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Evaluation of At-home Bleaching Times on Effectiveness and Sensitivity with 10% Hydrogen Peroxide: A Randomized Controlled Double-blind Clinical Trial

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Clinical Relevance

At-home dental bleaching with 10% hydrogen peroxide used for 15 minutes can be considered an alternative to the 30-minute protocol, as it achieved effective tooth whitening and caused similar tooth sensitivity.

SUMMARY

Objectives: The aim of this randomized double-blind controlled clinical trial was to evaluate different protocols for at-home use of 10% hydrogen peroxide in whitening effectiveness and tooth sensitivity.

Methods: Seventy-two patients were selected according to the inclusion and exclusion criteria, with the upper central incisors having color A2 or darker according to the Vita Classical scale (VITA Zahnfabrik, Bad Säckingen, Germany) and randomized into two groups: 10% hydrogen peroxide applied once daily for 15 minutes (HP

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15) or applied once daily for 30 minutes (HP 30). Bleaching was performed for 14 days in both groups. The color was evaluated before bleaching, during bleaching (1st and 2nd weeks), and 1 month after the bleaching treatment using the Vita Classical, Vita Bleachedguide 3D-MASTER, and Vita Easyshade spectrophotometer (VITA Zahnfabrik). Dental sensitivity was recorded by the patients using the numerical rating scale (0-4) and visual analogue scale (0-10 cm). Color data were evaluated by two-way analysis of variance (ANOVA) of repeated measures (group vs. treatment time). The Mann-Whitney test was performed to contrast the means (α=0.05). Tooth sensitivity was assessed by Fisher's exact test (p=1.00) and intensity of tooth sensitivity was evaluated by the Mann-Whitney test (α=0.05) for both scales.

Results: A significant whitening effect was observed after 2 weeks of bleaching for all color measurements (p=0.01), with no difference between HP 15 and HP 30 (p>0.05). Also, the absolute risk and intensity of tooth sensitivity were similar (47%; p>0.05).

Conclusions: The effectiveness and tooth sensitivity of at-home bleaching carried out with 10% hydrogen peroxide applied for 15 minutes or 30 minutes are similar.

INTRODUCTION

Oral aesthetics have become increasingly important for many patients in recent years. The growing interest among the populace for whitening teeth and having a harmonious smile has led to higher demand for aesthetic procedures, including tooth whitening.[1-4] There are several bleaching methods, such as whitening strips, in-office, and at-home bleaching, and the combination of these two techniques.[5]

Among these modalities, the use of 10% carbamide peroxide (CP) for at-home bleaching has become popular, and several studies have shown quite satisfactory results.[5,6] Due to the low concentrations of CP applied at home when compared to in-office bleaching, the at-home technique has several advantages, including less irritation to tissues, low cost, and shorter office time.[7] However, some authors have shown concerns regarding the extended length of time required for using at-home bleaching trays (6-8 hours), mainly because this could increase discomfort to patients[8] during sleep[9] and increase the possibility of ingesting bleaching agents.[10,11]

Due to these concerns, the original technique has undergone modifications. Changes in tray material, tray design, active ingredient concentrations, time of custom-tray use, and type of active ingredients are examples of such modifications.[9,12] One modification was the introduction of hydrogen peroxide (HP) gels for at-home bleaching. As opposed to CP gels, HP bleaching gels undergo a faster degradation rate[13-15] and therefore should be used for shorter periods of time. As pointed out by Haywood (2003), the potential additional benefit to the "simplified regimen" is that it was perceived to be the most convenient and comfortable.[16]

However, in the literature consulted, clinicians and researchers have followed different application regimens with variations mainly in the time that the gel remains in contact with the teeth. For instance, 7.5%-10% HP was recommended for 1 hour/daily or two 30-minute treatments per day,[7,17,18] as well as shorter daily regimens such as 30 minutes.[19-22] Although those studies showed the same whitening effectiveness, since a minimal 14 days of daily use was applied, a high degree of tooth sensitivity has been reported, ranging from 58% to 80%.[7,17,18,20,21]

A potential way to mitigate tooth sensitivity is to apply HP-based bleaching gel for a shorter time, mainly because HP-based gels have fast degradation kinetics. It was shown that the amount of released HP was higher in the first 10 minutes, and up to 50% of the active ingredient was released within 15 to 20 minutes.[14,15]

Therefore, the objective of this randomized, parallel, double-blind clinical trial was to evaluate if there is equivalence among the bleaching effectiveness (primary outcome) of at-home bleaching performed with 10% HP applied for 15 min (HP 15) and 30 min (HP 30). Furthermore, the absolute risk and intensity of tooth sensitivity were evaluated as secondary outcomes. The null hypothesis was that at-home bleaching using 10% HP used daily for 15 or 30 minute intervals would have significant differences regarding: 1) tooth whitening, or 2) the absolute risk, or 3) intensity of tooth sensitivity.

METHODS AND MATERIALS

The present study was prepared using the protocol established by the Consolidated Standards of Reporting Trials statement.[23]

Trial Design, Settings, and Locations of Data Collection

This was a double-blind, controlled, parallel, randomized clinical trial, in which the evaluator and statistician were blinded to the group assignment. This study was

performed from November 2016 to June 2017 at the Clinics of the School of Dentistry of the State University of Ponta Grossa, PR, Brazil.

Recruitment

Two weeks prior to the bleaching procedures, all of the volunteers—who sought treatment at the clinic of the dental school—received a dental prophylaxis with pumice and water in a rubber cup and signed an informed consent form. Recruitment was carried out by placing printed ads throughout the university.

Eligibility Criteria

Patients included in this clinical trial were at least 18 years old and had good oral and overall health. All patients underwent an exam of teeth and soft tissues, and there could be no changes such as cavities, dental wear, friction, visible cracks, gingivitis, periodontitis, or injuries. Participants were required to have six caries-free maxillary anterior teeth, with absence of any restorations or periodontal disease. The maxillary central incisors had to be shade A2 or darker, as judged by comparison with a value-oriented shade guide (Vita Classical, VITA Zahnfabrik, Bad Säckingen, Germany). Two calibrated investigators performed this evaluation, and they were required to have at least 85% agreement (Kappa statistic). The calibration process was performed before beginning the study evaluation.

Participants with prostheses, anterior restorations or dental braces, or severe internal tooth discoloration (tetracycline stains, fluorosis, and pulpless teeth) were not included in the study. Additionally, participants with any other pathology that could cause sensitivity (such as dentin exposure, recession, or the presence of visible cracks in the teeth); pregnant or breastfeeding women; smokers; people with bruxism; or participants who had previously undergone tooth-whitening procedures were also excluded.

Sample Size Calculation

The calculation of the sample size was based on the color variation (ΔE). A minimum of 58 participants was required to exclude a mean difference of 2.66 in ΔE (50%:50% acceptability threshold with a power of 90% and an alpha of 5%, considering that the standard deviation of ΔE is approximately 3.[24] To account for possible dropouts by patients, an additional 25% of the sample was added; therefore, the final calculation was 72 participants. This limit of equivalence (difference of means) was based on the fact that only an ΔE greater than 2.66 is considered clinically perceptible.

Randomization, Allocation, Concealment, and Blinding

Blocked randomization was used (block sizes of 2 and 4), and an equal allocation ratio was used to form the allocation list for the two comparison groups. The randomization list was prepared using software freely available online (www.sealedenvelope.com). Opaque, sealed, and consecutively numbered envelopes containing the identification of the groups were prepared by a third person, who was not involved in the research protocol. The envelopes were only opened immediately before the beginning of the bleaching procedure.

Participants and operators could not be blinded to the study groups, as they could easily identify the two protocols used. However, the evaluator who performed the color assessments and the statistician were blinded to the treatments. To maintain evaluator blinding, the two protocols—15 minutes (HP 15) and 30 minutes (HP 30) per day with 10% hydrogen peroxide (White Class, FGM, Joinville, SC, Brazil)—were explained to the patients by a researcher who was not an evaluator; the protocols were coded as either A or B. Only the research coordinator knew the coding system.

Study Intervention

Alginate impressions (Avagel, Dentsply, Petrópolis, Rio de Janeiro, Brazil) of each subject's maxillary arch were made, and after disinfection with 2% glutaraldehyde for 10 minutes, these impressions were filled with dental stone (Asfer, Asfer Indústria Química Ltda., São Caetano do Sul, SP, Brazil). A 0.9-mm soft vinyl material (FGM, Joinville, SC, Brazil) was used to fabricate the custom-fitted tray that would hold the whitening gel in Plastivac P7 (BioArt, São Carlos, SP, Brazil). The excess material from the labial and lingual surfaces was trimmed to 1 mm from the gingival junction.

At this time, group assignments were revealed and each patient received the bleaching tray and their respective time-of-use protocol. All participants were instructed to wear the tray with the bleaching agent for 15 or 30 minutes (according to group allocation) once a day for 14 days. The participants were also instructed to remove the tray after each bleaching period and wash it with water.

As a measure of adherence to the experimental protocol, participants were given a diary in which they were asked to take note of the number of times they used the tray during the study. If they wore the bleaching tray 14 times, this would result in a 100% adherence to the protocol. Verbal instructions about oral hygiene were also provided, encouraging participants to brush their teeth regularly with fluoridated toothpaste containing

no whitening components. There was no restriction in the diet of the volunteers.[25]

Color Evaluation

Two calibrated evaluators recorded the shade of each subject's teeth at baseline, during treatment (after the first and second week of bleaching treatment), and at one-month post-bleaching. In the event of disagreements between the examiners during shade evaluation, a consensus was reached through discussion. The color evaluation was performed using two value-oriented shade guide units: Vita Classical (VITA Zahnfabrik, Bad Säckingen, Germany)[26] and Vita Bleachedguide 3D-MASTER (VITA Zahnfabrik)[27-29] and with the aid of a spectophotometer (Easyshade, VITA Zahnfabrik).[18,26]

For color evaluation with the Vita Classical scale, the 16 tabs of the shade guide were arranged from highest (B1) to the lowest (C4) value. Although this scale is not linear in the truest sense, for the purpose of analysis, the changes were treated as though they represented a continuous and approximately linear ranking.[30] The Vita Bleachedguide 3D-MASTER contains lighter shade tabs and is already organized from highest (0M1) to lowest (5M3) value.[31,32] The measurement area of interest for shade matching was the middle third of the facial surface of the anterior central incisor.[33] Color changes were calculated from the beginning of the active phase through to the individual recall times by calculating the change in the number of shade guide units (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs.

For color evaluation with the Vita Easyshade (VITA Zahnfabrik) spectrophotometer, an impression of the maxillary arch was taken with dense silicone paste (Speedex Putty, Coltene, Rio de Janeiro, Brazil). The impression was extended to the maxillary canine and served as a standard color measurement guide for the spectrophotometer. For each dental component evaluated, a window was created on the labial surface of the molded silicone guide using a metal device with a radius of 6 mm and well-formed borders.[7,29,31] The shade was determined using the parameters of the Easyshade device whereby the following values were indicated: L*, (a*), and (b*), where L* represented the value from 0 (black) to 100 (white) and a* and b* represented the shade, where a* was the measurement along the red-green axis and b* was the measurement along the yellow-blue axis. The color comparison before and after treatment was given by differences between the two colors (ΔE), which was calculated using the formula: $\Delta E=[(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.[34] Despite the tooth color, measurements were performed for all maxillary anterior teeth (central and lateral incisors and canines); for statistical purposes, only the maxillary right central incisor was used. The measurement area of interest for shade matching was the middle third of the facial surface of the maxillary right central incisor.

Tooth Sensitivity Evaluation

All subjects were asked to keep a daily record of whether they experienced sensitivity. Each patient was asked to indicate the numerical value of the degree of sensitivity using a five-point Numeric Rating Scale (NRS) where 0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = severe.[29,35,36] The subjects were also asked to express their pain intensity using the Visual Analogue Scale 0-10 (VAS).[29,37,38] This scale is a 10-cm horizontal line with scores of 0 and 10 at each end, where 0 = no sensitivity and 10 = severe sensitivity. Patients marked a vertical line across the horizontal line of the scale that corresponded to the intensity of sensitivity. The distance in mm from the zero end was then measured with the aid of a millimeter ruler.

The worst score from the NRS scale and the highest numerical value obtained in the VAS scale during the entire bleaching treatment was considered for statistical purposes, in such a way that only a single value was taken from the two-week treatment period. The values were arranged into two categories: absolute risk of tooth sensitivity (TS), which represented the percentage of patients that reported TS at least once during treatment, and overall TS intensity.

Statistical Analysis

The analysis followed the intention-to-treat protocol and involved all participants who were randomly assigned (Figure 1).[23] In cases of missing data, the last observation was carried forward. The statistician was blinded to the study groups. The data were first analyzed using the Kolmogorov-Smirnov test to assess whether the data followed a normal distribution, as well as the Bartlett test for equality of variances to determine whether the assumption of equal variances was valid. After that, the absolute risks of bleaching-induced TS were determined using the Fisher exact test. The relative risk was calculated, as well as the confidence interval for the effect size. For comparison of TS intensity (NRS and VAS data) of the two groups, the worst score of the each group was calculated. After that, the Mann-Whitney test was applied. The color changes between groups (ΔSGU on both scales and ΔE) at each time point were compared using a Mann-Whitney U test. For the comparisons between times within each group, the Friedman test was applied. In all statistical tests, the significance level was 0.05. We performed all analyses

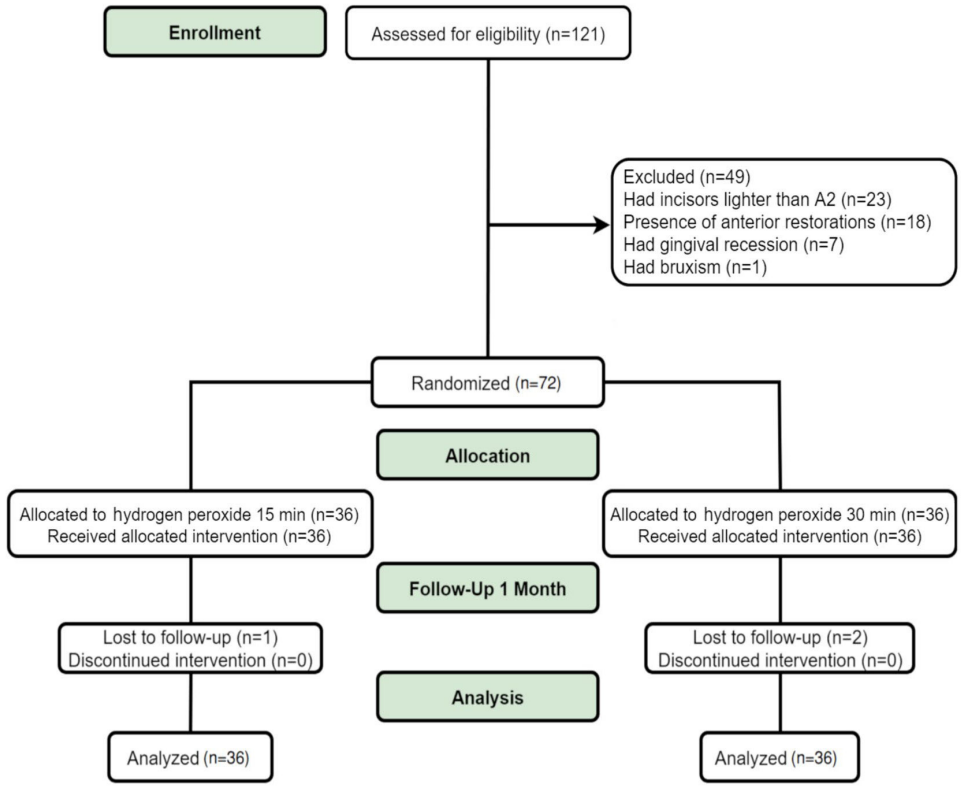

Figure 1. Flow diagram of study design phases including enrollment and allocation criteria.

by using SigmaPlot version 11.0 software (SPSS Inc, IBM, Armonk, NY, USA).

RESULTS

Characteristics of Participants

In all, 121 volunteers were evaluated for selection of the study sample, and 72 participants met the study inclusion criteria (Figure 1). The patients were randomly divided into HP 15 (n=36) and HP 30 (n=36). The mean age of all participants was similar, and the majority of participants included in the sample were female (Table 1).

Adherence to the Protocol

Adherence to the protocol was 86% for HP 15 and 78% for HP 30. Three participants did not attend the one-month recall visit—one in HP 15 and two in HP 30. For these participants, the last observation was carried forward for statistical purposes in order to maintain the intention-to-treat analysis.

Color Evaluation

Color change effectiveness of dental bleaching was verified through the mean and standard deviation of the ΔSGU using the subjective (Vita Classical and Vita Bleachedguide 3D-MASTER, VITA Zahnfabrik)

Table 1: *Demographic Characteristics of the Participants*

	HP 15 (n=36)	**HP 30 (n=36)**
Baseline color (SGU; mean ± SD)	6.1 ± 1.6	5.4 ± 1.0
Age (years; mean ± SD)	20.9 ± 3.0	22.8 ± 6.4
Gender (female; %)	78	58

Abbreviations: HP 15, hydrogen peroxide 15-minute protocol; HP 30, hydrogen peroxide 30-minute protocol; SD, standard deviation; SGU, shade guide unit measured by Vita Classical.

and objective (spectrophotometer) scales, and through the ΔE values (Table 2) in the different evaluation periods (p<0.05). Whitening of approximately 3.3 to 4.8 ΔSGU (Vita Classical) and 3.9 to 6.9 ΔSGU (Vita Bleachedguide), and ΔE of approximately 6.6 to 9.0 were detected for both groups at one month after bleaching (Table 2). Although a significant whitening effect was observed after only two weeks of bleaching (p=0.01), no statistically significant difference was observed between the study groups at the different periods (p>0.06). For all color measurements, the mean difference ranged from -0.6 to 1.0 and was not clinically important (Table 2).

Tooth Sensitivity

There was no significant difference in tooth sensitivity between the groups evaluated (p=1.00) (Table 3). Hydrogen peroxide 10% applied for either 15 or 30 minutes per day produced a 47% risk of tooth sensitivity. Regarding the intensity of dental sensitivity (Table 3), there were no significant differences between the two groups analyzed with the two pain scales used for this study (Table 4; p>0.36).

DISCUSSION

According to the results of the present study, the 10% HP-based bleaching gel applied for 15 or 30 minutes per day showed a significant whitening effect after two weeks. This is a noteworthy result, mainly because an application time as short as 15 minutes was enough to produce highly effective whitening.

Several manufacturers have launched HP-based gels on the market, due to the lengthy tray-wearing time of CP-based gel during at-home bleaching. The idea is that HP should bring about faster results than CP. This could occur during short active bleaching sessions, because unlike an HP-based gel, a CP-based gel first needs to break down into hydrogen peroxide and urea upon exposure to conditions of moisture before achieving the whitening effect.[17,19,39] The fast kinetics of degradation of HP when compared to CP seems to confirm this statement.[14,40]

However, as oxidization of an organic substance involves a series of consecutive steps and takes time to occur, there may be a limit as to how rapidly a chemical substance is released in HP-based gels. Therefore, part of the substance released from the

Table 2: *Color Change in Shade Guide Units (ΔSGU) and ΔE at Different Bleaching Periods for the 2 Bleaching Protocols Along with the Effect Size (95% Confidence Interval)*

	Periods	HP 15[a]	HP 30[a]	Mean Difference (95% CI)	p-value[b]
ΔSGU (Vita Classical)	After 1 week	3.3 ± 1.0 A	3.6 ± 1.0 A	-0.03 (-0.77 to 0.17)	0.09
	After 2 weeks	4.2 ± 1.3 B	4.8 ± 1.3 B	-0.06 (-1.21 to 0.01)	0.06
	After 1 month post bleaching	4.2 ± 0.8 B	4.7 ± 1.4 B	-0.05 (-1.04 to 0.04)	0.06
ΔSGU (Vita Bleachedguide)	After 1 week	3.9 ± 1.5 A	4.1 ± 1.8 A	-0.02 (-0.98 to 0.58)	0.72
	After 2 weeks	6.8 ± 2.5 B	6.9 ± 1.6 B	-0.01 (-1.09 to 0.89)	0.87
	After 1 month post bleaching	6.8 ± 2.5 B	6.8 ± 1.6 B	0.0 (-0.99 to 0.99)	0.97
ΔE (Vita Easyshade)	After 1 week	6.6 ± 3.8 A	7.2 ± 3.7 A	-0.6 (-2.36 to 1.16)	0.40
	After 2 weeks	7.9 ± 3.8 AB	8.4 ± 3.7 B	-0.5 (-2.26 to 1.26)	0.53
	After 1 month post bleaching	9.0 ± 3.8 B	8.0 ± 3.2 B	1 (-0.65 to 2.65)	0.28

Abbreviations: CI, confidence interval; HP 15, hydrogen peroxide 15-minute protocol; HP 30, hydrogen peroxide 30-minute protocol; SGU, shade guide unit.

[a] *Color change for different periods and evaluation methods. Means identified with the same capital letter are statistically similar values (Friedman test;* p>*0.05).*

[b] *For color change evaluation of different groups in each period (Mann-Whitney test;* p>*0.05).*

Table 3: *Comparison of the Number of Patients Who Experienced Tooth Sensitivity During the Bleaching Regimen in Both Groups Along with Absolute and Risk Ratio*

Treatment	Tooth Sensitivity (Number of Participants)		Absolute Risk (95% CI)	Risk Ratio (95% CI)
	Yes	No		
HP 15	17	19	47.2 (31.9-62.9)	1.0 (0.61-1.62)
HP 30	17	19	47.2 (31.9-62.9)	

Abbreviations: CI, confidence interval; HP 15, hydrogen peroxide 15-minute protocol; HP 30, hydrogen peroxide 30-minute protocol.
**Fisher exact test (p=1.00).*

HP-based gels may not even have time to contact the organic substance of the teeth, thereby decreasing the whitening effect.[41]

A recent systematic review of clinical studies showed that, even when HP-based products were used for a shorter period of time compared to CP-based gels, both at similar concentrations, there were no significant color changes in the shade guide units, with an equivalent level of gingival irritation and tooth sensitivity when comparing CP-based to HP-based gels for at-home bleaching.[41,42]

In this study, the HP 15 and HP 30 groups showed a significant whitening effect of approximately 4.2 to 6.8 shade guide units for different scales, and the ΔE varied by approximately 8 to 9 units, which corroborates with the findings of previous studies that applied more highly concentrated HP in at-home bleaching.[7,20,21,43] For example, in the study by Cordeiro and others[21] who evaluated the 10% HP wearing 30 minutes a day, a significant whitening effect of approximately 3 to 7 shade guide units for different scales was observed, as well as a whitening effect of 7 to 10 units of ΔE. Also, Chemin and others[7] evaluated a 10% HP applied twice a day for 30 minutes, and approximately 4 units on the Vita Classical scale and 6 units of Vita BleachedGuide were observed. When a color was measured with a spectrophotometer, an approximate ΔE 8 was observed, a significant whitening effect.

These results lead us to accept the first null hypothesis. It is worth noting that, even when applied for 15 minutes, 10% HP showed clinically important whitening when evaluated with the three instruments used for color evaluation. It is noteworthy that more than one color evaluation was performed, in order to provide data that can be compared with different clinical studies.

Regarding tooth sensitivity, HP has a low molecular mass, which is associated with its fast kinetics of degradation,[14,40] and helps it to diffuse rapidly into tooth substrates and reach the pulp chamber; it has already been observed that HP was found inside the pulp chamber after 5 minutes.[44,45] These factors may be responsible for the tooth sensitivity reported by most patients who have undergone bleaching procedures.[12] Considering that irritation to the pulp cells is proportional to the HP concentration used,[44,46] one would expect a lower tooth sensitivity in the HP 15 group compared to the HP 30 group. However, no significant differences were observed for either group, leading us to accept the second and third null hypotheses.

Actually, the risk of tooth sensitivity in this study was around 47% in both groups, a lower percentage

Table 4: *Means (Standard Deviations) and Medians (Interquartile Range) of Worst Score of the Tooth Sensitivy Intensity Using the NRS and VAS Scales*

Pain Scales	Means and Standard Deviations		*p*-value[a]	Medians and Interquartile Range		*p*-value[a]
	HP 15	HP 30		HP 15	HP 30	
NRS	0.7 ± 2.8	0.6 ± 0.7	0.55	0 (0–1)	0 (0–1)	0.78
VAS	0.9 ± 4.1	0.6 ± 0.3	0.36	0.1 (0–1.5)	0 (0–1.1)	0.54

Abbreviations: HP 15, hydrogen peroxide 15-minute protocol; HP 30, hydrogen peroxide 30-minute protocol; NRS, numerical rating scale; VAS, visual analogue scale.
[a] For each pain scale, the comparison was performed to different groups (Mann-Whitney test).

than that observed in clinical studies in which 10% HP was evaluated.[7,17,18] For instance, de La Pena[18] showed 58.3% tooth sensitivity and Chemin[7] indicates that the use of 10% HP causes around 80% tooth sensitivity. Nevertheless, a closer view regarding these studies showed that both of them applied HP once daily for one hour or twice daily for 30 minutes,[7,17,18] in comparison to the 15- or 30-minute applications in the present study. Therefore, it was assumed that the lower percentage of patients with tooth sensitivity, and the lower intensity thereof, in the present study is due to the shorter application time evaluated.

Also, when 10% HP-based gels are applied, gingival irritation is a very common finding.[21,22,39] This may occur because the 10% HP could react with soft tissue and cause injuries such gingival irritation and burning.[47] In contrast, none of the patients reported any problems related to gingival irritation in the present study (no data shown). Once again, the short application time of HP could justify the results herein.

The results of the present study show that application times as short as 15 minutes a day were enough to produce effective whitening, with a low number of adverse effects reported. This has an important clinical implication, as it reduces the total wearing time, favoring those patients who do not want to wear the bleaching tray for prolonged periods of time. However, only a one-month trial was performed. As color stability is considered a problem when bleaching gels are applied for short periods of time,[48] long-term follow-up should be performed in order to confirm the results of the present study.

CONCLUSION

The use of 10% hydrogen peroxide for 15 and 30 minutes daily is equally effective after two weeks of at-home tooth whitening, and produces equivalent absolute risk and intensity of tooth sensitivity.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the human subjects oversight committee guidelines and policies of the State University of Ponta Grossa. The approval code issues for this study is 1.958.304.

Conflict of Interest

The authors 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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