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Efficacy of and Effect on Tooth Sensitivity of In-office Bleaching Gel Concentrations: A Randomized Clinical Trial

A Reis • S Kossatz • GC Martins
AD Loguercio

Clinical Relevance

Faster bleaching was observed with Whiteness HP Blue 35 (35% hydrogen peroxide) and tooth sensitivity was similar to that found with the lower concentration Whiteness HP Blue 20 (20% hydrogen peroxide). These results cannot be extrapolated to other in-office 35% hydrogen peroxide gels.

*Alessandra Reis, DDS, PhD, professor, Restorative Dentistry, Universidade Estadual de Ponta Grossa, Ponta Grossa, Brazil

Stella Kossatz, DDS, MS, PhD, professor, Restorative Dentistry, University Estadual de Ponta Grossa, Ponta Grossa, Brazil

Gislaine Cristine Martins, DDS, MSc, PhD, Restorative Dentistry, Universidade Estadual de Ponta Grossa, Ponta Grossa, Brazil

Alessandro D Loguercio, DDS, MS, PhD, professor, Restorative Dentistry, University Estadual de Ponta Grossa, Ponta Grossa, Brazil

*Corresponding author: Rua Carlos Cavalcanti, 4748, Bloco M, Sala 64A–Uvaranas, Ponta Grossa, PR 84030-900 Brazil; e-mail: reis_ale@hotmail.com

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SUMMARY

With the aim of reducing the side effects of in-office bleaching agents, less-concentrated hydrogen peroxide (HP) gels have been released by manufacturers. We evaluated the tooth sensitivity (TS) and bleaching efficacy (BE) of two HP concentrations in this study. Gels containing 35% and 20% HP (HP35 and HP20, respectively) were applied on teeth of 60 caries-free patients. Color was recorded at baseline and one week after the first and second bleaching sessions using the Vita Classical shade guide. TS was recorded on a 0-4 scale. BE at each weekly recall was evaluated by Kruskall-Wallis and Mann-Whitney tests (α=0.05). Absolute risk of TS and its intensity was evaluated by Fisher exact and Mann-Whitney tests, respectively (α=0.05). After two

bleaching sessions, color change of approximately eight tabs was obtained with HP35; whereas, with HP20 it was six tabs ($p<0.05$). Only 26.7% (HP35) and 16.7% (HP20) of the participants reported TS, and no statistical differences were detected among them. Both in-office bleaching gels showed similar TS intensity, but the 35% HP agent produced faster bleaching.

INTRODUCTION

The at-home bleaching system is by far the most frequently recommended treatment for discolored vital teeth. However, some patients prefer not to use a bleaching tray or wish to obtain a faster whitening result. In this case, in-office bleaching procedures, using high hydrogen peroxide (HP) concentrations (30%-35%), are appropriate alternatives to the at-home bleaching techniques. The effectiveness of in-office bleaching is well documented in the literature. An overall color change of five to eight shade guide units (SGUs) is usually obtained after two bleaching sessions.[1-5]

In spite of this, most clinical studies have demonstrated that more than 70% of the patients who undergo in-office bleaching complain of tooth sensitivity (TS),[1,5,6] and this is the main deterrent to patients successfully completing their whitening treatment. Although the results of *in vitro* studies do not necessarily correlate to events that occur in an *in vivo* condition, one may hypothesize that the rapid transenamel and transdentinal diffusion of HP to the pulp, or other toxic components released with the degradation of the bleaching gels,[7,8] may be responsible for the high prevalence of TS. These by-products released from the bleaching gel act as free radicals and may cause oxidative stress in the pulp cells due to the imbalance between reactive oxygen species and endogenous and exogenous antioxidants.[9,10] In some cases, the oxidative stress produced by high HP concentrations applied for 45 minutes is so intense that it causes irreversible pulp damage by coagulation necrosis in the mandibular incisors.[11]

It is known that the diffusion of HP through dentin depends on the original concentration of the bleaching agent[7,12] and the length of time the agent is in contact with the dentin. This fact has led some manufacturers to release in-office bleaching gels with lower HP concentrations, with the aim of minimizing the side effects produced by bleaching products while retaining the same bleaching efficacy. Although empirically, it could be anticipated that the higher the concentration of the bleaching gel, the more likely it is to produce TS, this was not proved when 10% and 16% carbamide peroxide gels were compared with each other in a clinical trial.[13]

To the extent of the authors' knowledge, no clinical study has so far addressed the bleaching efficacy and TS produced by low-concentration bleaching gels. Therefore, the aim of the present investigation was to compare the bleaching efficacy and TS of 20% and 35% HP in-office bleaching gels. The null hypothesis to be tested was that both HP gels can yield similar bleaching efficacy and TS.

MATERIAL AND METHODS

The local university's Ethics Research Committee approved this clinical investigation (Protocol no. 05530/09). The experimental design was in accordance with the Consolidated Standards of Reporting Trials statement.[14] Based on pre-established criteria, 60 volunteers from the city of Ponta Grossa, Paraná, Brazil, were selected for this study. Two weeks before the bleaching procedures, all the volunteers received dental screening and dental prophylaxis with pumice and water in a rubber cup and signed a form of free and informed consent.

Study Design

This was a randomized, double-blind, parallel-group clinical trial with an equal allocation rate to receive either of two treatments. The study was conducted in the clinic of the School of Dentistry of the State University of Ponta Grossa from January 2010 to February 2011.

Inclusion and Exclusion Criteria

Patients included in this clinical trial were at least 18 years old and had good general and oral health. Participants were recruited by means of local advertisement. A total of 270 participants were examined, seated in a dental chair, to check whether they met the inclusion and exclusion criteria (Figure 1). The participants were required to have caries-free maxillary and mandibular anterior teeth, without restorations on the labial surfaces. The central incisors had to be shade C2 or darker, judged by comparison with a value-oriented shade guide (Vita Lumin, Vita Zahnfabrik, Bad Säckingen, Germany). Participants who had undergone previous tooth-whitening procedures, presented anterior restorations, were pregnant or lactating, and/or had severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth), bruxism habits, or any other pathology that could cause sensitivity

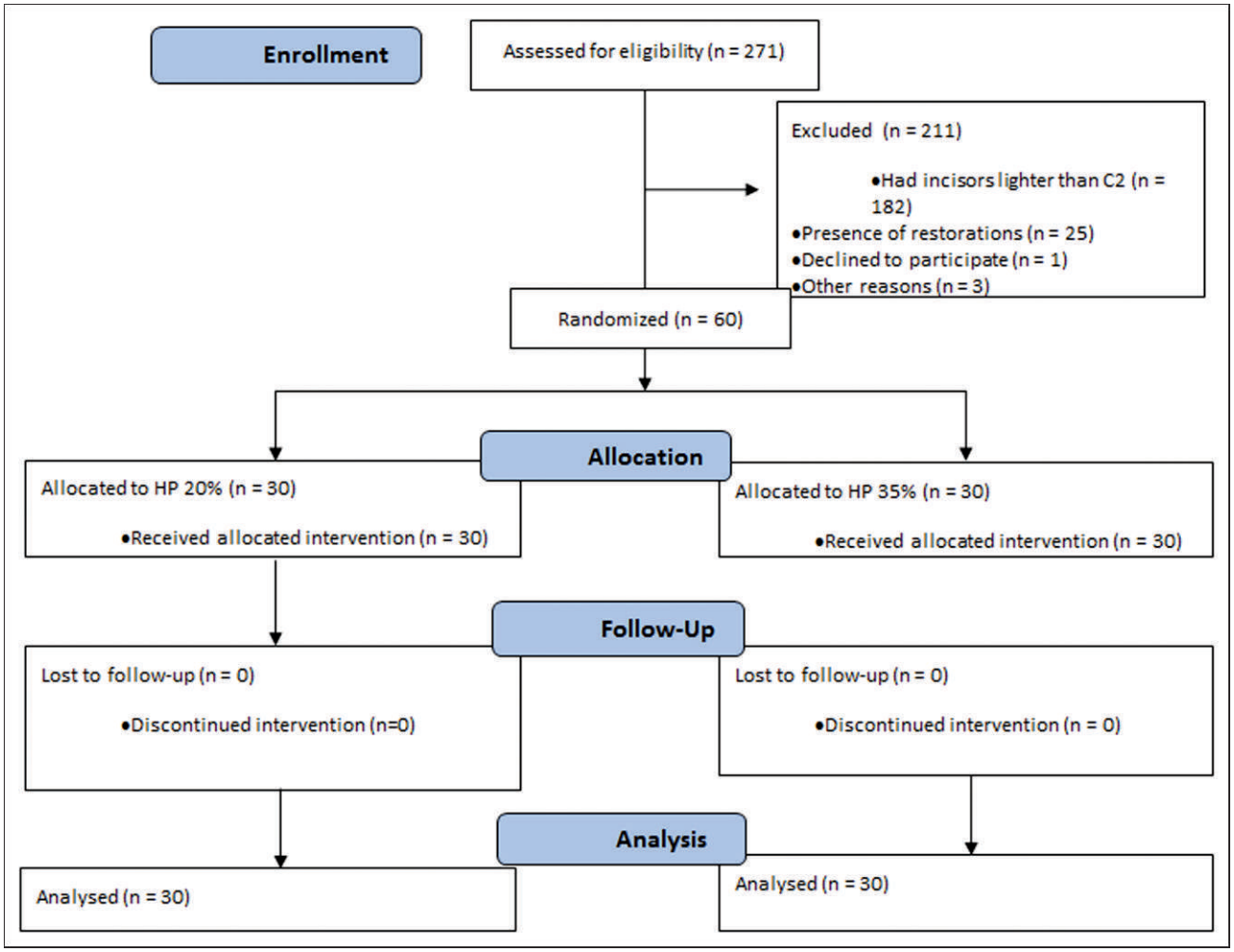

Figure 1. *Flow diagram of the clinical trial, including detailed information on the excluded participants.*

(such as recession, dentin exposure) were excluded from the study. This was because they would not be immediately eligible for a cosmetic treatment such as bleaching, for the other restorative needs would need priority attention. The patients were asked about previous experience of TS the week before the bleaching therapy began, using the criteria described in the "Tooth Sensitivity Evaluation" section. Patients with TS equal to or greater than mild were also excluded from the study.

Sample Size Calculation

The primary outcome of this study was the absolute risk of TS. Given that no study has so far reported the risk of TS for the products used in this study, the sample size calculation was based on the absolute risk of TS of another 35% HP gel from the same company (Whiteness HP Maxx, FGM Dental Products, Joinville, Brazil), which was reported to be approximately 87%.[1] Thus, 60 patients were required to have an 80% chance of detecting a significant decrease in the primary outcome measure, from 87% in the control group to 57% in the experimental group, at the level of 5%.

Study Intervention

The randomization process was performed by computer-generated tables prepared by a third person not involved in the research protocol. Details of the allocated group were recorded on cards contained in sequentially numbered, opaque, sealed envelopes. These were prepared by a third person not involved in any of the phases of the clinical trial. Once the participant was eligible for the procedure and had completed all baseline assessments, the allocation assignment was revealed by this envelope being opened by the aforementioned third person. Neither the participant nor the operator knew the group allocation, both being blinded to the protocol.

Table 1: *Products, Composition, and Application Regimens*

Products	Composition	Application Mode
Whiteness HP Blue 35	35% hydrogen peroxide, thickeners, inert violet, neutralizing agent, calcium gluconate, glycol, and deionized water.	1. Attach the two syringes to each other.
		2. Mix the contents of both phases by alternately pressing the plungers of the syringes in opposite directions up to 8 times.
		3. Press the entire mixture content into one of the syringes.
		4. The bleaching gel should be applied by means of the syringe on the teeth surfaces and left on for 40 min. Then the material should be removed with an aspirator.
Whiteness HP Blue 20	20% hydrogen peroxide, thickeners, inert violet, neutralizing agent, calcium gluconate, glycol, and deionized water.	1. Attach the two syringes to each other.
		2. Mix the contents of both phases by alternately pressing the plungers of the syringes in opposite directions up to 8 times.
		3. Press the entire mixture content into one of the syringes.
		4. The bleaching gel should be applied by means of the syringe on the teeth surfaces and left on for 50 min. Then the material should be removed with an aspirator.

The gingival tissue of the teeth to be bleached was isolated using a light-polymerized resin dam (Top Dam, FGM Dental Products). Depending on the randomization, participants received either the 35% or 20% HP gels (Whiteness HP Blue 35 and Whiteness HP Blue 20, FGM Dental Products), which were used according to the manufacturer's instructions (Table 1). Two bleaching sessions were performed with a one-week interval between them. All participants were instructed to brush their teeth regularly using fluoridated toothpaste (Sorriso Fresh, Colgate-Palmolive, São Paulo, Brazil).

Shade Evaluation

The color was recorded at baseline and one week after the first and second bleaching sessions using a Vita shade guide. The shade evaluation was done in a single room with artificial lighting. The 16 tabs of the Vita Classical shade guide were arranged from highest (B1) to lowest (C4) value, as can be seen in Table 2. Although this scale is not linear in the truest sense, the changes were treated as though they represented a continuous and approximately linear ranking for the purpose of analysis. Two calibrated evaluators recorded the shade of each participant's teeth at baseline and weekly. The measurement area of interest for shade matching was the middle third of the facial surface of one of the central incisors, which was chosen by tossing a coin. The two examiners were required to have an agreement of at least 85% (κ statistic) before beginning the study evaluation.

Table 2: *Ordering of Vita Shade Guide by Value*[a]

Tab	B1	A1	B2	D2	A2	C1	C2	D4	A3	D3	B3	A3.5	B4	C3	A4	C4
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

[a] *Light-to-dark ranking by manufacturer.*

Tooth Sensitivity Evaluation

The patients recorded their perception of TS on a 5-point verbal rating scale during bleaching and up to 24 hours after each session. Subjects were asked to keep a daily record of whether they experienced sensitivity, using the following criteria: 0 = *none*, 1 = *mild*, 2 = *moderate*, 3 = *considerable*, and 4 = *severe*. Given that two bleaching sessions were performed, the worst scores obtained in the two bleaching sessions were considered for statistical purposes. The values were arranged into two categories: overall percentage of patients who reported TS at least once during treatment (absolute risk of TS) and TS intensity at each of the assessment points.

Statistical Analysis

The analysis followed the intention-to-treat protocol and involved all participants who were randomly assigned.[14] The statistician was blinded to the study groups. The agreement between the examiners' objective evaluation was assessed using the κ statistic. The primary outcome absolute risk of TS was compared by using the Fisher exact test (α=0.05, a test for comparison of independent proportions data. The relative risk as well as the confidence interval (CI) for the effect size was calculated.

TS intensity (secondary outcome) was also analyzed statistically. The median and interquartile ranges of the pain scale were calculated. The data sets of TS intensity were plotted on histograms and inspected for normal distributions. Data did not appear to be normally distributed, and therefore the two groups were compared using the Mann-Whitney U-test (α=0.05).

Color change, another secondary endpoint, was used to assess the efficacy of the bleaching treatment. Means and standard deviations of the SGU at each assessment point were calculated. In order to evaluate whether the bleaching therapies were effective over time, the data of each group were submitted to Kruskall-Wallis test and the Mann-Whitney test for pairwise comparisons (α=0.05). At each assessment point, color changes of the two groups were compared with each other by the Mann-Whitney test (α=0.05).

RESULTS

Of the 60 participants who took part in this investigation, all completed the study. The mean age of the participants in this study were similar between the groups (HP35: 25.0 ± 6.8 years and HP20: 29 ± 9.9 years). Of the participants from the HP35 and HP20 groups, 45% and 43%, respectively, were men. Figure 1 depicts the participant flow in the different phases of the study design.

Tooth Sensitivity

The data from 60 patients were used in this study, following the intention-to-treat analysis.[14] With regard to the absolute risk of TS (primary outcome), no significant difference was observed between groups (Fisher exact test, p=0.53). The absolute risk of TS was 26.7% (95% CI, 14.2%-44.5%) and 16.7 (95% CI, 7.0%-33.6%) for the HP35 and HP20 groups, respectively.

The medians (25 and 75 percentiles) of TS intensity were shown to be 0 (0-0) for HP20 and 0 (0-1) for the HP35 groups. Similarly, no significant difference was detected between groups (Mann-Whitney test, p=0.36). Figure 2 depicts the distribution of TS scores between the two groups.

Color Change

The level of agreement between the two evaluators by means of the κ statistic was 82%. The means and standard deviations of SGUs are shown in Table 3. The mean color of the teeth in SGUs before the treatment began was 9.4 (between A3 and D3 in the Vita Classical shade guide) for the HP35 group and 9.3 (between A3 and D3 in the Vita Classical shade guide) for the HP20 group. The mean tooth color at baseline was similar for the two groups (p>0.05).

After two bleaching sessions, a change of approximately eight tabs occurred for the HP35 group (1.6 [between B1 and A1 in Vita Classical shade guide]), whereas a change of six tabs occurred for the HP20 group (3.5 [between D2 and B2 in Vita Classical shade guide]. This difference is statistically significant (p<0.05) (Table 3).

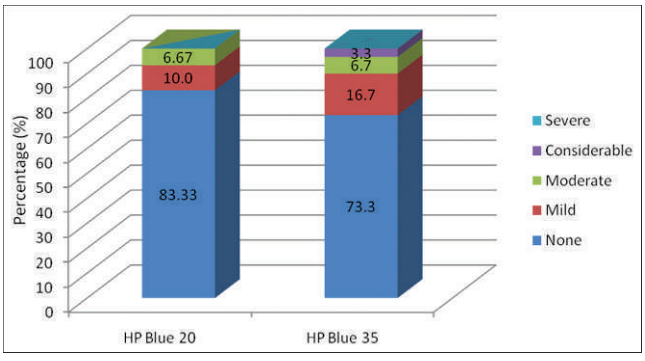

Figure 2. *Levels of sensitivity (%) perceived by the participants in both groups immediately after the bleaching protocol.*

Table 3: *Means and Standard Deviations of Shade Guide Units Between Assessment Points for the Two Treatment Groups*[a]

Assessment Point	HP35	HP20
Baseline	9.4 ± 1.3 aA	9.5 ± 1.4 aA
1 week after the first session	4.0 ± 1.2 bB	5.3 ± 0.9 bB
1 week after the second session	1.6 ± 0.7 dC	3.5 ± 1.0 cC

[a] *Comparisons between groups at each assessment point are represented by lowercase letters (Mann-Whitney test). Comparisons between assessment points in each group (Kruskall Wallis and Mann-Whitney tests) are represented by uppercase letters. Similar lower and uppercase letters indicate statistically similar means.*

DISCUSSION

The results of this study indicate that both groups demonstrated significant tooth color enhancement when compared with baseline (Table 3). Bleaching of eight and six SGUs was detected for the HP35 and HP20 groups, respectively. When the two materials were compared with each other, the 35% HP gel was capable of faster whitening than the 20% HP after two bleaching sessions.

HP is a thermally unstable chemical agent with a high oxidative power, which may dissociate into water, oxygen, and some free-radical species.[15] These species are responsible for the whitening process, and therefore one may assume that the bleaching effectiveness depends, among other factors, on the amount of free radicals produced by the bleaching gel when in contact with the dental structure. It was recently demonstrated that the concentration of HP in a proprietary bleaching gel had a marked effect on the number of applications required to produce an optimal shade outcome.[16] This means that bleaching gels with a higher peroxide concentration needed fewer applications to produce a similar bleaching effect.[16] Therefore, it was hypothesized that similar bleaching with HP20 and HP35 would have been achieved if three, instead of two, bleaching sessions had been performed for the former.

In spite of the lower whitening effect after two bleaching sessions, the overall color change produced by HP20 was within the range reported in the literature. A variation of five to nine SGUs after bleaching with 35% HP gels has been shown.[1-5,17] This means that other factors apart from the HP concentration play an important role in the bleaching effectiveness.

With regard to TS, the present study is not in agreement with previous findings in the literature. Although lower TS rates (16.7% to 26.7%) were reported in this study, TS rates three to four times higher were reported in earlier studies. For instance, Marson and others[2] reported that 63% of the participants in their clinical study reported TS. Higher TS rates such as 70%[6] and 80%[1,5] have also been reported.

One important difference between the two bleaching gels used in this study and other bleaching gels available on the market is that they contain 2% calcium gluconate, which is extensively used in the pharmaceutical industry as a source of calcium replacement in the body. Although calcium gluconate was added to the bleaching gel with the aim of preventing enamel demineralization, the fact cannot be ruled out that this addition might have played a role on the lower TS reported by the calcium-containing products. Perhaps the 2% of calcium gluconate dissolved in the HP gel was able to decrease dentin permeability and block enamel surface defects, similarly to that which is believed to occur with bleaching gels containing amorphous calcium phosphate.[18]

In addition, according to the manufacturer, the two bleaching gels used in this study maintain a high and stable pH (8.0-9.0) throughout the bleaching procedure, which allows them to be used in a single 40- or 50-minute application protocol. These pH values claimed by the manufacturer were also confirmed by the authors of this study by means of pH measurements in triplicate. Most of the in-office bleaching gels are delivered in a low pH (2.4 to 6.5)[19,20] to allow them to be stored for prolonged periods.[21] The decomposition kinetics and the by-products produced by HP depend on the pH of the media. It has been reported that HP delivered in an alkaline medium increases the bleaching effectiveness.[22] For instance, in a pH of 9, the dissociation rate of the HP was shown to be 2.7 times higher than in an acidic solution[22] (pH=4.4), most probably due to the fact that the dissociation constant (pKa) of the HP is around 11.5.

The free radicals released from HP depend on the pH of the media, and they may play a role in the prevalence and intensity of TS. In an acidic solution, higher concentrations of hydroxyl anions are produced; however, in an alkaline media there is a higher concentration of perhydroxyl ions.[23] Little is known about the deleterious effects of these different oxidizing agents on the dental-pulp complex, and therefore future studies should be encouraged in

order to elucidate whether this has any correlation with the lower TS observed for the calcium-containing products used in this study. Ongoing studies are being conducted to evaluate the effects of these products on the dental-pulp complex, and this will certainly partially clarify these issues.

It should be pointed out that the comparison between 35% HP and 20% HP products was performed as per manufacturer's instructions, and for this reason the 20% HP product was applied for an additional 10 minutes each session. However, even under this "improved" condition, the bleaching speed of this product was not equivalent to that of the 35% HP gel, which probably means that this additional application time was not enough to provide equivalent bleaching in the same time interval of two weeks.

In summary, the 35% HP gel tested in this study produced whiter teeth after two bleaching sessions, with TS rates similar to those produced by the 20% concentration. It is worth mentioning that this may not be true for other bleaching gel compositions.

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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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