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The Effect of Perioperative Ibuprofen Use on Tooth Sensitivity Caused by In-Office Bleaching

E Paula • S Kossatz • D Fernandes
A Loguercio • A Reis

Clinical Relevance

The anti-inflammatory drug ibuprofen reduced the intensity of tooth sensitivity up to one hour after in-office bleaching treatment.

SUMMARY

Objective: This study determined the effect of the administration of perioperative ibuprofen 400 mg on tooth sensitivity caused by in-office bleaching.

Methods: A triple-blind, parallel-design, randomized clinical trial was conducted on 30 adults who received placebo or ibuprofen before and after bleaching. The drugs were administered three times per day for 48 hours; the first dose was given one hour prior to the bleaching treatment. Two bleaching sessions with 35% hydrogen peroxide gel were performed with a one-week interval. Tooth sensitivity was recorded on two scales: visual analogue and five-point verbal rating scale up to 48 hours after bleaching. The shade evaluation was performed with a visual shade guide and spectrophotometer, before and 30 days after bleaching. The absolute risk of tooth sensitivity and its intensity were evaluated by Fisher exact and Mann-Whitney tests, respectively. The shade changes were evaluated by Student's t-test.

Results: Both groups showed similar absolute risk of tooth sensitivity ($p>0.05$). Lower tooth sensitivity was observed in the experimental group only up to one hour postbleaching ($p=0.04$). Similar tooth sensitivity was observed in the other periods of time.

Conclusion: The perioperative use of the anti-inflammatory ibuprofen was not able to avoid tooth sensitivity but reduced its intensity up to one hour after bleaching.

Eloisa Andrade de Paula, DDS, MS, Universidade Estadual de Ponta Grossa, Restorative Dentistry, Ponta Grossa, Brazil

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

Daniel Fernandes, MS, PhD, Pontra Grossa, Brazil

Alessandro Loguercio, DS, MS, PhD, Universidade Estadual de Ponta Grossa, Restorative Dentistry, Ponta Grossa, Brazil

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

The desire for whiter teeth has made tooth bleaching one of the most sought-after cosmetic procedures in dentistry. Available bleaching modalities include dentist-prescribed at-home bleaching and dentist-supervised in-office bleaching.[1] Even though the at-home bleaching system is the most frequently recommended treatment for vital teeth, some patients do not want to use a bleaching tray or do not want to wait two to three weeks to see the results of the treatment.[2] Thus, another bleaching option, the in-office bleaching procedure, is often requested.

However, the in-office procedure using 35% hydrogen peroxide has a long history of tooth sensitivity and gingival irritation.[2,3] Incidence levels of tooth sensitivity have been reported to be as high as 87%,[4-6] which seems to result from the easy passage of the peroxide through the enamel and dentin to the pulp,[7] causing pulpal damage with inflammation.[8] Pulp tissue damage caused by dental bleaching is likely to lead to the release of cell-derived factors, such as adenosine triphosphate[9] and prostaglandins, which excite or sensitize pulpal nociceptors.[10]

The use of desensitizing agents such as fluorides and potassium nitrate before or after bleaching was capable of reducing the experience of tooth sensitivity during the bleaching treatment.[2,5,11,12] However, this approach adds another step to the bleaching protocol, which is against the clinicians' preference for simplification. Another approach recently investigated was the preoperative use of ibuprofen,[13] which is a nonsteroidal anti-inflammatory drug capable of blocking the cyclooxygenase (COX) pathway.[14] Although this clinical alternative seemed promising, the preoperative use of a single dose of ibuprofen 400 mg before the in-office bleaching protocol was shown to reduce tooth sensitivity only during but not after the treatment period.[13] As mentioned by the authors of the previous study,[13] the half-life elimination of ibuprofen is two to four hours, and thus, more than one dose may be required to keep the ibuprofen serum level sufficiently high for optimum analgesic effect.

Therefore, the current study tested the primary hypothesis that the preventive and perioperative use of ibuprofen 400 mg for 48 hours, starting one hour before the bleaching session, would reduce the absolute risk of tooth sensitivity. A secondary hypothesis tested was that the use of this anti-inflammatory drug would reduce the intensity of sensitivity without affecting the bleaching efficacy and shade change.

MATERIALS AND METHODS

This clinical investigation was approved (protocol No. 17836/2010) by the scientific review committee and the committee for the protection of human subjects of the local university. The experimental design followed the Consolidated Standards of Reporting Trials statement.[15] Based on preestablished criteria, 30 volunteers from the city of Guarapuava, Paraná, Brazil were selected for this study and signed a term of free and informed consent to participate. Two weeks before the bleaching procedures, all the volunteers received a dental screening and dental prophylaxis using a rubber cup with pumice and water slurry.

Study Design

This was a randomized, placebo-controlled, triple-blind, parallel-group clinical trial, with an equal allocation rate to receive one of two treatments. The study took place in the clinic of the Brazilian Association of Dentistry in Guarapuava, Paraná, from January 2011 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 radio and television advertisement. A total of 247 participants were examined, in a dental chair, to check if they met the inclusion and exclusion criteria (Figure 1). The participants should have at least eight maxillary and mandibular anterior teeth that were caries free and without restorations on the labial surfaces. The central incisors were C2 or darker as judged by comparison with a value-oriented shade guide (Vita Lumin, Vita Zahnfabrik, Bad Säckingen, Germany). Participants who had undergone tooth-whitening procedures, had preexisting anterior restorations, were pregnant/lactating, had severe internal tooth discoloration (tetracycline stains, fluorosis or pulpless teeth), had bruxism habits, or had any other pathology that could cause sensitivity (such as recession or dentin exposure) were excluded from this study to minimize confounding experimental variables or side effects from bleaching. Participants who reported a history of health problems in the stomach, heart, kidney, or liver or participants using any continuous drug with anti-inflammatory and antioxidant action were also excluded from the study.

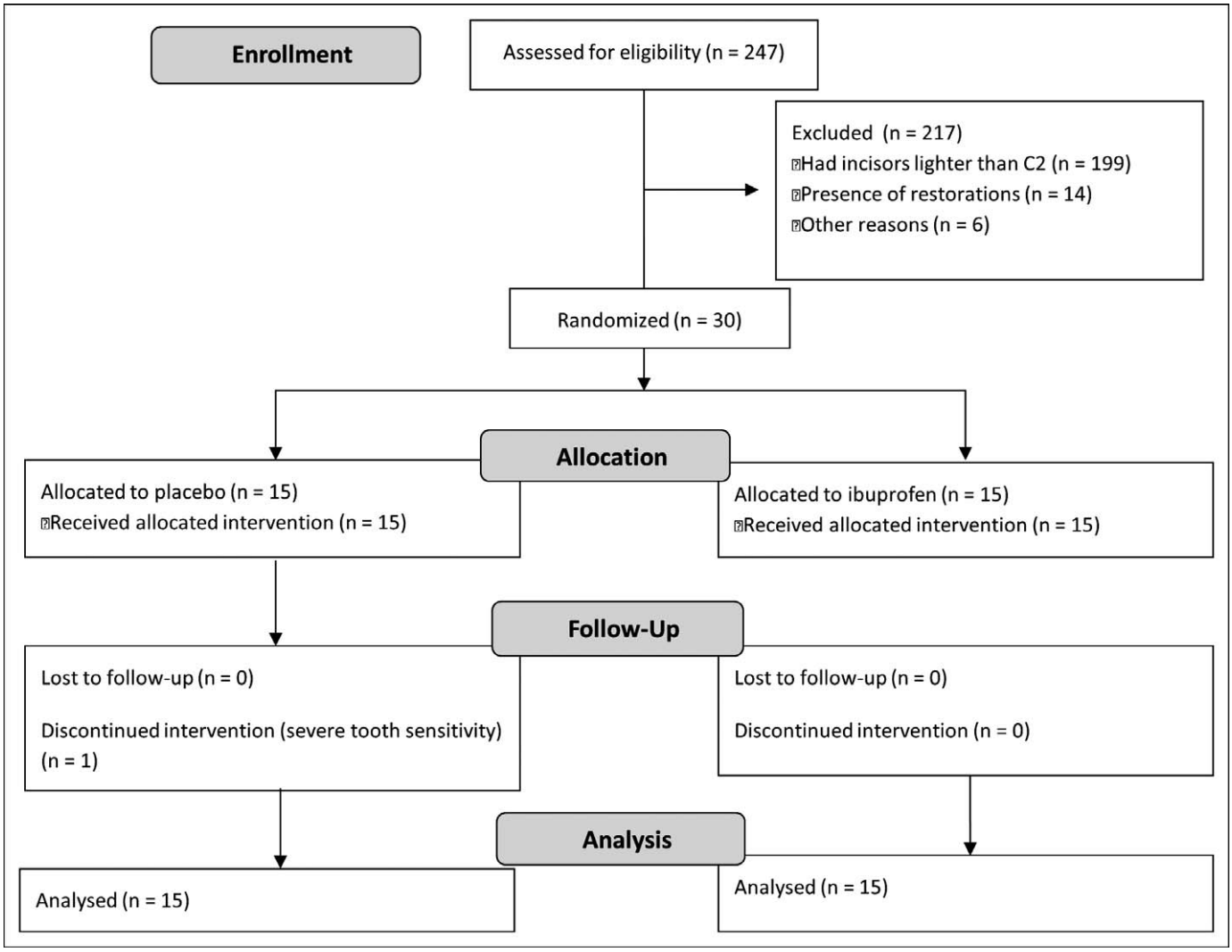

Figure 1. *Flow diagram of the clinical trial including detailed information on the excluded participant.*

Sample Size Calculation

The primary outcome of this study was the absolute risk of tooth sensitivity. This risk was reported to be approximately 87% for the bleaching product Whiteness HP Maxx (FGM, Joinville, SC, Brazil).[4] Thus, 30 patients were required to have an 80% chance of detecting, as significant at the two-sided 5% level, a decrease in the primary outcome measure from 87% in the control group to 41% in the experimental group.

Study Intervention

Participants were randomly stratified by sex into the placebo and ibuprofen groups. The randomization process was performed by computer-generated tables by a third person not involved in the research protocol. Details of the allocated groups were recorded on cards contained in sequentially numbered, opaque, sealed envelopes. These cards 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 completed all baseline assessments, the allocation assignment was revealed by opening this envelope by this third person. Neither the participant nor the operator knew the group allocation, with both being blinded to the protocol.

The participants from the placebo group received a placebo (Talco pharma S M-200 Henrifarma Prod Quím Farm LTD, São Paulo, SP, Brazil), and participants from the ibuprofen group received a dose of nonsteroidal anti-inflammatory ibuprofen 400 mg (Uniprofen, União Quím Farm Nacional S/A, Embu-Guaçu, SP, Brazil). All participants were

watched to ensure that they took the drugs or placebo one hour prior to treatment. Other doses of placebo or ibuprofen (400 mg) were administered every eight hours after the first dose during a period of 48 hours. When it was time for the participants to take the other doses of medicine and placebo, the research assistant called all patients to remind them to take the drugs. This procedure was done to increase adherence to the protocol.

The gingival tissue of the teeth to be bleached was isolated from the bleaching agent using a light-polymerized resin dam (Top Dam, FGM, Joinville, SC, Brazil). The 35% hydrogen peroxide gel (Whiteness HP Maxx, FGM) was used in three 15-minute applications for both groups following the manufacturer's directions. The in-office bleaching agent was refreshed every 15 minutes during the 45-minute application period. Two bleaching sessions, with a one-week interval, were performed on each patient. All participants were instructed to brush their teeth at least three times a day using fluoridated toothpaste (Sorriso Fresh, Colgate-Palmolive, São Paulo, SP, Brazil).

Shade Evaluation

Shade evaluation was recorded before and 30 days after the bleaching treatment using two methods: the subjective evaluation using a shade guide (Vita Lumin, Vita Zahnfabrik) and an objective evaluation using the spectrophotometer (Easyshade, Vident, Brea, CA).

For the subjective examination, the 16 shade guide tabs were arranged from highest (B1) to lowest (C4) value, making the minimum qualifying shade C2 as number 7 (seventh tab on the value-ordered arrangement). 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. The measurement area of interest for shade matching was the middle one third of the facial surface of the anterior central incisor. For calibration purposes, five patients who were not included in the sample because they were used in the pilot study participated in the training phase of this study. The two examiners, blinded to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at baseline and 30 days after the procedure. The two examiners were required to have an agreement of at least 85% (Kappa statistics) before beginning the study evaluation.[5] The shade comparison before and after treatment is given by the difference between the baseline and 30-day shades (ΔSGU).

For the objective evaluation, a preliminary impression of the maxillary arch was made using dense silicone Adsil (Vigodent S/A Ind Com, Rio de Janeiro, RJ, Brazil). The impression was extended to the maxillary canine and served as a standard shade measurement guide for the spectrophotometer. A window was created on the labial surface of the molded silicone guide for the central incisor to be evaluated. The window was made using a metal device with well-formed borders and radius of 3 mm.[3,16] The measurement was made by only one operator, in all 30 patients, using Vita Easyshade (Easyshade, Vident) before and 30 days after the bleaching therapy. The shade was determined using the parameters of the Easyshade device, which indicated the following values: L*, a* and b*, in which L* represents the value from 0 (black) to 100 (white) and a* and b* represent the shade, where a* is the measurement along the red-green axis and b* is the measurement along the yellow-blue axis. The shade comparison before and after treatment is given by the differences between the two shades (ΔE),[3,16] which is calculated using the formula $\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.

Tooth Sensitivity Evaluation

The patients recorded their perception of tooth sensitivity during the first and second bleaching sessions using two pain scales. A five-point verbal rating scale (0 = *none*, 1 = *mild*, 2 = *moderate*, 3 = *considerable*, and 4 = *severe*)[4,5] and a visual analog scale[17-19] (using a 10-cm horizontal line with words *no pain* at one end and *worst pain* at the opposite end) were used in this study. The subjects were asked to record whether they experienced sensitivity during the treatment up to one hour after the bleaching, from one hour to 24 hours and from 24 hours to 48 hours after bleaching, individually, for both maxillary and mandibular arches. As two bleaching sessions were performed, the worst score/numerical value obtained in both bleaching sessions was considered for statistical purposes. The values were arranged into two categories: overall percentage of patients who reported tooth sensitivity at least once during treatment, regardless of the assessment point (absolute risk of tooth sensitivity), and tooth sensitivity intensity at each of the assessment points. These values were computed for both the maxillary and mandibular arches.

Table 1: *Comparison of the Number of Patients Who Experienced Tooth Sensitivity on the Maxillary and Mandibular Arches During the Bleaching Regimen in Both Groups Along With Absolute and Relative Risks*[a]

Treatment	Maxillary Arch				Mandibular Arch			
	Tooth Sensitivity (No. of Participants)		Absolute Risk (95% CI)	Relative Risk (95% CI)	Tooth Sensitivity (No. Participants)		Absolute Risk (95% CI)	Relative Risk (95% CI)
	Yes	No			Yes	No		
Placebo	12	3	80 (55-93)	0.92 (0.67-1.3)	14	1	93 (70-98)	1.16 (0.87-1.6)
Ibuprofen	13	2	87 (62-96)		12	3	80 (54-93)	

[a] *Fisher test,* p=*1.0 for maxilla and* p=*0.59 for mandibular arches.*

Statistical Analysis

The analysis followed the intention-to-treat protocol and involved all participants who were randomly assigned.[15] The statistician was blinded to the study groups. The agreement between examiners' objective evaluation was evaluated using the kappa statistics. The primary outcome of absolute risk of tooth sensitivity was compared using Fisher exact test (α=5%). The relative risk and the confidence interval for the effect size were calculated.

Tooth sensitivity intensity (secondary outcome) was also statistically analyzed. The mean/median and standard deviation/interquartile range of the two pain scales were calculated. The data sets of tooth sensitivity intensity were plotted on histograms and inspected for normal distributions. Some data did not appear to be normally distributed. Therefore, nonparametric statistical tests were used to compare the various treatments. Statistical analyses of two pain scales comparing the two groups at the three different assessment points were performed using the Mann-Whitney U test. Comparisons between times within each group were performed using the Friedman tests. In all statistical tests, the significance level was 5%.

The data from the placebo group were used to compare the absolute risk of tooth sensitivity and its intensity between the maxillary and mandibular arches. For the former, Fisher exact test at a level of 5% was used. For the latter, the Mann-Whitney U-test was used at the same level of significance.

Color change, another secondary endpoint, was used to assess the efficacy of the bleaching treatment associated with the perioperative use of ibuprofen. The ΔSGU, ΔL, Δa, Δb, and ΔE values of both groups were evaluated by Student *t*-test. In all statistical tests, the significance level was set at alpha of 5%.

RESULTS

The mean age (years) of the participants in this study was similar between the groups (placebo: 26.4 $\pm$ 6.8, and ibuprofen: 32.9 $\pm$ 9.9 years). Fifty-three and 33% of the participants from the placebo and ibuprofen groups were male. Figure 1 depicts the participant flow diagram in the different phases of the study design.

Tooth Sensitivity

The data from 30 patients were used in this study, following the intention-to-treat analysis. In regard to the absolute risk of tooth sensitivity (primary outcome), no significant difference was observed between groups, as seen in Table 1 (p=1.00 for maxilla and p=0.59 for mandibular arches). The relative risk, along with the 95% confidence interval, is also evidence that the use of the experimental drug had no effect on the tooth sensitivity reduction.

In the comparison between the dental arches, no significant difference was detected for both groups, with regard to the absolute risk of tooth sensitivity ($p>0.05$) and tooth intensity ($p>0.05$).

Most of the tooth sensitivity complaints occurred within the first 24 hours ($p<0.001$), and none of the participants experienced pain after 24 hours. When using the visual analogue scale, the tooth sensitivity intensity (Table 2) was less intense for ibuprofen than the placebo group in both arches only up to one hour (p=0.04 for maxillary and p=0.008 for mandibular arches). This was also observed for the five-point verbal rating scale in the mandibular arch (p=0.006), but not in the maxillary arch, which showed no statistical difference between groups (p=0.06).

Significant whitening was observed in both study groups by means of the subjective and objective evaluation methods ($p<0.001$). Whitening of approximately 5.3 and 4.3 shade guide units was detected for placebo and ibuprofen groups, respectively (Table 3), and a variation of 7.8 to 5.9 in the ΔE was observed for the placebo and ibuprofen groups, respectively. The results of the subjective (visual shade guide) and the objective evaluation (spectro-

Table 2: *Comparison of Tooth Sensitivity Intensity Experienced on the Maxillary and Mandibular Anterior Teeth by Patients From the Treatment Groups at Different Assessment Points Using the Pain Scales*[a]

	Five-Point Verbal Rating Scale (0-4)[b]				Visual Analog Scale (0-10)[c]			
	Maxillary Arch		Mandibular Arch		Maxillary Arch		Mandibular Arch	
	Placebo	Ibuprofen	Placebo	Ibuprofen	Placebo	Ibuprofen	Placebo	Ibuprofen
Up to 1 hour	2 (1/3)^{aA}	1 (0/2)^{aA}	3 (1/4)^{aA}	1 (0/2)^{bA}	3.3 ± 2.9^{aA}	1.5 ± 2.0^{bA}	4.3 ± 3.6^{aA}	1.5 ± 2.4^{bA}
1 hour to 24 hours	2 (0/2)^{aB}	2 (1/3)^{aA}	2 (0/3)^{aB}	2 (1/3)^{aB}	2.4 ± 2.7^{aB}	3.0 ± 2.8^{aB}	3.7 ± 3.6^{aA}	3.2 ± 3.0^{aB}
24 hours to 48 hours	0 (0/0)^{aC}	0 (0/0)^{aB}	0 (0/0)^{aC}	0 (0/0)^{aC}	0.0 ± 0.0^{aC}	0.0 ± 0.0^{aC}	0.0 ± 0.0^{aB}	0.0 ± 0.0^{aC}

[a] *Comparisons are valid only within the same pain scale. At each period, the two treatments were compared with the Mann-Whitney U-test, and differences are represented by different superscript lowercase letters. For each treatment, the three periods were compared with the Friedman test (α=0.05), and differences are represented by different superscript uppercase letters.*
[b] *Medians (first/third interquartile) values.*
[c] *Means and standard deviations.*

photometer) matched the hypothesis of equality between the groups after bleaching ($p \approx 0.6$ for both methods).

DISCUSSION

It has been reported that tooth-whitening solution applied to human mandibular incisors was shown to cause structural damage to the pulp, such as disruption of the odontoblast layer and the production of inflammatory infiltrates.[8] Tissue damage triggers the creation of bradykinin[20] and prostaglandins.[21,22] Each of these compounds either activates or sensitizes nociceptors and causes pain.[20,21]

The category of prostaglandins, which has been known to play a critical role in the pathogenesis of pulpal disease, involves the COX pathway. There are at least two variants of COX, the COX-1, which is involved in physiological functions and inducible COX-2, which is believed to be involved in the inflammatory response[14] and has been responsible for the production of prostaglandins mediating inflammation and pain due to pulp inflammation.[21]

Table 3: *Change Between Baseline and 30-Day Assessment (Means and Standard Deviations) for ΔSGU, ΔL, Δa, Δb, and ΔE for the Two Treatment Groups*[a] *for the Maxillary Arch*

	Placebo	Ibuprofen
Subjective evaluation (delta visual shade guide)		
Δ shade guide units	5.3 ± 1.9 A	4.3 ± 2.7 A
Objective evaluation (spectrophotometer)		
CIELab		
ΔL	2.2 ± 1.6 A	0.7 ± 4.4 A
Δa	−1.3 ± 1.4 A	−0.7 ± 0.8 A
Δb	−7.0 ± 3.2 A	−3.9 ± 1.6 B
ΔE	7.8 ± 3.3 A	5.9 ± 2.1 A

[a] *Comparisons are valid only within rows. Similar uppercase letters indicate statistically similar means (Student t-test, α=0.05).*

Ibuprofen is a nonsteroidal anti-inflammatory drug, and its mechanism of action results from acetylating the COX enzyme, which in turn inhibits the synthesis of prostaglandins.[22] However, contrary to one's previous expectation, the use of a nonsteroidal anti-inflammatory drug (ibuprofen 400 mg) in a preventive approach was not capable of avoiding the tooth sensitivity arising from bleaching. The lack of efficacy of ibuprofen in preventing tooth sensitivity could be that several other inflammatory mediators,[22] apart from COX-1 and COX-2, are probably involved in the inflammatory reaction in the pulp tissue that leads to pain and symptoms of neurogenic inflammation.

For instance, bradykinin[20] and substance-P have long been known to be involved in the process of pulp pain and inflammation.[23] Unfortunately, ibuprofen cannot prevent the production of these mediators. If many mediators act synergistically to produce both pain and inflammatory reaction after bleaching, an anti-inflammatory drug that inhibits several initial inflammatory events, such as the glucocorticoids,[24] may be more effective in reducing tooth sensitivity arising from bleaching. Chrousos and others[25] reported that some side effects have been reported with short-term oral glucocorticoid therapy such as insomnia, mild mood changes, stomach upset, facial flushing, and weight gain; however, these events are not often observed when glucocorticoid therapy is performed in young, healthy adults, and it is considered a relatively safe procedure. This strategy should be a focus of future clinical investigations that attempt to reduce tooth sensitivity caused by bleaching.

Dental pulp is densely innervated with sensory afferents with conduction velocities in the A"β, Aδ, and C-fiber range.[26] Thus, hydrogen peroxide may cause direct cellular damage to nerve cells via free radicals and other reactive oxygen species[27] produc-

ing lipid peroxidation of membrane protein and nucleic acid oxidation.[28,29] If this is the cause of tooth sensitivity, the use of an anti-inflammatory drug, such the one investigated in the present study, would not reduce the pain experience.

It is worth mentioning, however, that the intensity of tooth sensitivity in the ibuprofen group was lower during the first hour after bleaching in the present investigation, similar to the findings observed in the study by Charakorn and others.[13] This means that this medicine can be used to reduce the intensity of tooth sensitivity only during and immediately after the bleaching session.

However, no significant difference between groups was observed in the following assessment points. In Charakorn and others' study,[13] this finding was explained by the decreasing amount of ibuprofen in patients' serum as time passes. However, the results of the present investigation do not support this hypothesis since ibuprofen was administered in six doses during a period of 48 hours after bleaching and not in a single dose, as in Charakorn and others' study.[13] This finding suggests that the prostaglandins produced by COX[14] probably occur in the first hours after bleaching. As time goes by, other inflammatory mediators, not inhibited by the ibuprofen, may be expressed and trigger the tooth sensitivity.

Costa and others[8] in a histological pulp evaluation after bleaching, showed notable damage to the pulp tissue of mandibular incisors but not premolars. In a literature review, Haywood[30] reported that tooth sensitivity from bleaching usually affects the smaller teeth, such as the maxillary lateral incisors and the mandibular incisors, although the present clinical study found no significant difference in tooth sensitivity intensity or in the absolute risk of tooth sensitivity between dental arches; in other words, the tooth sensitivity may be related to the thickness of the hard dental tissues rather than to the arch itself. Further studies should be conducted to identify the most painful teeth and follow up their vitality in the long run after bleaching, suggesting that tooth sensitivity intensity may be a reliable signal of significant changes in the pulp tissue.

With regard to the bleaching outcome, the results of this study indicated that both groups demonstrated equivalent and significant tooth shade enhancement when compared with baseline values (Table 3). It is difficult to make a comparison of shade change after in-office bleaching with studies in the existing literature, because of the different methods of measurement (shade guides and spectrophotometer) and different units of measurement (CIELab system, shade guide units, etc) used. However, studies that used 35% hydrogen peroxide and reported their results in shade guide units usually observed an overall shade change of five to eight shade guide units after two bleaching sessions,[4,5,6] which is in agreement with the results of the present investigation.

Finally, one could not ignore that the small sample size of this study is a clear limitation of the present study. The study was designed to find a high effect size, that is, reduction in 50% of the tooth sensitivity among participants in the experimental group. Thus, it can be concluded that an effect as large as this was not observed, but one cannot rule out the fact that smaller effect sizes do exist. Conducting the same experimental design using larger sample sizes should be encouraged to rule out this hypothesis. Moreover, the selected sample was mainly composed of young participants, which also limits the ability to generalize for older adults.

CONCLUSION

The perioperative use of ibuprofen 400 mg for a period of 48 hours, starting one hour before in-office bleaching treatment, does not reduce the absolute risk of tooth sensitivity but may reduce the tooth intensity up to one hour after the bleaching session without jeopardizing the whitening effect.

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