

Comparison of Effectiveness and Sensitivity Using Two In-Office Bleaching Protocols for a 6% Hydrogen Peroxide Gel in a Randomized Clinical Trial

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Clinical Relevance

Simplifying the bleaching procedure by an abbreviated protocol saves materials and can decrease the risk of gel contact with soft tissues surrounding the teeth. The effectiveness of the low-concentration hydrogen peroxide gel was maintained via this outpatient technique.

SUMMARY

Objective: The aim of this blinded and randomized clinical trial was to compare two application protocols (one 36-minute application vs three 12-minute applications). We then assessed the effectiveness of the bleaching and

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any increase in sensitivity that was induced by bleaching via a split-mouth design.

Methods and Materials: Thirty patients were treated. One group had a half arch of teeth treated with a traditional application protocol (group A: 3 × 12 minutes for two sessions). The other received an abbreviated protocol (group B: 1 × 36 minutes over two sessions). Two sessions were appointed with a two-day inter-

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val between them. The tooth color was registered at each session, as well as one week and one month after completing the treatment via a spectrophotometer. This measured L^* , a^* , and b^* . This was also evaluated subjectively using the VITA classical A1-D4 guide and VITA Bleachedguide 3D-MASTER. Tooth sensitivity was registered according to the visual analogue scale (VAS) scale. Tooth color variation and sensitivity were compared between groups.

Results: Both treatments changed tooth color vs baseline. The $\Delta E^* = 5.71 \pm 2.62$ in group A, and $\Delta E^* = 4.93 \pm 2.09$ in group B one month after completing the bleaching ($p=0.20$). No statistical differences were seen via subjective evaluations. There were no differences in tooth sensitivity between the groups. The absolute risk of sensitivity reported for both groups was 6.25% ($p=0.298$). The intensity by VAS was mild ($p=1.00$).

Conclusions: We used hydrogen peroxide (6%) that was light activated with a hybrid LED/laser and two different protocols (one 36-minute application vs three 12-minute applications each for two sessions). These approaches were equally effective. There were no differences in absolute risk of sensitivity; both groups reported mild sensitivity.

INTRODUCTION

Tooth bleaching is the treatment of choice for dental discoloration.¹ Color enhancement increases esthetics and self-esteem.² However, bleaching can also produce adverse effects such as tooth sensitivity—this is an important problem.³

In-office bleaching sessions usually include three applications of peroxide gel for effectiveness.⁴ This includes multiple steps for the dentist and the patient, which can generate discomfort and be time consuming. There is currently no rationale for this protocol in the literature. Caneppele and others recently published an *in vitro* study showing no differences in color change when comparing different abbreviated protocols (1 × 40 minutes) using in-office bleaching gels.⁵ Matis and others showed that, after one hour of contact, 10% and 22% hydrogen peroxide gels still have an activity of 30%.⁶ This means that a prolonged application should have the same bleaching effect as three short applications. This would use less material, save time, and minimize irritation. Reis and others showed that prolonged application of

35% hydrogen peroxide was as effective as three applications of 15 minutes with a risk of absolute sensitivity of 15% with mild or moderate intensity.⁷ There are no reports of clinical trials with low concentration (6%) gels catalyzed with a LED lamp or laser light for prolonged application. It is important to study the effectiveness and adverse effects related to the bleaching procedure.

De Paula and others showed that a reduction in intervals between in-office bleaching sessions with conventional concentrations had no statistically significant differences on sensitivity and effectiveness.⁸ However, this trial also shows a risk of absolute sensitivity of 60% in treated patients. Thus, this problem still lacks a solution.

There is a recent tendency to reduce the concentration of hydrogen peroxide for in-office bleaching. The active ingredients are catalyzed with titanium dioxide nanoparticles and a hybrid (LED/laser). This allows 6% to still be effective with a reduced risk of sensitivity.⁹⁻¹¹ This could reduce the intervals between sessions, abbreviate the protocol, and produce less sensitivity.

The objective of this trial was to compare two application protocols: 1) one application of 36 minutes and 2) three applications for 12 minutes. Both protocols were applied twice. We then assessed their effect on the effectiveness of bleaching and bleaching-induced sensitivity via a split-mouth design. The null hypothesis was that there is no difference in the effectiveness and bleaching-induced sensitivity from the abbreviated application protocol vs the traditional protocol.

METHODS AND MATERIALS

The Ethics Committee of the local Faculty of Dentistry approved this clinical study. The study was conducted between July 2015 and October 2015. It was registered on the Clinical Trials Registry (#NCT02603354) and was conducted according to the Consolidated Standards of Reporting Trials Statement¹² (Figure 1) and Helsinki Declaration of 1975 (revised in 2000).

Thirty volunteers were selected and received a gingival debridement to remove supragingival deposits when appropriate. There was then a coronal cleaning with a soft nylon cup and pumice paste to remove stains. Subsequently, all patients were instructed in a standardized tooth brushing technique. They were given a toothbrush and toothpaste for the period of treatment and evaluation. They also signed a written informed consent.

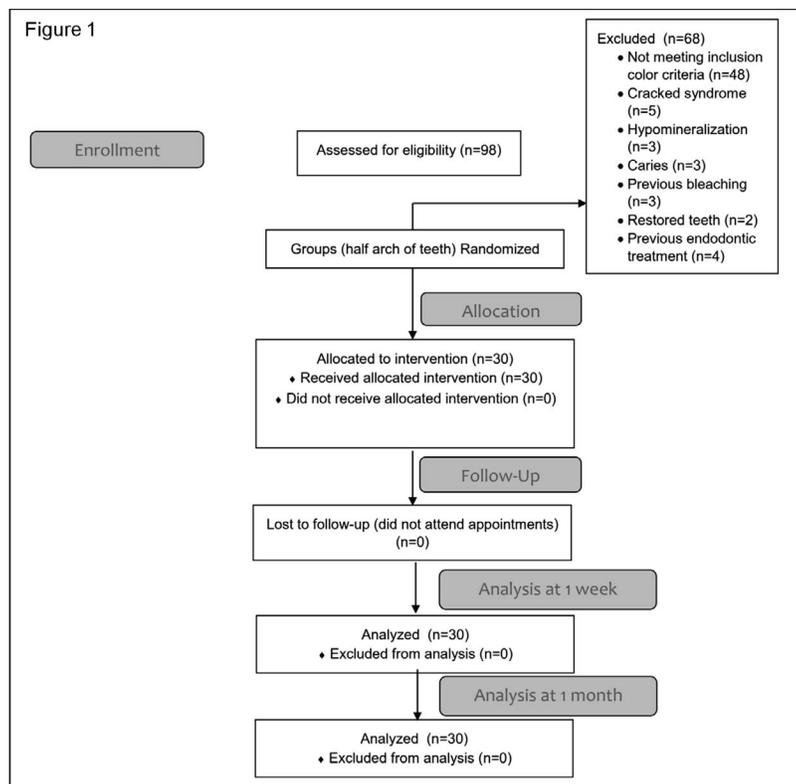


Figure 1. CONSORT flow diagram.

This was a randomized, blinded (evaluator) trial using a split-mouth design¹³ (one half arch was treated by the abbreviated protocol [1 × 36 minutes for two sessions] and the other by the traditional application protocol [3 × 12 minutes for two sessions]). This was followed with nonprobability sampling. The patients were invited to participate in the study through posters posted around the city or recruited from participants in other studies in the same department who were contacted by email or phone.

A total of 98 patients were examined in a dental chair to confirm that they met the inclusion criteria. The patients included in this study were over 18 years old and had two central incisors shade A2 or darker determined with a value-oriented shade guide. The exclusion criteria were patients who were pregnant or lactating; had moderate or severe fluorosis, tetracycline stains, orthodontic treatment, periodontal disease, orofacial tumors, trauma, or tooth malformation; or were taking analgesic, anti-inflammatory, or antibiotic drugs. Patients with restored anterior teeth, previous bleaching procedures, cervical lesions, or dental pain were also excluded.

Two trained operators (restorative dentistry professors) performed the bleaching treatments. A third

participant that did not have contact with the patients conducted the randomization. The group allocation (half arch of teeth) was performed by random drawing using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) from coding assigned to each participant. There were two experimental groups. Group A was the control, and a hydrogen peroxide bleaching compound 6% (Lase Peroxide Flex 6%, DMC Equipamentos, São Carlos, SP, Brazil) was applied to the maxillary group of teeth with a conventional protocol application (three rounds of 12 minutes per two sessions). Group B was the experimental group. The other maxillary half arch of teeth was treated with the same peroxide gel (6%) but with a reduced application protocol (one round for 36 minutes over two sessions). Both groups were bleached with the same compound catalyzed by titanium oxide nanoparticles and activated with a blue hybrid light and an infrared laser during the complete times.

Sample Size Calculation

The primary outcome was color alteration (ΔE). Previous studies^{2,14-16} showed that the use of in-office bleaching agents containing hydrogen peroxide with or without LED/laser light leads to a ΔE^* value of 2.0-7.0 after two bleaching sessions. We wanted an

80% chance of detecting significance at 5%. The increase in the primary outcome measurement was 5.5 in the control group and 4.5 in the experimental group. This difference was determined by a preliminary pilot study considering the maximum SDs obtained. Thus, a power calculation showed that 25 participants were required for sufficient statistical power. Due to the higher dropout rate seen in our previous two studies, we included 20% more patients: this led to 30 patients in each group.¹⁷

Bleaching Protocol

In each session, volunteers received prophylaxis with pumice powder and water. The gingival tissue was protected with a light-cured resin gum barrier applied according to the manufacturer's instructions (Lase Protect, DMC Equipamentos). The bleaching agent was prepared by mixing hydrogen peroxide and thickening compounds according to the manufacturer's instructions (three peroxide drops for one drop of thickener). The resulting gel was distributed uniformly on the maxillary teeth (right or left). A total of eight teeth between the second premolars were bleached for each patient. In each bleaching session, the bleaching gels were applied three times for 12 minutes each (group A). The other group received one treatment of 36 minutes (group B) per session. In each application, the surface of the gel was light activated with continuous irradiance using LED/laser light with a total power of 1800 mW for photocatalysis (Whitening Lase Plus, DMC Equipamentos). This is specific equipment for in-office dental bleaching. It presents six LEDs (470 ± 15 nm, 300 mW each), generating 1800 mW of power, and three infrared laser diodes (810 nm, 200 mW each), generating 600 mW of power. This irradiates a total area of 8.5 cm² with an intensity of 300 mW/cm². Irradiation was the same for the two groups with a protocol of one minute of irradiation and one-minute rest during the entire process (the total irradiation time for each group was 36 minutes). Two bleaching sessions were completed, and the interval between the sessions was two days.

Efficacy Evaluation

Objective Evaluation—Two calibrated evaluators were used to measure the tooth color for baseline immediately after the first and second day, as well as one week and one month after the last session. The color evaluation was obtained from a 6-mm area located in the middle third of the labial surface of the left and right central incisors. To standardize this evaluation, an impression of the maxillary arch was

collected to make a guide for high-putty silicone (Zetaplus, Zhermack, Badia Polesine, Rovigo, Italy). A window was created on the labial surface in the middle third of the central incisor using a device with well-formed borders and a 3-mm radius corresponding to the reflectance of a reliable spectrophotometer (VITA Easyshade Compact, VITA Zahnfabrik, Bad Säckingen, Germany).¹⁸ The shade was determined using parameters L*, a*, and b*. The color alteration after each session was given by the differences between the values obtained at the session and the baseline (ΔE^*). The ΔE^* was calculated using the following formula: $\Delta E^* = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.

Subjective Evaluation—Subjective evaluation protocol used standardized light conditions (same place, time, patient positions, natural light source, all assessments were between 10:00 AM and 3:00 PM). There were two evaluators (κ interoperator = 0.85), and the color competition had 50:50% acceptability threshold (ISO TR 28642-2011). The viewing geometry, object-observer distance, visual angle, and background color were held constant between subjects. The 16 tabs of the shade guide (VITA classical A1-D4, Vita Zahnfabrik) were arranged from the highest (B1) to the lowest (C4) value, and the 15-tab shade guide was used (VITA Bleachedguide 3D-MASTER, Vita, Vita Zahnfabrik) to assess the color. Although the VITA classical A1-D4 scale is not linear in the truest sense, we treated the changes as continuous with linear ranking as done in several dental bleaching clinical trials. Two calibrated evaluators ($\kappa=0.85$) recorded the shade of the maxillary central left and right incisors at baseline with the same periods as the objective evaluation.

We checked the color in the middle third area of the labial surface of the anterior central incisor according to the American Dental Association guidelines.¹⁹ The color changes were calculated from the beginning of the active phase through the individual recall times by the change in the number of shade guide units (Δ SGU). This occurred toward the lighter end of the value-oriented list of shade tabs. In the event that the operators disagreed about color matching, a consensus was reached prior to dismissing the patient. The perceptibility threshold used for this study was 3.3 ΔE^* units.²⁰

Tooth Sensitivity Evaluation Induced by Bleaching

Tooth sensitivity (TS) was characterized via frequency and intensity with a self-completed form and clinical evaluation during the session and immedi-

Table 1: Baseline Color Features of Volunteers

Group	VITA classical A1-D4			VITA Bleachedguide 3D-MASTER		
	Median value	Minimum	Maximum	Median value	Minimum	Maximum
Group A	9 (A3)	5 (A2)	14 (C3)	8 (2.5M2)	7 (2M2)	12 (4.5M2)
Group B	9 (A3)	5 (A2)	12 (A3.5)	8 (2.5M2)	7 (2M2)	10 (3.5M2)
Mann-Whitney test <i>p</i> value	0.763			0.238		
	L*		a*		b*	
	Average value	SD	Average value	SD	Average value	SD
Group A	81.94	4.47	-0.96	1.07	24.66	3.40
Group B	82.33	4.07	-1.02	1.48	24.72	2.70
<i>t</i> -test <i>p</i> value	0.714		0.869		0.945	

ately after via the visual analogue scale (VAS). For the VAS, the investigators instructed the participants to place a line perpendicular to a 10-cm-long line with zero at one end indicating "no TS" and the other end indicating "unbearable TS." The occurrence was analyzed according to whether sensitivity was reported. The volunteers were instructed to fill out a form for each bleaching session and for the following days between sessions in case of sensitivity in any of the bleached teeth at any time.

Statistical Analysis

After verifying the normality of the data distribution and the homogeneity of the variance-covariance matrix, the efficacy of the treatments was evaluated with respect to color alteration (ΔE and ΔSGU) and analyzed by the Mann-Whitney test for between-group comparisons. The proportion of patients with sensitivity between groups was compared with a *Z*-test. The statistical analyses were performed using SPSS 23.0 (SPSS Inc, Chicago, IL, USA) with $\alpha=0.05$.

RESULTS

Baseline Characteristics

Of the 98 patients, 30 were enrolled. The sample consisted of 14 women (53.3%) and 16 men (46.7%), with average ages of 27.63 ± 7.1 years for men and

26.71 ± 9.3 years for women. The entire cohort was 27.24 ± 8.0 years. Features of color at baseline are shown in Table 1.

Spectrophotometer Data

Color changes measured via ΔE^* , ΔL^* , Δa^* , and Δb^* from the baseline are shown in Table 2. There was not a significant ΔE^* difference according to the Mann-Whitney test between the two groups at all times ($p>0.30$; values shown in Table 3).

Shade Guide Data

Color changes measured subjectively expressed by VITA classical A1-D4 and VITA Bleachedguide 3D-MASTER ΔSGU units are shown in Table 4. For both scales, there was no significant difference between the different evaluations ($p>0.10$).

Occurrence and Intensity of Sensitivity

The absolute risk of sensitivity reported for both groups was 6.25% ($n=2$ [same patients in both groups]). There was no statistically significant difference when comparing the proportions of patients by the *Z*-test ($p=0.298$). The intensity of the sensitivity by the VAS scale ($\bar{X} = 0.15 \pm 0.61$) and maximum value per patient immediately after sessions ($\bar{X} = 0.18 \pm 0.88$) were mild, and there

Table 2: ΔL^* , Δa^* , and Δb^* of Each Group Between Baseline and Each Checkpoint

	ΔL^*				Δa^*				Δb^*			
	First session	Second session	Week control	Month control	First session	Second session	Week control	Month control	First session	Second session	Week control	Month control
Group A	1.31 ± 3.40	2.04 ± 4.09	2.79 ± 3.55	2.22 ± 3.25	0.07 ± 1.24	-0.38 ± 0.83	-1.00 ± 1.04	-1.08 ± 0.73	0.03 ± 2.77	-1.75 ± 3.57	-3.45 ± 2.85	-3.72 ± 2.98
Group B	0.67 ± 4.14	1.64 ± 4.33	1.35 ± 4.17	1.94 ± 2.59	-0.09 ± 1.13	-0.25 ± 1.33	-0.94 ± 1.29	-0.77 ± 1.03	0.01 ± 2.46	-1.30 ± 3.05	-3.69 ± 2.37	-3.38 ± 0.42
<i>t</i> -test <i>p</i> value	0.503	0.708	0.149	0.717	0.593	0.630	0.846	0.188	0.981	0.587	0.721	0.620

Table 3: Color Change, Expressed as ΔE^* , of Each Group Between Baseline and Each Checkpoint

	ΔE^*			
	First session	Second session	Week control	Month control
Group A	3.76 ± 2.93	5.06 ± 3.26	5.83 ± 2.71	5.71 ± 2.62
Group B	4.13 ± 2.89	5.03 ± 3.01	5.98 ± 2.27	4.93 ± 2.09
t-test p value	0.617	0.864	0.950	0.207

was no statistically significant difference between groups ($p=1.00$).

DISCUSSION

This trial assessed the influence of an abbreviated protocol (single application of 36 minutes per two sessions) of hydrogen peroxide of low concentration (6%) compared with traditional application of three applications for 12 minutes per two sessions with 72 minutes of total contact gel time per tooth. Dentists generally look to streamline their procedures and use of consumables. A simplified protocol would have less gel contact on the soft tissues surrounding the teeth. This avoids possible adverse effects or patient discomfort. There is no clear argument in the literature regarding a 3 × 12-minute application or other protocols for in-office gels.

Chen and others showed that the time to achieve effectiveness of hydrogen peroxide during the bleaching process should be more than 20 minutes of contact²¹ in an *in vitro* trial. The strips and/or toothpaste that contain low concentrations (6%) of hydrogen peroxide come with instructions for prolonged use—even several hours (>20) to achieve effective color change. These manufacturers argue that because of its low concentration, cell damage and postoperative problems are less likely.²²

The results show no difference in effectiveness and sensitivity reported by patients with the two protocols. This means one less step in clinical practice for the dentist; the null hypothesis was accepted. This split-mouth²³ experimental design is a good model to compare experimental and control groups under

similar conditions. This controls for confounding variables like habits, diet, and hygiene.

We found no difference between the two groups. Both groups had a change in E of about 5 units—this is considered effective bleaching.²⁴ These results agree with Martin and others who describe a change of 5 E* units with 6% gel in the office,² but with different application protocols: 1) three sessions with two applications, each for 12 minutes; 2) two sessions with three applications for 12 minutes, and 3) two sessions with one application of 36 minutes. All of these approaches are equally effective.

Traditionally, the use of bleaching gels in trays for home bleaching uses contact times of more than two hours with higher concentrations of hydrogen peroxide than in this clinical trial. This is because the effectiveness of the gel is reduced after only two hours of contact.²⁵ However, the difference in using a gel at home or a gel technique in-office is that the tray allows a reservoir to maintain a more humid environment. The gel used in the in-office technique is exposed to the environment and seemingly loses water faster. This is the argument used by manufacturers to recommend applications of 15 minutes. Kwon and others used a linear low-density polyethylene wrap to prevent dehydration of the gel during a prolonged bleaching session without replenishment of the whitening gel.²⁶ This trial demonstrates that continuous use of hydrogen peroxide gel for 36 minutes of low peroxide concentration gel activated by light LED/laser is effective but with an abbreviated application protocol.

Table 4: Delta SGU by VITA classical A1-D4 and VITA Bleachedguide 3D-MASTER Guides of Both Groups at Each Checkpoint

	VITA classical A1-D4				VITA Bleachedguide 3D-MASTER			
	First session Δ SGU median (min/max)	Second session Δ SGU median (min/max)	Week control Δ SGU median (min/max)	Month Δ SGU median (min/max)	First session Δ SGU median (min/max)	Second session Δ SGU median (min/max)	Week control Δ SGU median (min/max)	Month Δ SGU median (min/max)
Group A	4 (-1/11)	6 (2/13)	6 (-1/10)	6 (-1/10)	2 (0/5)	3 (1/6)	2.5 (0/6)	2 (0/5)
Group B	5 (0/9)	6 (0/11)	6 (0/9)	5.5 (0/10)	3 (1/6)	4 (1/7)	3 (0/6)	2 (-1/6)
Mann-Whitney test p value	0.808	0.669	0.898	0.580	0.395	0.522	0.401	0.773

Effectiveness was measured subjectively on two scales—the VITA classical A1-D4 and VITA Bleachedguide 3D-MASTER guide. There were no differences between the two protocols on either scale. The VITA classical A1-D4 scale is a simple scale to use and is popular among dentists. However, the distribution of colors is not symmetrical according to the dimensions of color. Thus, the validity of this instrument to capture the variation in teeth is not completely reliable. For this, we also decided to use the VITA Bleachedguide 3D-MASTER Guide scale that is distributed more uniformly according to brightness. This allows greater consistency and reproducibility to measure changes during tooth bleaching.²⁷ However, we emphasize the split-mouth design. There is a high risk of bias in measuring a neighboring tooth because the human eye cannot distinguish between fewer than two E* units. This could affect data collection²⁸—a problem described by Martin and others in a similar study.²

Matis and others²⁵ showed that about 30% of the hydrogen peroxide remained active after 30 minutes. This suggests that the 6% gel with activated LED/laser light applied for 36 minutes is equal to the group with three applications of 12 minutes. The chemical reaction catalyzed by the blue light LED uses titanium dioxide as a semiconductor nanoparticle to catalyze the formation of hydroxyl radicals from hydrogen peroxide. On the other hand, the infrared laser can also hyperpolarize nerve pain and generate immediate sensitivity control. This is reflected in the low rates of sensitivity and intensity induced by bleaching.¹⁵ One of the gel change justifications for the bleaching session is because of the pH of the bleaching gel.²⁹ With the passage of time, a greater quantity of free radicals will be released. Thus, there is a pH decrease.³⁰ It is known that more demineralization will occur when the pH of the bleaching gel becomes more acidic.³¹ This mineral loss disrupts the enamel prisms and increases the possibility of sensitivity—often described as “zinger” pain.³²

The intervals studied here were shorter than the commonly used seven days. De Paula and others⁸ showed that there was no impact on the postbleaching sensitivity by shortening intervals to two days between sessions. Our results are consistent with the results of this trial because there was no difference. It is also important to consider that postbleaching sensitivity is dependent on the concentration of hydrogen peroxide gel. Trial reports using gels of 35% or even 15% show higher absolute values and intensity of postbleaching sensitivity

than our results.^{7,10,24,33,34} However, we must consider that the low values of sensitivity in this work are due to activating the bleaching gel by hybrid infrared LED/laser.¹⁵ There must be an immediate influence on nerve fibers (ΔA) by the action of hyperpolarization of the laser. This mediates the sensitivity and should not have been influenced by the studied application protocols. The sensitivity and intensity values were low relative to the literature.^{7,24,35-40}

The actual role of the blue light (cold lamp) is unknown. It could be a catalyst for a chemical reaction. Other data show that the use of light does not increase the effectiveness of in-office bleaching.³ Titanium oxide is a semiconductor under blue light and theoretically catalyzes the formation of hydroxyl radicals from hydrogen peroxide.⁴¹ The exact role by which light or titanium oxide nanoparticles catalyze the mechanism of action remains unclear. In the literature, 6% hydrogen peroxide gels should be applied for >20 hours for effective bleaching.³⁶ In this trial, there was a contact of only 72 minutes. This assumes that the light (LED/Infrared Laser) is the catalyst for the chemical reaction. The effect of the infrared laser clearly influenced the values of absolute risk and intensity of sensitivity induced by bleaching. It coincides with Martin and others,² who described a 36.6% risk of mild sensitivity from bleaching vs the 6.25% shown here. Some authors correlate the presence of an acute inflammatory reaction in dental pulps of human bleached teeth with gel in high concentrations (>35%). This suggests that some released mediators of the inflammatory reaction such as bradykinin⁴² or substance P⁴³—probably due to the low concentrations of peroxide—are lower, and their effect is a nonexistent mediator of the sensitivity reported by patients.

The limitations of this study include the impossibility of blinding the operators and patients regarding the change of technique. However, the calibrated blinding of evaluators was very strict. The split-mouth design is an excellent tool³⁹ because it allows different groups within the same patient. Thus, each patient is his or her own control. This eliminates confounding variables. The major problem of this design is a potential leakage of the treatment effect from one site to another called the carry-across effect, in this study potentially reflected as a bias in sensitivity assessment.²³

CONCLUSIONS

There was no significant difference in tooth whitening with 6% hydrogen peroxide bleaching gel in one

36-minute application compared with the traditional three 12-minute applications. There were no differences in sensitivity noted for these two protocols.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of the University of Chile. The approval code for this study is: 2015-01b.

Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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