0000, respectively), but the two-week scores were not significantly different from the 6-months scores (p=0.11). The active group mean decreased from a baseline shade unit of 11.4 to 5.1 at 6 months 4.6 at two weeks see (Table 1) and from a baseline shade unit of 11.4 to 5.1 at 6 months (see Table 2). On average, the placebo and active agent groups did not differ at baseline in averaged shade scores (p=0.77). The two groups did differ significantly at two weeks (p=0.0000) and at six months (p=0.0000).

In terms of the ADA criteria of maintenance of a 2 shade unit decrease, the two groups also were significantly different in the proportion of subjects who showed at least a 2 shade unit change. Shade unit is also defined as shade value. By two weeks, 12 subjects (50%) of the placebo group had a minimum of a 2 shade unit change (p<0.0001). All 23 subjects in the active group had a minimum of a 2 shade unit change (p<0.0001). At six months, only 7 subjects (29%) of the placebo group had maintained the two unit decrease while 22 subjects (96%) of the active group had a minimum two unit decrease in shade (p<0.0001).

For the measurements of sensitivity, vitality, plaque index, gingival index, and attached gingival, descriptive statistics as well as graphs are provided for all baseline, one week, two week, three month, and six month data as well as the changes that occurred in each of these measures over time. The Savage test, a non-parametric test, analyzes Savage scores which are the expected order statistics for the exponential distribution. This test was chosen for the comparison of the placebo and agent groups at baseline, two weeks, six months for these measurements since the data tended to cluster at a single score with only a small percentage of subjects with scores in between the minimum and the maximum. This distribution of values closely approximates an exponential distribution.

There were no statistically significant differences between the placebo and active agent groups at baseline for any measure. At two weeks, the sensitivity and plaque scores of the two groups were significantly different
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(p=0.03 and p=0.009, respectively). None of the other scores differed at two weeks. Although statistically different, the median difference between the two groups at two weeks for plaque was only 0.11 units and the median changes scores from baseline to two weeks were identical for the two groups. For sensitivity, the median two-week values were identical, but the active group had more patients who were experiencing sensitivity on at least one tooth at two weeks. There was no statistically significant difference between the placebo group and agent group at six months for any measure.

Table 1. Comparison of median Baseline
2 Week Shade Differences of Teeth # 6, 7, 8, 9, 10, and 11 for the placebo group (n=24) and the active group (n=23).

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<th>Teeth #</th>
<th>Placebo Group</th>
<th>Active Group</th>
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<tbody>
<tr>
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<td>9</td>
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<td>11</td>
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Table 2. Comparison of median Baseline
6 Month Shade Differences of Teeth # 6, 7, 8, 9, 10, and 11 for the placebo group (n=24) and the active group (n=23).

<table>
<thead>
<tr>
<th>Teeth #</th>
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<tbody>
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DISCUSSION

The purpose of this study was to determine the clinical efficacy and the duration of teeth whitening effect of Nite-Whiteâ manufactured by Discus Dental Inc, at 6 months post-treatment. Each tooth (tooth #6-11) in the active group displayed a significant decrease in shade units from baseline to 2-week and from baseline to 6-month. (Tables 1,2). In addition, there was no significant difference between the 2-week shade and the 6 month shade. (Table 1,2) Thus, effect of teeth-whitening was sustained for at least 6 months after baseline. Since all the teeth showed the same degree of whitening, anatomical or morphological and canines did not affect the overall whitening process. At two weeks, the sensitivity and plaque scores of the two groups were significantly different (p=0.03 and p=0.009, respectively). None of the other scores differed at two weeks for sensitivity, the median two-week values were identical, but the active group had more patients who were experiencing sensitivity on at least one tooth at two weeks.
Based on our findings regarding gingival index, attached gingival, soft tissue evaluation, sensitivity, and pulpal vitality, there appears to be significant concern for patient safety, as no statistically significant differences were observed for these indices at baseline and two weeks whitening and at baseline and six months post-treatment (p<0.05).

**CONCLUSION**

A study of 23 subjects in the active group and 24 subjects in the placebo group given a carbamide peroxide bleaching gel or placebo for 14 consecutive nights gave the following results:

1. At the end of 6 months, the teeth in the active group had a statistically significantly greater mean shade change than in the placebo group.

2. No significant changes resulting from treatment were found in pulpal vitality, attached gingival, soft tissue evaluation, or gingival index measurements.

The active 10% carbamide peroxide whitening agent was effective in whitening teeth and this effect was sustained for 6 months after treatment. There were no significant adverse events reported between the active and the placebo group.

**REFERENCES:**


