

# clinical data

## Clinical Studies - Tooth Whitening

**ADA Seal of Acceptance Certification Study for Discus Dental, Inc.**  
Efficacy, side effects, and six month status of a 10% carbamide peroxide whitening solution

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### **PURPOSE**

The purpose of this study was to determine the clinical efficacy and duration of a whitening solution made by Discus Dental, Inc (Nite White<sup>®</sup>). This study to satisfy a portion of the ADA guidelines for acceptance of peroxide containing oral hygiene products<sup>1</sup>, but in no way guarantees acceptance.

### **MATERIAL AND METHODS**

The project was a double-blind study involving human subjects. Each subject that satisfied the criteria of the study (see APPENDIX A) completed and signed a registration form, a medical history form, and an approved human consent form (see APPENDIX B). An oral screening exam, pre- and post-treatment radiographs of the study teeth, and an endodontic evaluation (Histofreeze) of the study teeth was performed on each of the subjects (see APPENDIX C). Subjects were randomly assigned to either an experimental or control group. The control group used the same type of delivery system and product vehicle as the experimental group, but without the whitening or oxygenating agent. A stratified blocked randomization approach was used to assign subjects and bleaching agent in which the stratification factors. Subjects had no gingivitis or only a modest level as measured by the Loe-Silness Gingivitis Index (GI) on the study teeth: maxillary second premolar (4-13). Each subject received an oral prophylaxis at least two weeks prior to

beginning the active whitening phase of the study. Subjects were asked to brush and floss twice daily, after breakfast and before bedtime, using the instructions given to them.

A maxillary polyvinylsiloxane impression was taken of each patient and sent to the manufacturer (Discus Dental) for fabrication to the bleaching tray. The bleaching tray (0.0035") was fabricated having a 0.5 m facial reservoir on teeth 6-11 and trimmed as described in the manufacturer's instruction (APPENDIX D). Only the maxillary arch was evaluated for potential lightening. The study teeth were the four maxillary central and lateral incisors in which sufficient enamel was present to evaluate the lightening technique. These are the recommended teeth as set forth in the ADA guidelines for the acceptance of peroxide-containing oral hygiene products.<sup>1</sup> All study teeth were Vita shade A-3 or darker. Shade determinations were performed in the same clinic with blinds lowered, color-corrected lights, and a blue patient napkin on the patient's chest. All lipstick, chapstick, etc., was removed from the patient's lips before shade determinations were made.

At the insertion appointment, a minimum of two weeks after the oral prophylaxis, the bleaching tray was delivered and adjusted intraorally according to the guidelines prescribed by Discus Dental, Inc. This began an active phase of the whitening study which continued for a total of 14 treatment days (See APPENDIX E for each appointment procedure). A Reprosilâ impression was taken of the maxillary and mandibular anterior teeth (facials only) for SEM evaluation. A baseline enamel shade for teeth # 7, 8, 9, 10 was determined by Vita shade tabs when arranged in order of value. A smaller number means the tooth is getting lighter. The shade recorded was the one agreed upon by two examiners. Intra-oral color slides were taken to record enamel shade with the appropriate Vita shade tab using a Micro-Nikkor 105 f4 lens and a nikon M ring, 1:1 or 1:2 magnification, with Kodachrome color transparency film. The baseline Vita shade tab was photographed at the incisal edges of the study teeth at each appointment as well as the current shade. Each patient's baseline maxillary (Teeth 4-13) Loe-Silness Gingival Index (GI) was determined at this appointment.<sup>2</sup> Information about the whitening process and written instructions were given to each patient, as well as a daily log form to record perceived enamel shade changes, tooth sensitivity, gingival irritation, and other comments or concerns (APPENDIX F).

Subjects were seen after 7 and 14 days of total treatment to evaluate enamel shade change, GI, soft tissue effects, 2-5 and concerns of the patient. Shade changes were evaluated using both the Vita shade guide and intra-oral photography. Active bleaching was discontinued at the end of 14 treatment days, the log form collected, the second Reprosilâ impression taken, and the patient told to discontinue the whitening process. Subjects were seen at 3 and 6 months post-treatment to evaluate enamel shade changes, gingival index, plaque index, soft tissue effects, and to complete a questionnaire on their perception of the NGVB procedure (APPENDIX G). At the 6 month recall exam, the third Reprosilâ impression was taken and post-treatment radiographs taken.

## STATISTICAL ANALYSIS

A priori sample size determination indicated that the number of patients included in the study was sufficient to demonstrate a statistical difference between the experimental and control groups at  $\alpha=0.05$  with 90% power. Criteria used was a two-value oriented shade change in at least 50% of the experimental population a 6 months post-bleaching, assuming that no more

than 10% of the control group have two value-oriented shade change. Teeth evaluated were the two maxillary central incisors and the and two maxillary lateral incisors.

## **CALIBRATION OF EXAMINERS**

Examiners completed a calibration sessions on shade determination, Loe-Silness Gingival Index, and Plaque Index prior to beginning the study.

## **INFECTION CONTROL**

Infection control protocol as outlined in the UNC School of Dentistry's Control Manual was adhered to at all times when treating patients, handling impressions, and when taking Vita® shades and photographs.

## **PACKAGING OF WHITENING SOLUTIONS**

The two products, active and inactive, was packaged in identical containers. Each container was marked with a randomly generated identification number. Patient instructions were given to each patient. Active and placebo packages were labeled by Dr. Ceib Phillips with unique sequence numbers prepared using random numbers generated by PROC Plan (SAS). The master key containing the treatment assignment was not broken until after the completion of the trial. The investigator and patients were masked to treatment assignment. However, since the same investigator often saw a patient on multiple visits, any knowledge of treatment assignment gained from visible inspection could not be prevented. Envelopes with the treatment assignment contained inside were prepared and given to the patient at the 6 month visit. One error in labeling occurred. Container 8574 (CONTROL) was mislabeled and should have been labeled as 8974.

## **PATIENT REIMBURSEMENT**

Patients completing the entire study (through the 6 month patient exam) and following the guidelines of the study received \$100.00 plus up to \$15.00 parking for their participation. The payment was made at the end of the 6 month patient exam for both control and experimental groups.

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## **RESULTS**

### **DEMOGRAPHICS**

Fifty-one patients were enrolled in the trial and randomized to placebo or agent group. Three patients were excluded from the analysis (5582, PEM because of job relocation; 6191, JSN because of heart attack; and 6877, DCO because of the use of a tooth whitening toothpaste between 3 and 6 month phase of study). The loss of 3 patients (retention rate = 94%) is not considered sufficient to perform both intent-to-treat and efficacy analyzable analyses. 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. The group comparison will only be performed on the 48 patients (24 control and 24 active agent) who completed the trial. Three product containers (3552, 8160, 9847) were not dispensed to subjects.

For the subjects who completed the trial, 24 were randomized to placebo and 24 to agent. Ninety percent were Caucasian. Fifty-eight percent were female. Sixty one percent had no allergies. The average age of the subjects was 41.2 yrs . (s=11.95 yrs) and ranged from 18.9 to 73.1. There was no statistically significant difference in the mean age of the subjects randomized to two groups (P=0.80).

## SECONDARY MEASURES

(Sensitivity/Vitality/Plaque Index/Gingival Index/Attached Gingiva/Soft Tissues Changes)

Descriptive statistics as well as charts (charts 1-6) 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 week, and six months for these secondary measures since these measures tend 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 agent groups at baseline, at two weeks, or six months for any measure (See inferential section for analyses and graphics for visual displays, data notebook and table 2).

<b>P Values</b>			
<b>Measure</b>	<b>Baseline</b>	<b>Two Weeks</b>	<b>Six Months</b>
Attached Gingiva	1.00	1.00	1.00
Gingival Index	0.82	0.46	0.49
Sensitivity	1.00	0.36	0.53
Vitality	0.37	0.36	0.53
Soft Tissue	1.00	1.00	1.00
Plaque	0.11	0.56	0.35

## PRIMARY OUTCOME (Shade)

Descriptive statistics as well as charts (charts 7, 8, and 9) for the placebo and agent groups are provided for the baseline, one week, two week, three month, and six month data collection times as well as all possible changes between successive time points. These descriptive statistics are given by tooth as well as for the average of the 4 maxillary teeth and the average of the 4 mandibular anterior teeth.

The averaged shade values were analyzed using a weighted least squares approach for a repeated measure analysis of variance ( PROC CATMOD, SAS) which is a more appropriate model than a parametric repeated ms ANOVA since the shade values are ordinal in nature (Categorical Data Analysis using the SAS System. M.E. Strokes, C.S. Davis, G.G. Koch, Kary, NC:SAS Institute Inc, 1995). This approach analyzes the mean response functions and partitions the variation in shade scores among the possible sources among the possible sources of time (baseline, two weeks, and 6 months), 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 procedures.

## MAXILLARY TEETH

There was a significant interaction between time and treatment indicating that the change in averaged shade scores from baseline to two weeks to six months was not the same in the placebo and active agent groups ( $p < 0.0001$ ). In the placebo group, the averaged shade scores did not change significantly over time ( $p = 0.10$ ). From baseline to two weeks, the mean averaged shade decreased .77 units but increased from two weeks to 6 months by .57 units. For the active agent group, the averaged shade scores changed significantly over time ( $p < 0.0001$ ). In the active agent group, the baseline averaged shade scores were significantly different from the two week and the 6 month scores ( $p < 0.0001$  and  $0.0001$  respectively) and the two week scores were significantly different than the 6 month scores ( $p = 0.0003$ ). The active group mean decreased from a baseline Vita shade of 9.85 to 2.7 at two weeks (7.2 units of change) and 4.2 at 6 months (5.7 units of change). On average, the placebo and active agent groups did not differ at baseline in averaged shade scores ( $p = 0.08$ ). The two groups did differ significantly at two weeks ( $p < 0.0001$ ) and a six months ( $p < 0.0001$ ). See Table 3 and Figures 1-9.

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. By two weeks, 13% (3) of the placebo group but 92% (22) of the active group had a minimum of a 2 shade unit change ( $p < 0.0001$ ). At six months only 4% (1) of the placebo group had maintained the two unit decrease while 88% (21) of the active group had a minimum two unit decrease in shade ( $p < 0.00001$ ).

## MANDIBULAR TEETH

The interaction between time and treatment group was not statistically significant for the averaged mandibular shade values ( $p = 0.42$ ) indicating that the pattern of change in the mean shade values was similar for the placebo and active agent groups. There was no statistically significant difference between the placebo and treatment groups ( $p = .28$ ) but the change in the mean shade values was statistically significant over time ( $p = 0.02$ ).

## RADIOGRAPHIC EVALUATION

Pre and post (6 months) radiographs were taken on each consenting patient. Evaluation of the radiographs by three examiners revealed no detectable difference between the pre and post radiographs.

## QUESTIONNAIRE RESULTS (Active Group, Table 4-6)

At 6 months post-whitening, 81% (13/16) of the active group reported no obvious change or only a slight darkening not noticeable by others to their teeth. This corresponds to the slight darkening seen clinically by the examiners. Clinically, the examiners noticed from the 2 week-whitening appointment to the 6 month post-whitening appointment, a increase of 1.5 vita shade units, but still 5.7 units lighter than at baseline. No participant thought that significant darkening had occurred such that their teeth were

back to their original color. This perception was also observed clinically by the examiners.

One participant (5%) reported tooth sensitivity (TS) at the 6-month appointment that was thought to be whitening related, but no one reported gingival irritation (GI) during the 6 month post-whitening period. The patient that reported the tooth sensitivity at 6 months did not report it at 3 months. Thirty percent of the active group reported normally sensitive teeth on a daily basis before whitening as well as being sensitive after a prophylaxis. This may help explain the percent of patients reporting tooth sensitivity/gingival irritation. Thirty percent of the control group reported sensitive teeth before the study and 35% while undergoing the vital bleaching procedure. Again, this is the patient's perception of discomfort. No one quit the study due to tooth sensitivity and/or gingival irritation. There were no statistically significant differences between the active and control groups with respect to their perception on TS/GI during the study ( $p < 0.15$ ). No active participant had to have a crown or root canal on any of the teeth whitened during the 6 month post-whitening period.

Ninety percent of the active participants thought their teeth were lighter now than at baseline (clinically, the examiners recorded a 95% efficacy rate). Ninety-five percent said they would recommend the procedure to a friend; ninety percent said they were glad they went through the whitening process; and 85% would go through it again.

## SEM EVALUATION

The purpose of this study was to evaluate the effect of a 10% carbamide peroxide whitening solution on tooth enamel morphology as viewed under the scanning electron microscope (SEM). Ten patients, from the active group, participating in a Nightguard Vital Bleaching (NGVB) study were randomly selected for this project. Each subject wore a guard filled with the active whitening solution for 8-10 hours per day for 14 treatment days. At baseline, on the fourteenth day of treatment, and at six months the teeth were cleaned and an impression taken (Reprosilâ). The impression was rinsed, disinfected, dried, and filled with polybed epoxy resin. The epoxy resin was cured overnight at 65°C. The epoxy cast was removed from the impression, mounted on a specimen stub, and sputter coated with gold-palladium (Polaron 5200 sputter coater), and examined under the SEM. Scanning electron microscopic photographs at baseline, after 14 treatment days, and 6 months post-whitening were obtained for each patient at X200 and X2000. To evaluate changes in enamel surface morphology, 6 examiners were asked whether a discernable difference existed between the baseline/14 day photograph, and baseline/6 months post-whitening photograph of each patient. Examiners did not know which photograph was baseline, 14 day, or 6 month post-whitening. Sixty percent of the baseline/14 day comparisons were determined to be similar with no visually distinguishable changes to the enamel morphology. Forty-eight percent of the baseline/6 month comparisons were determined to be similar. Still masked, the examiners also compared each patient's baseline/14 day and baseline/6 month photographs with photographs of a known standard. The knowns ranked as: untreated tooth (0), pumiced tooth with prophylaxis paste (1), and teeth acid etched for either 5(3), 10(4)..., or 60(9) seconds. The Wilcoxon matched-pairs signed-ranks test was used to determine if a significant change occurred in enamel morphology.

Ninety percent of the baseline/14 day comparisons with a known standard were ranked by the examiners as being similar to either the control tooth, or tooth pumiced with prophylaxis paste. The average control photograph selected

for both baseline and 14 days was the pumiced tooth which was expected at baseline since all patients received a prophylaxis before the trial. The average change in score was small for X200 and X2000 ( $\bar{x}$ =0.27 and 0.24), (median=0.33 and -0.08) but the shift was significant at X200 ( $p$ =.03) but not at X2000 ( $p$ =0.48).

Ninety-one percent of the baseline/6 month post-whitening comparisons with a known standard were ranked by the examiners as being similar to either the control tooth, or tooth pumiced with prophylaxis paste. The average score for both baseline and six months post-whitening was between the pumiced tooth and control tooth. The average change in score was similar for X200 and X2000 (median=0.25 and 0.16) and the shift was not significant at either X200 and X2000 ( $p$ >.11).

In conclusion, a 14 day regimen of NGVB using a 10% carbamide peroxide whitening solution has minimal effects on the surface morphology of teeth. All control and experimental tooth surfaces differed significantly in surface morphology from the 5% or greater etched enamel standard. Figures 10-27.

## DISCUSSION

The purpose of this double-blind study was to determine the clinical efficacy and duration of efficacy at 6 months post-treatment of a whitening solution (Nite-White<sup>®</sup>) made by Discus Dental Inc. Results of this study showed that the average mean shade change for the active group was 7.2 Vita shade units after two-weeks whitening and 5.7 units lighter at 6 months post-whitening (Table 3). However, the control group average shade change was only 0.8 after two weeks whitening and 0.3 units at 6 months post-whitening. The 5.7 units shade change at 6 months post-whitening of the active group is well beyond the 2 unit shade change as set forth in the ADA Guidelines for the acceptance of peroxide - containing oral hygiene products. Also, evaluated clinically were safety issues such as plaque index, gingival index, attached gingival changes, mucosal changes, tooth vitality, tooth sensitivity, and gingival irritation. No statistically significant differences were noticed for these variables at baseline and two weeks whitening and baseline and 6 months post-whitening ( $p$ >0.05).

The patient's perception of safety issues and shade change were also evaluated. Initially 30% of the active group (30% of the control group) reported sensitive teeth before beginning the study. Thirty percent of the active group also reported their teeth being sensitive after prophylaxis while only 11% of the control group did. This difference in pre-whitening sensitivity between the active and control group may help explain the difference seen in tooth sensitivity/gingival irritation during the active phase of the whitening process. Sixty-seven percent of the active group reported some type of sensitivity while 35% of the control group reported sensitivity. It is important to note that no one quit the study due to sensitivity and at 3 month post-whitening no one in either group reported sensitivity. However, one patient reported sensitivity of 6 month post-whitening but did not report this at 3 months.

The patient's perception of shade change in the active group corresponded well with the examiners clinical evaluation. Ninety percent of the active group reported shade change and 95% of the examiners reported a clinical shade change. At the 6 month post-whitening appointment both patient and examiners noted a slight darkening since stopping the whitening process.

No on in the active group had to have a root canal or crown due to the whitening procedure at the 6 month post-whitening post-treatment appointment. Overall, patients in the active group were glad they went through the NGVB procedure, would recommend it to a friend, and thought their teeth were lighter at 6 months post-whitening than at baseline.

The final parameter evaluated in this study was to determine enamel surface changes that occur during active whitening. Ten active patients were randomly selected for this study. Six examiners compared SEM photographs of the study teeth against known standard. All control and experimental tooth surfaces differed significantly in the surface morphology from the 5% or greater etched enamel standard. It was determined that a 14 day regimen of whitening using a 19% carbamide peroxide solution has minimal effects on the surface morphology of teeth. CONCLUSIONS The active 10% CP whitening solution was effective in lightening teeth, and this effect was sustained at 6 months post-treatment. When evaluating the safety issues as described in this report, there were no statistically significant adverse effects between and active 10% CP whitening solution and a placebo. Finally, a 14 day regimen of NGVB using a 10% carbamide peroxide whitening solution has minimal effects on the surface morphology of teeth.

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