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Clinical Research

Efficacy and Safety of 10% and 16% Carbamide Peroxide Tooth-whitening Gels: A Randomized Clinical Trial

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Clinical Relevance

This clinical trial suggests that two carbamide peroxide concentrations, when used once a day for three weeks, were well tolerated by patients and were effective in tooth whitening. Although some tooth sensitivity occurred during treatment, this side effect was mostly mild and transient.

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SUMMARY

This double-blind randomized clinical trial evaluated the efficacy and safety of two carbamide peroxide concentrations used in at-home vital bleaching. Ninety-two volunteers with a shade mean of C1 or darker for the six maxillary anterior teeth were randomized into two balanced groups (n=46) according to bleaching agent concentration: 10% (CP10) or 16% (CP16) carbamide peroxide. The patients were instructed to use the whitening agent in a tray for two hours once a day for three weeks. Shade evaluations were done with a value-oriented shade guide and a spectrophotometer at baseline and one week post-bleaching (four-week evaluation). Tooth sensitivity was measured daily using a scale ranging from 0 (no sensitivity) to 4 (severe sensitivity). At the end of the study, the volunteers filled out a

questionnaire with seven questions aimed to give their opinion about the adopted treatment regimen. Both carbamide peroxide concentrations resulted in significantly lighter teeth at the four-week evaluation compared to the baseline for all color parameters ($p<0.0001$) and shade median ($p<0.001$). There was no significant difference between the two groups in terms of shade change difference with either the spectrophotometer ($p=0.1$) or the shade guide ($p=0.7$). Also, no statistically significant difference was found in relation to ΔL^* (p=0.7), Δa^* and ΔE^* ($p=0.5$). A significant reduction in yellowness (Δb^*) was observed for CP16 compared to CP10 ($p=0.05$) in crude analysis, which disappeared after controlling for b* parameter at baseline. The group treated with CP16 experienced more tooth sensitivity during the first ($p=0.02$) and third (p=0.01) weeks of treatment compared to the CP10 group. However, no major difference was observed ($p=0.09$) when the degree of tooth sensitivity between groups was compared. Both 10% and 16% carbamide peroxide concentrations were equally effective and safe for a three-week at-home tooth-bleaching treatment.

INTRODUCTION

Professionally supervised at-home vital tooth bleaching has become a popular method used to treat tooth discoloration. The popularity of this method is related to its quick esthetic improvement, low incidence of side effects and ease of technique with reduced chair time.[1-4] Until recently, the most common and widely accepted at-home tooth whitening method has been the one first proposed by Haywood and Heymann,[5] in which a custom tray with 10% carbamide peroxide is used by the patient for a select number of hours.[6-7] However, today, other bleaching products, including gels, rinses, gums, dentifrices, whitening strips or paint-on films (over-the-counter products)[1,8-9] are freely available at pharmacies, supermarkets and over the Internet,[10] and have been considered alternative methods for at-home bleaching.

Manufacturers have introduced different concentrations of carbamide peroxide (5% to 22%)[11-12] or hydrogen peroxide (3% to 14%) for at-home whitening.[9-10,13-14] In 2006, the American Dental Association (ADA)[15] published new program guidelines for the acceptance of dentist-dispensed home-use tooth-bleaching products that assure the safety and efficacy of tray-applied 10 ± 1% carbamide peroxide based on published clinical trials.[16-18] Few controlled clinical trials have observed the improved efficacy of at-home whitening when increasing concentration of the bleaching agent. Additionally, an increase in side-effects has been detected.[4,16,19]

The aim of this randomized clinical trial was to evaluate the efficacy, safety and volunteers' opinion when being treated with two carbamide peroxide concentrations (10% or 16%) using the at-home vital tooth whitening technique.

METHODS AND MATERIALS

This double-blind randomized clinical trial was approved by the local Ethics Committee. Each volunteer received an informational document covering the risks and benefits of treatment and signed an informed consent form prior to enrollment in the study.

Before starting the study, the two examiners received calibration training in order to determine the shade of the anterior teeth of the 16 volunteers. The shade was recorded by the study supervisor and the two examiners using a digital spectrophotometer (Vita Easyshade, Vita Zahnfabrik, Bad Säckingen, Germany) and a value-oriented shade guide (Vitapan Classical, Vita Zahnfabrik). These examinations were performed in the afternoon, with sunlight and room illumination, and without any communication between the examiners.

The visual evaluation was made by comparing the shade tabs with the middle-third of the maxillary canines and incisors. The 16 shade tabs in the guide were arranged from B1 (highest value—1) to C4 (lowest value—16). The digital spectrophotometer analysis was adopted as the gold standard. At each evaluation period, the shade of the upper six anterior teeth was measured three times, with the active point of the instrument in the middle-third of each tooth, and the spectrophotometer automatically averaging the three readings for each tooth.

The digital spectrophotometer measures the shade of teeth based on the CIEL*a*b* color space system, allowing the determination of color in a three-dimensional space. This system was defined by the International Commission on Illumination in 1967 and is referred to as CIELAB.[20] The L* represents the value (lightness or darkness); the a* value is a measure of redness (positive a*) or greenness (negative a*); the b* value is a measure of yellowness (positive b*) or blueness (negative b*) and the color difference between the color coordinates is calculated as $\Delta E^* = [(\Delta L^*)2 + (\Delta a^*)2 + (\Delta b^*)^2]^{1/2}$. Tooth whitening mainly occurs as a reduction in yellowness (lower b*) and an increase in lightness (higher L*).[15,21] This study began when the examiners achieved agreement with the gold standard at greater than 70% according to the grouping by chroma.[22]

Calculation of the sample size was implemented based on a previous study.[4] To detect the bleaching effect with a power of 0.90 when the significance level was $\alpha=0.05$, a sample size of $n=80$ volunteers was necessary. An additional 15% of volunteers were selected for the current study, taking into consideration potential loss or refusal to participate, giving a total sample

Table 1: *Inclusion and Exclusion Criteria*

Inclusion Criteria	Exclusion Criteria
Six maxillary anterior teeth present, with a shade mean C1 or darker compared to the value-ranked Vita shade guide	Volunteers with orthodontic treatment or with tetracycline-stained teeth
Six anterior teeth should not have more than 1/6 of their buccal surfaces restored, and the location of the restoration should not interfere with placement of the spectrophotometer	Volunteers who have had previous hypersensitivity or had non vital incisors or canines
Volunteers in good dental health (without active caries in six maxillary anterior teeth; without gingivitis, moderate or advanced periodontal diseases or without gross pathology of the soft or hard tissues of the oral cavity)	Volunteers who have used tooth whiteners within the past three years
Volunteers in good general health (without medical disease that may interfere with the study results)	Smokers, pregnant or lactating women
Volunteers were required to be at least 18 years of age	Volunteers without schedule availability

size of n=92 volunteers (46 in each group). These individuals were recruited to participate in this clinical trial through advertisements in a local newspaper, a radio station and a university website.

Prior to the dental examination, each volunteer filled out a medical history form and a complete dental prophylaxis was performed to remove extrinsic stains. One hundred and eighty-three volunteers showed up for the study, and 92 individuals who met the inclusion/exclusion criteria (Table 1) were enrolled.

After the initial evaluation, the baseline tooth shade was measured using the Vita shade guide and the digital spectrophotometer on the middle-third of the buccal surface of the six maxillary anterior teeth, similar to the protocol of the calibration exercise. The participants were then randomly assigned to two experimental groups (n= 46) according to the bleaching agent concentration: 10% (CP10) or 16% (CP16) carbamide peroxide (Whiteness Perfect, FGM Dental Products, Joinville, Brazil). A randomization table to allocate the participants in each study group was prepared in advance by an epidemiologist who was not directly involved with the clinical part of the study.

Two alginate impressions (Jeltrate regular set, Dentsply International Inc, Milford, DE, USA) were made per patient and stone molds were prepared. The buccal surfaces of the anterior teeth on each mold were blocked out with five coats of nail polish, starting approximately 1.0 mm from the gingival margin. This area created a reservoir in the tray (about 1.0 mm thick) for the bleaching gel. The custom trays were fabricated using a 3-mm thick soft vinyl material (FGM Dental Products) and a vacuum-formed process. The excess on the buccal and lingual surfaces was trimmed just short of the gingival margin.

The concentration seal for each bleaching gel syringe was removed in order to mask the treatment groups. To mask the tubes, half of their plungers were covered with white adhesive tape. The same member responsible for volunteer allocation performed this procedure. Therefore, the examiners and patients were blinded to the agent concentration that was being delivered.

The patients were recalled in another clinical session to receive their trays and three tubes of bleaching gel. They were instructed to use the dispensed gel at night for two hours for three weeks. Both arches were bleached simultaneously. All the patients received a hands-on practical demonstration and written instructions regarding the proper use of the bleaching agents and restrictions regarding diet during the course of treatment. The subjects also received toothbrushes and dentifrices without whitening agents to standardize their oral hygiene regimen.

Each subject was instructed to record tooth sensitivity on a daily basis for three weeks. They used a standardized grading scale ranked as follows: 0 = no sensitivity; 1 = mild sensitivity; 2 = moderate sensitivity; 3 = considerable sensitivity and 4 = severe sensitivity.[23] Patients who experienced more than a moderate degree of sensitivity received potassium nitrate desensitizing gel (Desensibilize KF 2%, FGM Dental Products). The subjects were instructed to place the desensitizing gel in their tray and wear it for 20 minutes once a day, as recommended by the manufacturer.

Participant compliance was evaluated based on the amount of gel used. Participants returned all used and unused syringes containing bleaching gels to ensure completion of the at-home bleaching. The syringes were weighed before and after the whitening treatment (Analytical balance AG 200, Gehaka Ltda, São Paulo, SP, Brazil).

Treatment efficacy was evaluated one week post-bleaching (four-week evaluation) by applying the same evaluation protocol that was used at the baseline. The average shades at the end of treatment, as well as the mean shade change in each treatment group, were compared. The groups were compared by intention-to-treat, with all study subjects analyzed according to their random assignments. The volunteers received a questionnaire that included seven questions that asked

their opinion regarding the treatment regimen adopted. They were instructed to respond according to scores ranging from positive to negative, as follows: 1—agree; 2—somewhat agree; 3—no opinion; 4—somewhat disagree and 5—disagree. The questions related to sufficient instruction, ease of use, comfort level, perceived taste and overall satisfaction (Table 2).[11]

The data records were checked for normal distribution using the Kolmogorow Smirnov test; however, distribution was not normal, and the Wilcoxon Signed Rank test was used to determine the significance of differences in tooth shade, tooth lightness and sensitivity within the same treatment group. The Mann-Whitney-U test for independent samples was applied for statistical comparison between the two groups at baseline and after treatment results. Chi-Square tests were used to compare the significant differences in categorical variables. Differences were considered statistically significant when $p<0.05$.

Table 2: *Medians of Response Scores of Volunteers Who Completed the Three Weeks of Bleaching in Different Treatment Groups*

Questions	**CP10 (n=46) Medians**	**CP16 (n=45) Medians**	***p 10-16***
1. Enough instructions to conduct the treatment?	1.0	1.0	0.3
2. Easy to use?	1.0	1.0	0.5
3. No interference with talking?	1.0	1.0	0.02*
4. Comfortable during application?	2.0	2.0	0.6
5. No discomfort after application?	1.0	2.0	0.04*
6. Pleasant taste?	1.5	3.0	0.07
7. Satisfactory whitening effect?	1.0	1.0	0.7

**Difference statistically significant between groups (p<0.05).*

Table 3: *Demographic Characteristics and Bleaching Agents' Weight (g), According to Treatment Groups*

Variables	**Categories**	**CP10 (*n*=46)**	**CP16 (*n*=46)**	**p 10-16**
Gender	Male	14 (30.4%)	17 (37%)	0.5
	Female	32 (69.6%)	29 (63%)	
Age (years)		26.4 (±9.2)	24.2 (±6.2)	0.4
	≤20	11 (23.9%)	13 (28.3)	
	21-22	10 (21.7%)	12 (26.1%)	0.4
	23-24	9 (19.6%)	6 (13%)	
	25-26	3 (6.5%)	7 (15.2%)	
	≥27	13 (28.3%)	8 (17.4%)	
Education level				0.8
	Middle and high school	8 (17.4%) 10 (21.7%)	7 (15.2%) 11 (23.9%)	
	Complete college	28 (60.9%)	28 (60.9%)	
	Incomplete college			
Profession				0.6
	Student	33 (71.7%)	34 (73.9%)	
	Liberal professions	11 (23.9%)	8 (17.4%)	
	Public server	2 (4.3%)	4 (8.7%)	
Median weight of bleaching agents (g)	Initial	23.5	23.4	0.03
	Final	14.4	14.7	0.4
	ΔFinal-Initial	9.1	8.7	0.3

RESULTS

Ninety-one subjects completed the study. One subject from the CP16 group failed to continue treatment, complaining about an unpleasant taste from the whitening agent and tooth sensitivity on the first day of application. The participants' ages varied from 18 to 55 years, with the mean (SD) age being 25.3 (± 7.9) years. Sixty-one participants were female (66.3%) and 31 male (33.7%). At baseline, the treatment groups were balanced for age, gender, profession and education level (Table 3).

Initial syringes (with whitening gels) weighed significantly more for the CP10 group than the CP16 group ($p=0.03$). However, at the end of treatment, neither the final weight ($p=0.4$) nor the whitening agents consumption ($p=0.3$) changed significantly between groups (Table 3).

Spectrophotometer Data

At baseline, the median tooth shades for the groups to be treated

Table 4: *Shade Medians, Shade Difference and* p*-values in Different Evaluation Periods for Groups Treated with 10% or 16% Carbamide Peroxide Concentrations*

Evaluation Period	Spectrophotometer Evaluation			Shade Guide Evaluation Shade Medians		
	CP10	CP16	*p 10-16*	CP10	CP16	*p 10-16*
Baseline	8.5	8.8	0.8	8.7	8.0	0.2
4-weeks	2.7	2.3	0.04*	2.3	2.0	0.01*
Difference	5.8	6.5	0.1	6.4	6.0	0.7

**Difference statistically significant between groups (p<0.05).*

Table 5: *Tooth Color Parameters at Four-week Evaluation for Groups Treated with 10% or 16% Carbamide Peroxide*

	4-week Evaluation		
Tooth Color Parameters	**Means Change (SD) From Baseline**		
	CP10 (*n*= 46)	**CP16** (*n*= 45)	***p 10-16***
ΔL*	3.8 (±2.4)	3.7 (±2.4)	0.7
Δa*	-0.6 (±0.7)	-0.5 (±1.0)	0.5
Δb*	-1.0 (±1.4)	-1.5 (±1.3)	0.6
ΔE*	4.3 (±1.9)	4.6 (±2.0)	0.5

Means change from baseline for ΔL, Δa*, Δb* and ΔE*; ΔE* means were not adjusted for baseline.*
**Adjusted for b* parameter at baseline.*

Table 6: *Means (SD) Values for Weekly Tooth Sensitivity and Degrees of Tooth Sensitivity Reported by Volunteers During Three Weeks in Different Treatment Groups*

Tooth Sensitivity	CP10 (n=46)	CP16 (n=45)	*p 10-16*
First week of treatment	0.53 (±0.7)	0.67 (±0.8)	0.02*
Second week of treatment	0.53 (±0.7)	0.65 (±0.8)	0.1
Third week of treatment	0.47 (±0.7)	0.66 (±0.8)	0.01*
None	27 (58.7%)	25 (55.6%)	0.87
Mild	17 (37.0%)	17 (37.8%)	
Moderate	2 (4.3%)	3 (6.7%)	
Considerable	---	---	
Severe	---	---	

**Difference statistically significant between groups (p<0.05).*

with CP10 or CP16 were 8.5 and 8.8, respectively (Table 4). The mean values (SD) for L* (lightness), a* (redness) and b* (yellowness) for the group to be treated with CP10 were 77.4 (± 4.1), -0.2 (± 1.0) and 0.2 (± 1.7), respectively. For the group to be treated with CP16, the mean values (SD) for L*, a* and b* were 78.5 (± 2.7), -0.5 (± 1.0) and 1.1 (± 1.5), respectively. The groups did not have significant differences at baseline for tooth shade (p=0.8), L* (p=0.2) and a* (p=0.7). However, a significant difference was observed for the b* parameter (p=0.02) between groups before initiating the study.

One week after the whitening treatment (four-week evaluation), both concentrations tested resulted in teeth lighter than the baseline (p<0.001). The shade median for CP16 was significantly lighter than the CP10 group (p=0.04). However, the shade change of 5.8 units for CP10 compared to 6.5 units for the CP16 group was not statistically significant (p=0.1) (Table 4). The means values (SD) for ΔL*, Δa*, Δb* and ΔE* from the CP10 and CP16 groups are shown in Table 5. Both treatment groups were significantly lighter one week after the end of the active phase than the baseline for all color parameters (p<0.0001). For ΔL*(p=0.7), Δa* and ΔE* (p=0.5), differences were not significant between groups. However, the CP16 group had a reduction in Δb* (negative change in b* represents a color improvement) (p=0.05) in crude analysis, that disappeared after controlling for b* parameter at baseline (p=0.6).

Visual Assessment with a Shade Guide

At baseline, no statistically significant difference was observed between groups for tooth shade average (p=0.2). Both at-home bleaching regimens resulted in lighter teeth after three-weeks of treatment compared to the baseline (p<0.001), and the CP16 group produced a shade median significantly lighter than CP10 (p=0.01). Nevertheless, when considering the shade change from baseline to four weeks, there was no significant difference between groups (p=0.7) (Table 4).

Tooth Sensitivity Data

The CP16 group reported more tooth sensitivity than the CP10 group during the first (p=0.02) and the third week (p=0.01) of treatment. Four individuals who used 16% CP and one who used the 10% CP concentration requested the desensitizing agent. Details of the degree and incidence of tooth sensitivity are shown in Table 6.

Opinion About Treatment Regimen

Generally, participants from both whitening regimens reported positive opinions about the treatment (Table 2). Despite this, the CP10 group reported less interference with the tray when talking (question 3) (p=0.02) and less discomfort after application (question 5) (p=0.04) compared to the CP16 group.

DISCUSSION

Both carbamide peroxide concentrations tested in this clinical trial resulted in teeth being significantly lighter than the baseline. The teeth treated with 16% carbamide peroxide were lighter than the 10% carbamide peroxide group for spectrophotometer and visual shade matching evaluations, but the difference in whitening between the groups was not statistically significant after three weeks of treatment. Although this result might seem surprising, other studies that compare different carbamide peroxide concentrations used in at-home vital bleaching reported no difference in lightening at the end of the active phase[2,16] or in the first week of treatment.[4]

In the current study, both formulations resulted in whitening greater than five units according to the value-oriented Vita shade guide and more than 4.0 based on the CIEL*a*b* system, thus achieving the efficacy levels established by the ADA.[15] The spectrophotometer data for both experimental groups was not able to show significant differences in ΔL*, Δa*, Δb*and ΔE*. A reduction in b* has been reported to represent the most important indicator of color change in whitening treatment, since it occurs quicker and to a greater extent than the other components of CIELa*b*.[9,21,24] In the current study, a statistically significant difference was not observed in adjusted analysis between groups for the b* parameter.

Studies have reported that the most commonly adverse effects in at-home vital bleaching are mild-to-moderate tooth sensitivity and/or gingival irritation.[2-4,8,10-11] Furthermore, the higher concentrations of bleaching agent may increase these side effects.[1,6] Patients treated with 16% CP experienced significantly more tooth sensitivity in the first and third weeks of treatment than those treated with 10% CP. However, the degree of sensitivity reported by subjects was not different between the groups and the majority of the subjects experienced no or mild sensitivity. The subjects related that this sensitivity was transient and ceased soon after the whitening agent was removed. Previous clinical trials failed to demonstrate increased tooth or gingival sensitivity when comparing the effects of 10% and 15%[4,7] or 16.4% and 18%[2] carbamide peroxide agents used for at-home vital bleaching.

The current data showed that the bleaching efficacy was similar between the 10% and 16% CP groups. This raises the question whether it would be necessary to increase the concentration of carbamide or hydrogen peroxide to achieve satisfactory vital tooth bleaching. The efficacy and safety of 10% CP has been well established in published clinical trials.[16-18,25] A clinical evaluation that compared two whitening treatments, one with 35% hydrogen peroxide and the other with 10% CP, showed that the latter produced significantly lighter teeth than the in-office treatment.[3] Another clinical trial[10] compared the efficacy, side-effects and patients' acceptance of different bleaching agents and techniques. It showed that at-home bleaching with 10% CP had the same efficacy compared to the other techniques (over-the-counter or in-office whitening). Overall, at-home vital bleaching with 10% CP is more accepted by patients than in-office treatment with 35% hydrogen peroxide.[3,10] Considering safety issues when using 16% CP against a placebo or 10% CP used for nightguard vital bleaching, more gingival irritation was experienced by patients treated with 16% than a placebo or 10% CP.[26]

Both carbamide peroxide concentrations tested in this clinical trial were well tolerated by subjects, with a slight preference being shown for 10% CP. The group treated with 16% CP presented with greater discomfort after application. Therefore, this study suggests that 10% carbamide peroxide is the best choice for vital tooth bleaching, because it provides a lower incidence of tooth sensitivity than 16% CP with comparable whitening efficacy. Further longitudinal and clinical trials comparing 10% carbamide peroxide to 16% carbamide peroxide are needed to investigate whether the increasing concentration will influence the bleaching efficacy, long-term side effects and risk factors associated with the shade rebound effect.

CONCLUSIONS

It can be concluded that both of the evaluated carbamide peroxide concentrations were similarly effective in tooth shade improvement after three weeks of at-home vital bleaching. Additionally, the whitening agents produced no or mild transient tooth sensitivity, and the concentrations tested were well-accepted by the study participants, with a slight preference for 10% carbamide peroxide.

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