Brazilian Dental Journal (2019) 30(5): 498-504
http://dx.doi.org/10.1590/0103-6440201902762

ISSN 0103-6440

Preemptive Use of Piroxicam on Tooth Sensitivity Caused By In-Office Bleaching: A Randomized Clinical Trial

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This clinical trial evaluated the effect of preemptive use of the non-steroidal anti-inflammatory drug piroxicam in a single dose 30 min prior to in-office bleaching on the prevention of tooth sensitivity (TS) reported by patients. Fifty patients were submitted to two sessions of in-office tooth bleaching with 35% hydrogen peroxide used for 2 sessions, each consisting of a single 45-min application, with an interval of 7 days between session. Thirty minutes prior to the procedure, the patient randomly received a single dose of piroxicam (200 mg) or placebo in a double-blind, randomized, crossover design. The TS was evaluated using verbal rate (VRS) and visual analog (VAS) scales during the bleaching procedure and at 24 h after each session. The color changes were assessed by the Vita Bleachedguide scale 1 week after each bleaching session. Risk of TS was calculated from the VRS and analyzed by the McNemar test, while the level of TS was analyzed by the Mann-Whitney test. For the VAS, t-tests were used to compare data from the treatments at each assessment time. Data regarding color changes were subjected to Wilcoxon and Mann-Whitney tests (α=0.05). The preemptive administration of piroxicam did not affect the risk and level of TS compared to placebo, irrespective of the assessment time. The treatment sequence did not affect bleaching effectiveness. In conclusion, the administration of a single dose of piroxicam prior to in-office tooth bleaching was unable to significantly reduce the risk and level of TS.

Key Words: anti-inflammatory agents, hydrogen peroxide, tooth bleaching, tooth sensitivity.

Introduction

Tooth bleaching is a conservative approach commonly used to solve patients' concerns regarding tooth discoloration and is highly effective in obtaining the required tooth color, irrespective of the technique chosen. Despite the fact that at-home techniques are widespread and accepted by patients, mainly due to the reduced cost, in-office tooth bleaching remains largely performed in those patients who prefer not to use bleaching trays or present any contraindications for using at-home techniques (such as those with gastrointestinal disorders) (1,2). Despite the high success rate of bleaching protocols, the inflammatory process caused by the penetration of peroxide into the pulpal chamber yields tooth sensitivity (3), which has been reported by approximately 63% of patients who have undergone in-office bleaching (4).

The bleaching effects result from the oxidation of organic structures from tooth hard tissues caused by hydrogen peroxide and its sub-products (5). Due to a reduced, low molecular weight, these oxidizing agents can reach the pulpal chamber, causing oxidative stress and damage in the pulpal cells (6). The inflammatory response of pulpal tissue is mediated by the release of chemical mediators such as adenosine triphosphate and prostaglandins, which excite the pulp nociceptors (3). Clinically, this inflammatory response results in sharp and transient pain reported by patients in the first hours following the bleaching procedures (3). Since in-office tooth bleaching procedures are performed with highly concentrated peroxides, an increased risk and level of tooth sensitivity has been reported for this technique (4).

Several approaches have been attempted to reduce the tooth sensitivity, including the preemptive use of desensitizing agents (7) and antioxidants (8). However, despite promising results in the reduction of tooth sensitivity, these protocols increase the number of clinical steps. In contrast, the preemptive administration of anti-inflammatory agents could reduce the anti-inflammatory response of pulpal tissue without compromising the number of clinical steps. The preemptive administration of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (9-11), etoricoxib (12), and naproxen (13) did not show promising results for prevention of tooth sensitivity following in-office bleaching procedures.

In addition to the low effectiveness of these NSAIDs evaluated against bradykinin (14) and substance-P (15), important mediators of pulpal pain caused by tooth bleaching, the limited diffusion rate might compromise

their absorption and bioavailability, hindering proper action during the bleaching procedure. Cicladol (piroxicam incorporated with β-cyclodextrin) has been shown to be effective in the treatment of pain related to acute inflammation due to the improved bioavailability and pharmacological efficacy obtained with cyclodextrin (16). β-Cyclodextrin is known to enhance the analgesic and anti-inflammatory effect of NSAIDs by producing an improvement in oral bioavailability, reducing effective doses to produce pharmacological activity and attenuating at least some of the side effects (17,18). Moreover, piroxicam is effective over bradykinin and substance P (18) and can be administered as a single dose for the control of postoperative pain because of its long duration of action (19).

Therefore, this randomized controlled clinical trial was aimed to evaluate the effectiveness of the preemptive administration of Piroxicam versus placebo on the absolute risk of postoperative tooth sensitivity (primary outcome) associated with in-office bleaching. The null hypothesis was that administrating a single dose of Piroxicam prior to an in-office bleaching procedure would not affect the absolute risk or intensity of postoperative tooth sensitivity.

Material and Methods

This clinical trial was approved by the Research Ethics Committee of the Federal University of Sergipe (CAAE: 50511415.1.0000.5546). The study protocol was registered at clinicaltrials.gov under the number NCT03153657. All patients enrolled signed the informed consent.

Study Design

This study was a randomized, triple-blind, placebo-controlled clinical trial with a crossover design in which the study participants receive each treatment in a random order. The patients included were submitted to two in-office bleaching sessions and received a placebo (control) or Piroxicam prior to the bleaching procedure. The main outcome was absolute risk to postoperative sensitivity observed in the first 24 h following the procedure. Bleaching effectiveness and level of tooth sensitivity were assessed as secondary outcomes. A delay of one week between sessions (wash-out) was established. The study was conducted at the school of dentistry of the Federal University of Sergipe from April to June 2017.

Inclusion and Exclusion Criteria

The patients included in the study were older than 18 years and presented maxillary canines darker than the shade 2.5 M2 on the Vita Bleachedguide 3D Master (Vita-Zahnfabrik, Bad Sackingen, Germany). Patients were excluded if they were smokers, pregnant or lactating, had undergone prior tooth bleaching treatment, presented a known allergy to any component of the medication used in the study, or were under the continuous use of anti-inflammatory or analgesic drugs. A prior clinical examination was also performed, and patients were excluded if they had restored and/or endodontically treated anterior teeth, prior tooth sensitivity, teeth presenting complex intrinsic staining (i.e., tetracycline) or any alteration in the enamel (i.e., fluorosis), generalized periodontal disease, or use of fixed orthodontic appliances.

Sample Size Calculation

The sample size calculation was based on the absolute risk to tooth sensitivity (primary outcome) from a previous study using a similar bleaching protocol (10). The calculation was performed for a superiority trial with a binary outcome, considering a power test of 80%, a significance level of 5%, and a decrease of 30% for the experimental treatment compared to the control in a crossover design. Thus, 50 patients were included in the randomization.

Random Sequence Generation and Allocation Concealment

A randomized list was computer-generated by a person not involved in the intervention or evaluation. The participants were defined as a block in the randomization process, and the sequence of treatment (placebo or Piroxicam) was randomly set for each block by using computer-generated tables. The sequence was inserted into sealed envelopes numbered from 1 to 50 that were opened by the operator only at the moment of the intervention. The patients were numbered according to the sequence of enrollment. Neither the participant nor the operator knew the group allocation determining blinding to the protocol.

Baseline Measurements

A single, previously calibrated (Kappa coefficient >0.80) evaluator assessed tooth shade using the Vita Bleachedguide scale during the experiment. Only the initial color of the upper canines was assessed based on a match of color between the scale tabs and the middle third of the tooth crown. The shade tabs selected were converted to scores ranging from 1 (whiter shade – 0 M1) to 15 (darker shade – 5 M3).

Intervention

Identical capsules containing either Cicladol (200.8 mg of piroxicam β-cyclodextrin-based - equivalent to 200 mg of piroxicam) or placebo (inert content) were manufactured and stored in non-identified bottles by a researcher who did not participate in the intervention or evaluation. Therefore,

the content of the capsules was also not known by the participants. Thirty minutes prior to the in-office bleaching procedure, the patient received a single dose of a capsule containing Piroxicam or placebo. Dental prophylaxis was performed with pumice and water using a rubber cup, and a light-polymerized resin dam (Top Dam, FGM, Joinville, SC, Brazil) was applied over the gingival tissue corresponding to the teeth to be bleached. A 35% hydrogen-peroxide-based bleaching agent (Whiteness HP Maxx, FGM, Joinville, SC, Brazil) was mixed and applied over the surface of the teeth (both jaws up to 2nd premolar), remaining for 45 min without any replacement. Despite the manufacturer of bleaching agent recommends three 15-min applications, it has been demonstrated that a single 45-min application yields similar bleaching effect and tooth sensitivity with reduced number of clinical steps (20). Subsequently, the bleaching agent was removed, and the teeth were rinsed. A second bleaching session was performed after one week, following the same procedures described previously.

Evaluations

The tooth sensitivity reported by patients was recorded using both a visual analog scale (VAS) and a verbal rating scale (VRS). For the VAS, the patient set her/his sensitivity level by pointing with a pen to a colored 10-cm scale, which ranged from green (no pain) to red (extreme pain). The distance between the marking and the green border of the scale was recorded. Tooth sensitivity was also scored according to the VRS, where 0=none, 1=mild, 2=moderate, 3=considerable, and 4=severe. The maximum level of tooth sensitivity reported by the participants during the bleaching procedure was recorded at the end of each bleaching session. Twenty-four after each bleaching session, the patients reported the higher level of tooth sensitivity felt throughout the entire period after the tooth bleaching and the level sensitivity at that time. This binary outcome (main outcome) was used to define the risk to tooth sensitivity and was defined by the presence (score different from 0) or absence of tooth sensitivity assessed by the VRS. The color evaluation was repeated one week after each bleaching session. All evaluations were performed by two evaluators blinded to the allocation assignment.

Statistical Analysis

The analysis followed the intention-to-treat protocol and involved all the randomly assigned participants. Therefore, data from the prior appointment were repeated when the patient did not return for the subsequent appointment. The statistician was blinded to the study groups. Data from each patient's profile were analyzed regarding distribution of age, gender, and baseline color of the upper canines for each sequence of treatment. Age data were analyzed by t-test, proportions of each gender were analyzed by Fisher's Exact test, and the color of the upper canines at baseline was compared using the Mann-Whitney test.

Statistical analyses for tooth sensitivity did not consider the 'bleaching session' as an independent variable. The pooled outcomes for each treatment were analyzed according to time following the bleaching procedure. Absolute and relative risks to tooth sensitivity, reduction in absolute risk and number needed to treat were calculated based on the number of scores different from 0 on the VRS. For each assessment time, differences in the absolute risk were analyzed by McNemar's test. Data from the VRS were also analyzed regarding the level of tooth sensitivity. Comparisons between the treatments were performed by the Mann-Whitney test. For the VAS, data were submitted to t-tests to compare the treatments at each assessment time. The highest values of tooth sensitivity reported on the VRS and VAS were attributed to assessment times where it was not possible to re-evaluate the participants due to loss during follow-up, based on the intention-to-treat approach.

Data analysis was performed using the SigmaStat v.3.5 statistical software package (Systat Software Inc., Chicago, IL, USA). For the color evaluation, comparisons were performed among the sequences of treatment. Changes in the number of shade guide units (ΔSGUs) were calculated from baseline to express the color alteration. Treatments and bleaching sessions were compared by Mann-Whitney and Wilcoxon tests, respectively. The color score measured prior to the second bleaching session was repeated at the final evaluation for the participants who attended the last color evaluation, following the intention-to-treat approach. All statistical analyses were performed considering a significance level of 95%.

Results

A flow diagram of the trial is given in Figure 1, and the baseline characteristics of the participants are presented in Table 1. No differences in age or gender were found between the participants who were allocated to each sequence of treatment. Participants allocated to Piroxicam /Placebo presented upper canines darker than those included in other sequence of treatments.

The results of risk to tooth sensitivity are presented in Table 2. Irrespective of the assessment time, no difference was observed between the treatments. Figure 2 presents the results of tooth sensitivity level reported by participants using the VRS. The preemptive administration of Piroxicam did not affect the level of tooth sensitivity compared to the placebo, irrespective of the assessment time. Similar results were observed when data from the

VAS were analyzed (Table 3). The results of the color evaluation are presented in Figure 3. No significant difference in color change was observed between the sequences of allocation. For both sequences, higher values of ΔSGU were observed after the 2nd session of tooth bleaching.

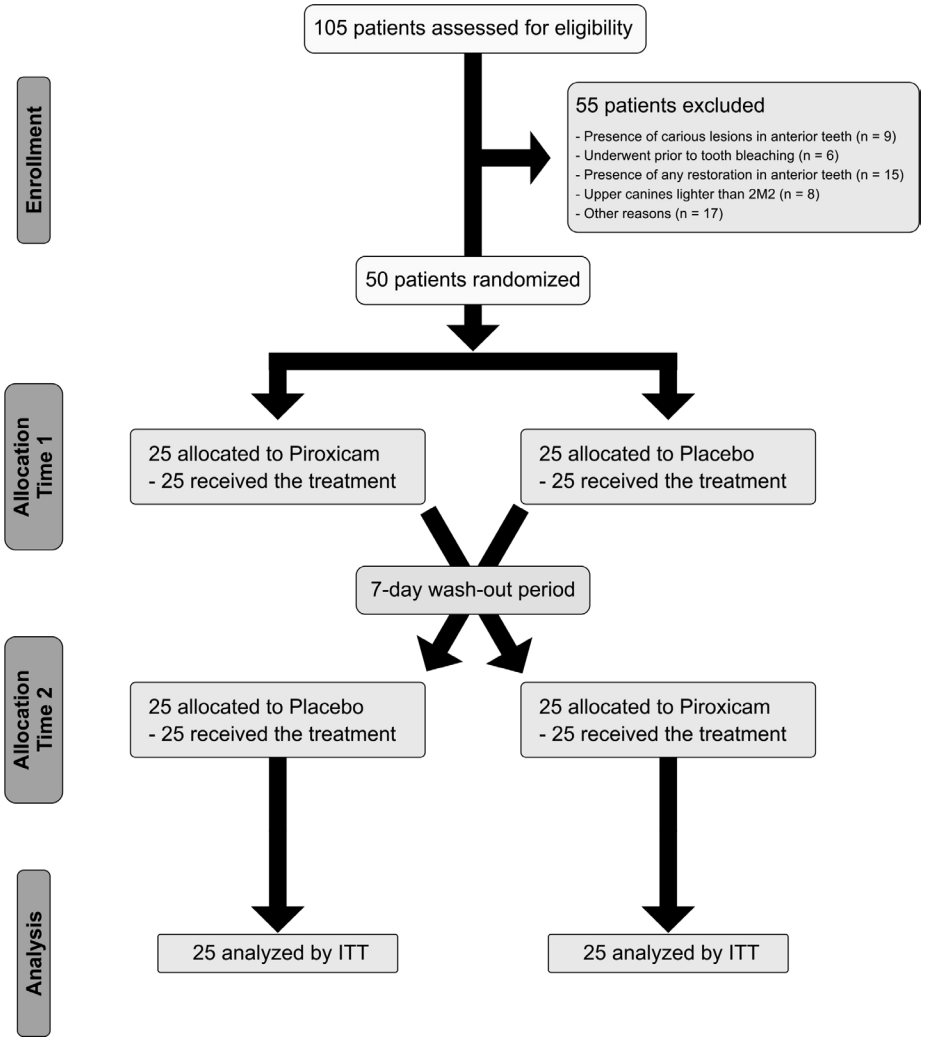

Figure 1. Flow diagram of the clinical trial.

Table 1. Baseline characteristics of patients included in the study

	Placebo/ Piroxicam	Piroxicam/ Placebo	p value	95% CI
Age (mean - 95% CI; years)	25.4 (23.6 to 27.2)	26.2 (23.6 to 28.7)	0.616[1]	-0.8 (-3.9 to 2.4) *
Gender (ratio of males -95% CI)	0.24 (0.12 to 0.43)	0.44 (0.27 to 0.63)	0.232[2]	1.83 (0.80 to 4.19) **
Upper canines' color[€] (mean - 95% CI)	10.3 (9.8 to 10.8)	11.1 (10.6 to 11.6)	0.042[3]	-0.74 (-1.45 to -0.03) *

[€]Scores from the Vita Bleachedguide scale - 1 to 15. *Mean difference from Placebo/ Piroxicam; **Relative risk, using Placebo/ Piroxicam as the control. 1. T-test; 2. Fisher's exact test; 3. Mann-Whitney test. CI - Confidence interval.

Discussion

The bleaching effect achieved using peroxides is mainly due to oxidation of the organic structure of dentinal tissue and/or increased opacity of enamel as a result of free radicals and other sub-products released by H_2O_2 breakdown (5). However, the low molecular weight of the H_2O_2 allows its molecules to reach the pulpal tissue, yielding an inflammatory response (6) by releasing inflammatory mediators such as bradykinin, prostaglandins and substance-P (3,14,15). Clinically, the inflammatory process in tooth pulp is reported by the patient as a transitory tingling or shooting pain without any stimulation. Therefore, although the tooth sensitivity tends to disappear a few hours following the bleaching procedure (3), its occurrence might interrupt the procedure and compromise the ultimate results.

In the present study, Piroxicam was preemptively administered in a single dose thirty minutes prior to in-office bleaching procedure, with the aim of reducing a possible inflammatory process caused by the bleaching procedure as well as tooth sensitivity trans- and post-bleaching. However, no effect of preemptive administration of Piroxicam was observed regarding the risk and level to tooth sensitivity, and the null hypothesis of the study was accepted. Cicladol is a complex molecule containing 20 mg of oxicam (Piroxicam) incorporated by a cyclic oligosaccharide β-cyclodextrin. Further, to reduce irritation of the gastro-intestinal tract,

inclusion complexation with β-cyclodextrin also enhances the solubility and bioavailability of low-soluble drugs, especially for analgesic and anti-inflammatory drugs commonly used in therapeutics (17,18). It has been reported that Cicladol has a rapid adsorption rate (15 to 30 min) and analgesic effect (21). Therefore, it was expected that any analgesic effect during the bleaching procedure with reduced tooth sensitivity would be reported. In fact, prior studies have demonstrated the effectiveness of a preemptive single dose of Piroxicam to prevent moderate to severe postoperative pain, including that observed after oral surgery (22). Unfortunately, the same expected effect was not observed in the present trial.

Preemptive analgesia can be defined as an antinociceptive treatment to prevent the establishment of alterations in central nervous system caused by tissue damage or inflammatory responses (23). Thus, the preemptive approach tends to be more effective than analgesic treatment started after the operatory procedure (22). Moreover, the preemptive treatment can be extended after the procedure since the nociceptive stimulation by inflammatory process can increase depending on the damage (24). In the present study, no post-procedure administration of Piroxicam was performed because tooth sensitivity caused by tooth bleaching tends to significantly reduce or disappear after 24 h. In fact, the outcomes demonstrated a low risk and sensitivity level at this time. Moreover, the elimination half-life (t½) of Cicladol is long (40 to 63 h), while any analgesic effect of a single dose use can be expected after 24 h (21). This t½ of Cicladol also demonstrated that a 1-week wash-out period was enough to avoid any residual effect of the anti-inflammatory agent administered in the first session.

In addition to pharmacokinetics favoring its preemptive single-dose usage, it has been demonstrated that Piroxicam can inhibit bradykinin and substance P, which are important mediators in the inflammatory process of pulpal cells caused by tooth bleaching (15). The lack of efficacy of Piroxicam in preventing tooth sensitivity reported by patients who underwent tooth bleaching can suggest that other mediators can be involved in the pulpal inflammation cause by peroxides. Therefore, it is reasonable to state that an anti-inflammatory drug with an inhibitory action in many of the initial events in an inflammatory response could be more

Table 2. Results for risk (95% CI) to tooth sensitivity observed for each treatment according to assessment time

Assessment time	Treatment	Absolute risk	Relative risk	p value*	Absolute risk reduction	Number needed to treat
During	Placebo	0.59 (0.45 to 0.72)	0.86 (0.60 to 1.24)	0.479	0.08 (-0.11 to 0.26)	12.3 (8.7 (Harm) to ∞ to 3.6 (Benefit))
	Piroxicam	0.51 (0.38 to 0.64)				
Up to 24 h	Placebo	0.80 (0.66 to 0.89)	1.05 (0.87 to 1.27)	0.789	-0.04 (-0.20 to 0.12)	24.5 (5.2 (Harm) to ∞ to 8.9 (Benefit))
	Piroxicam	0.84 (0.71 to 0.92)				
After 24 h	Placebo	0.35 (0.23 to 0.49)	0.77 (0.42 to 1.40)	0.453	0.08 (-0.10 to 0.26)	12.3 (10.0 (Harm) to ∞ to 3.8 (Benefit))
	Piroxicam	0.27 (0.16 to 0.40)				

CI – Confidence interval. *McNemar's test.

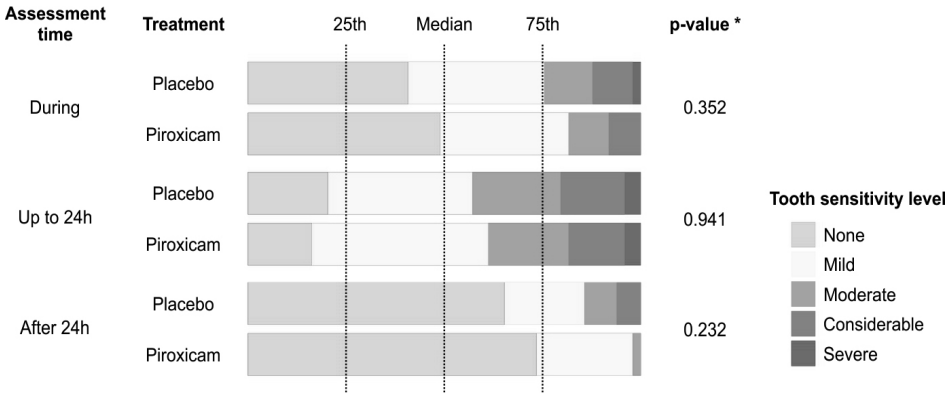

Figure 2. Tooth sensitivity level measured by the Verbal Rating Scale. * P-value calculated by the Mann-Whitney rank sum test.

Table 3. Means (95% CI) of the tooth sensitivity level reported by patients using the Visual Analog Scale

Assessment time	Treatment		p value*
	Placebo	Piroxicam	
During	1.77 (1.05 to 2.50)	1.14 (0.64 to 1.64)	0.386
Up to 24 h	2.69 (1.89 to 3.49)	2.49 (1.77 to 3.21)	0.977
After 24 h	0.81 (0.31 to 1.30)	0.30 (0.14 to 0.45)	0.413

CI – Confidence interval. * Mann-Whitney Rank Sum Test.

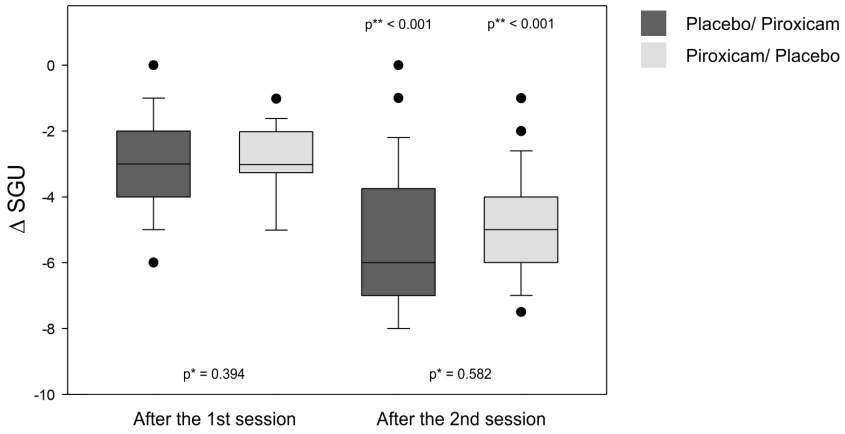

Figure 3. Box-plot presenting the results of color changes measured by the Vita Bleachedguide scale. * P-value calculated by the Mann-Whitney test – comparing the allocation sequences; ** P-value calculated by the Wilcoxon test – comparing the tooth bleaching sessions. SGU – Shade guide units.

efficient to prevent post-bleaching sensitivity. However, a prior study did not find any effect of dexamethasone (a glucocorticoid) to prevent tooth sensitivity following in-office tooth bleaching (25). In fact, no anti-inflammatory drug used preemptively in a single dose demonstrated effectiveness for preventing tooth sensitivity caused by bleaching procedures (9-13). The pulpal tissue is densely innervated with afferent sensitive nervous fibers with a speed of transmission at bands A"β, Aδ and C (3). Thus, the hydrogen peroxide can damage the nervous cells by direct activation of neuronal receptors yielding lipid peroxidation of the cell membrane and oxidation of nucleic acids (3,26). If these events are related to sensitivity caused by peroxides, it could be expected that the administration of anti-inflammatory agents would have a limited effect on pain prevention. Another explanation is that drugs administrated via oral and presenting systemic action have a limited effect on the pulp tissue, and topical application of anti-inflammatories could be more effective to minimize the inflammatory process (27,28). However, a prior large multicentric clinical trial did not find any effect of a single preemptive topical application of dipyrone over the enamel on post-bleaching tooth sensitivity (29).

Although the main outcomes of the study were related to tooth sensitivity since the effects of preemptive administration of an anti-inflammatory was evaluated, the color changes following the bleaching procedures were also assessed. Despite spectrophotometric analysis based on Commission Internationale de L'Eclairage (CIE) system is a more objective tool for color assessment, a shade guide was used in the present study to assess this outcome. In fact, Vita Bleachedguide is commonly used in clinical trials assessing bleaching effectiveness and the results obtained using this shade scale are easily communicable to clinicians (12,13,25). This outcome was assessed to demonstrate the efficacy of the bleaching procedures used, and the average color changes (approximately 5 shade guide units) were similar to those observed in other trials evaluating in-office tooth bleaching procedures (4). Therefore, the statistical analysis performed compared the sequence of treatments (which were randomized) instead of the treatments (Piroxicam or placebo) and demonstrated similar color changes among the participants allocated for each sequence.

The findings of the present study did not demonstrate any effect of preemptive use of Piroxicam in a single-dose 30 min prior to in-office bleaching on prevention of tooth sensitivity. It is important to emphasize that the outcomes of this study cannot be extrapolated to other protocols of anti-inflammatory administration or bleaching procedures. Factors such as peroxide concentration, interval between sessions, and variables related to patients can intervene in the inflammatory response and, ultimately, the tooth sensitivity reported by patients. Furthermore, anti-inflammatory administration protocols other than a preemptive single-dose must be evaluated before the use of anti-inflammatory drugs can be disregarded as a means to control post-bleaching pain.

Moreover, the ineffectiveness of Piroxicam to inhibit the tooth sensitivity after in-office bleaching may be related to the type of sensitivity imposed during the process by the stimulus created; even with the release of pro-inflammatory mediators and reactive oxygen specimens, the painful sensation seems to be mediated by central mechanisms (30). Thus, it is rational to propose procedures to reduce the sensation of pain, or at least the discomfort of the post-bleaching pain, using an association of central analgesic (oxycodone or codeine) with NSAIDs due to the sensorial nature of the procedure. This type of approach may be better explored in future research.

Resumo

Este ensaio clínico avaliou o efeito do uso preemptivo do anti-inflamatório não-esteroidal piroxicam em dose única 30 minutos antes do clareamento de consultório na prevenção de sensibilidade dentária (SD) relatada pelos pacientes. Cinquenta pacientes foram submetidos a duas sessões de clareamento dental em consultório com peróxido de hidrogênio a 35% por 2 sessões, consistindo de aplicação única de 45 minutos, com um intervalo de 7 dias entres as sessões. Trinta minutos antes do procedimento, o paciente recebia aleatoriamente dose única de piroxicam (200 mg) ou do placebo em um desenho duplo-cego, randomizado e cruzado. A SD foi avaliada usando a escalas de gradação verbal (EGV) e visual analógica

(EVA) durante o procedimento clareador e 24h após o procedimento. As mudanças de cor foram avaliadas usando a escala Vita Bleachedguide uma semana após cada sessão de clareamento. O risco de SD foi calculado a partir de EGV a analisado pelo teste de McNemar, enquanto o nível de SD foi analisada pelo teste de Mann-Whitney. Para EVA, testes T foram usados para comparar dados dos tratamentos em cada tempo de avaliação. Dados de mudança de cor foram submetidos aos testes de Wilcoxon e Mann-Whitney (α=0.05). A administração preemptiva de piroxicam não afetou o risco e nível de SD quando comparado ao placebo, independentemente do tempo de avaliação. A sequencia de tratamento não afetou a efetividade do clareamento. Como conclusão, a administração de dose única de piroxicam previamente ao clareamento dental de consultório não foi efetiva em reduzir significantemente o risco e nível de SD.

Acknowledgements

This study was supported by CNPq (grant #446157/2014-7).

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Received February 17, 2019
Accepted June 13, 2019