Brazilian Journal of Development

Combination of an analgesic and anti-inflammatory to avoid bleaching-induced tooth sensitivity: a randomized, triple-blind clinical trial

Combinação de um analgésico e antiinflamatório para evitar a sensibilidade dentária induzida pelo clareamento: um ensaio clínico randomizado triplo-cego

DOI:10.34117/bjdv6n8-210

Recebimento dos originais:08/07/2020
Aceitação para publicação:14/08/2020

Camila Basso Alpini
DDS, MS student, Department of Restorative Dentistry
State University of Western Paraná, Cascavel, PR, Brazil
Rua Integração 462, Universitário, Cascavel, Paraná, Brazil
camilabassoalpini@hotmail.com

Fabiana Scarparo Naufel
DDS, MS, PhD, Adjunctive professor, Department of Restorative Dentistry
State University of Western Paraná, Cascavel, PR, Brazil
Rua Artur Nisio 196, Cascavel, Paraná, Brazil
biberes@terra.com.br

Alessandra Reis
DDS, MS, PhD, Adjunctive professor, Department of Restorative Dentistry
State University of Ponta Grossa, PR, Brazil
Rua General Osório 422, Ponta Grossa, Paraná, Brazil
reis_ale@hotmail.com

Vera Lucia Schmitt
DDS, MS, PhD, Adjunctive professor, Department of Restorative Dentistry
State University of Western Paraná, Cascavel, PR, Brazil
Rua Rio de Janeiro 1929, Cascavel, Paraná, Brazil
veraschmitt@uol.com.br

Leonardo de Almeida
DDS, Resident student, Department of Restorative Dentistry
State University of Western Paraná, Cascavel, PR, Brazil
Rua Economia, 699, Cascavel, PR, Brazil
leonardoalmeida.tem@gmail.com

Camillo Anauate-Netto
DDS, MS, PhD, Professor, Department of Restorative Dentistry, University Metropolitana of Santos (UNIMES)
Conselheiro Nebias Avenue, 536, Santos, SP, Brazil - 11045-002
anauatenetto@uol.com.br

Brazilian Journal of Development

Bianca Medeiros Maran
DDS, MS, PhD, Professor, Department of Restorative Dentistry
State University of Western Paraná, Cascavel, PR, Brazil
Rua Engenharia, 464, Cascavel, Paraná, Brazil
medeiros.bianca@hotmail.com

Eloisa Andrade de Paula
DDS, MS, PhD, DDS, MS, PhD, Professor, Department of Restorative Dentistry
University Metropolitana of Santos (UNIMES), Santos, SP, Brazil
Rua Pedro de Toledo, 20, Santos, SP, Brazil
eloisadepaula@gmail.com

ABSTRACT
Aim. The administration of the single intra-oral drugs was not capable of avoid the bleaching-induced tooth sensitivity (TS). This trial assed if the combination of an analgesic and an anti-inflammatory could reduce bleaching-induced TS. A parallel, placebo-controlled, triple-blind, randomized trial was conducted on 115 healthy adults. The patients received the association of acetaminophen 750 mg/ ketorolac tromethamine 10 mg or placebo, 1 h before the in-office bleaching (35% hydrogen peroxide), and extra doses every 8 h for 48 h. The TS was recorded on VAS 0-10 and NRS 0-4 scales, during bleaching and 1 to 48 h post-bleaching. The color was measured before and one month after dental bleaching using two visual shade guides and spectrophotometer. An intent-to-treat analysis was used to analyze data from all patients who were randomly assigned. No significant difference (p=0.41) in the absolute risk of TS between the acetaminophen/ketorolac group (72%; 95% CI 60 to 82) and placebo (79%; 95% CI 68 to 89) with a relative risk of 0.92; 95% CI 0.7 to 1.1. The mean difference in intensity of TS for VAS was lower in the acetaminophen/ketorolac group in the periods 12 to 24 h (-0.7) and 24 to 48 h (-0.4). A whitening effect was observed in both groups with no statistically significant difference (p>0.05). The administration of the association ketorolac/acetaminophen prior to in-office bleaching did not reduce the risk of TS but reduced the intensity of TS after 12 h in a very small magnitude.
clinicaltrial.gov NCT03343392.

Keywords: Dentin Sensitivity, Hydrogen Peroxide, Tooth Bleaching, Clinical Trial.

RESUMO
Alvo. A administração de fármacos únicos intra-orais não foi capaz de evitar a sensibilidade dentária induzida pelo clareamento (TS). Este estudo avaliou se a combinação de um analgésico e um antiinflamatório poderia reduzir a TS induzida pelo clareamento. Um ensaio paralelo, controlado por placebo, triplo-cego e randomizado foi conduzido em 115 adultos saudáveis. Os pacientes receberam a associação acetaminofeno 750 mg / cetorolaco de trometamina 10 mg ou placebo, 1 hora antes do clareamento em consultório (peróxido de hidrogênio a 35%), e doses extras a cada 8 horas por 48 horas. O TS foi registrado nas escalas VAS 0-10 e NRS 0-4, durante o clareamento e 1 a 48 h pós-clareamento. A coloração foi medida antes e um mês após o clareamento dental por meio de dois guias visuais de cores e espectrofotômetro. Uma análise de intenção de tratar foi usada para analisar os dados de todos os pacientes que foram designados aleatoriamente. Nenhuma diferença significativa (p = 0,41) no risco absoluto de TS entre o grupo acetaminofeno / cetorolaco (72%; IC 95% 60 a 82) e placebo (79%; IC 95% 68 a 89) com um risco relativo de 0,92; IC de 95% 0,7 a 1,1. A diferença média na intensidade de TS para VAS foi menor no grupo paracetamol / cetorolaco nos períodos de 12 a 24 h (-0,7) e 24 a 48 h (-0,4). Efeito clareador foi observado em ambos os grupos sem diferença estatisticamente significante

Brazilian Journal of Development

(p> 0,05). A administração da associação cetorolaco / acetaminofeno antes do clareamento em consultório não reduziu o risco de ST, mas reduziu a intensidade da ST após 12 horas em uma magnitude muito pequena.
clinictrial.gov NCT03343392.

Palavras-chave: Sensibilidade Dentina, Peróxido de Hidrogênio, Clareamento Dentário, Ensaio Clínico.

1 INTRODUCTION

Due to its effectiveness and the increasing request for whiter teeth by the general population, tooth bleaching has become a popular aesthetic dental procedure (De Souza Costa et. al. 2010). Currently, there are two main dentist-supervised techniques: the at-home or in-office bleaching. In the at-home bleaching, patients are instructed to wear the bleaching tray daily, for periods ranging from 2 to 6 weeks. As some patients do not adapt to the daily use of bleaching trays (Cartagena et al. 2015), in-office bleaching has emerged as an alternative technique in which highly concentrate bleaching agents can be used in the dental office without the need of bleaching trays (Jacqz-Aigrain and Anderson 2006).

However, in-office bleaching using 35% hydrogen peroxide (HP) has in average (Haywood 2005) (Reis et al. 2011) tooth sensitivity (TS) levels that are four times higher than that produced by at-home bleaching (Rezende et al. 2016). In recent clinical trials, authors reported an absolute risk of TS varying from 67% to 100% (Rezende et al. 2016) (Bonafe et al. 2013) (De Paula et al. 2014), which means that in the best condition, 6 patients in every 10 will experience pain during treatment. The reasons of the bleaching-induced TS are not clear but it seems to result from the easy passage of the HP through the enamel and dentin reaching the pulp tissue and causing pulp damage and a reversible inflammatory process (De Souza Costa et. al. 2010).

Since 2009, some authors have investigated the use of anti-inflammatory drugs for reduction of this adverse effect (Rezende et al. 2016) (Charakorn et al. 2009) (De Paula et al. 2013). In their studies, the use of ibuprofen, a nonsteroidal anti-inflammatory, just reduced TS immediately up to 1 h after bleaching (Charakorn et al. 2009) (De Paula et al. 2013a). The administration of other medicines such as a selective anti-inflammatory drug (etoricoxib 60 mg), a steroidal anti-inflammatory drug (dexamethasone 4 mg) or the combination of codeine and acetoaminophen (Tylex® 30 mg) was not capable of reducing this side effect (Rezende et al. 2016) (De Paula et al. 2013a) (Da Costa Poubel La et al. 2019).

The lack of efficacy of the intra-oral drugs tested in preventing bleaching-induced TS could be originated from an inflammatory response of the dental pulp through with the liberation

of bradykinin (Lepinski et al. 2000) and substance P, which are involved in the process of inflammation and pulp pain (Rodd and Boissonade 2000) (Caviedes-Buchelli 2008).

The analgesic drug acetaminophen 750 mg (Graham et al. 2013) can block impulse generation within the bradykinin-sensitive chemo-receptors and it is also thought to have the analgesic effect by antagonizing the substance P in the spinal cord3 however, this drug showed weak anti-inflammatory activity (Botting 2000). To increase the analgesic efficacy of acetaminophen, authors suggested its use in combination with another anti-inflammatory activity (Hyllested et al. 2002).

The ketorolac tromethamine is member of a class of anti-inflammatory having potent analgesic effect, similar to opioids and moderate anti-inflammatory activity (Rooks et al. 1985) (Mcaleer et al. 2007).

Ketorolac has been reported to have similar efficacy to standard doses of morphine, providing relief from moderate to severe pain in most patients (Mcaleer et al. 2007).A single 10 mg tablet given orally to human volunteers following surgery is equivalent to that provided by 10 mg of morphine given intramuscularly, providing relief from moderate to severe pain in most patients (Rooks et al. 1985).

Perhaps the administration of analgesic and anti-inflammatorycan induce analgesia at a higher level than would do any of these drugs alone, being effective to reduce the risk and intensity of bleaching-induced TS. Therefore, this parallel, triple-masked, randomized clinical trial aimed to evaluate the effect of the association of acetaminophen 750 mg and ketorolac tromethamine 10 mg, administered perioperatively for 48 h, on the risk of bleaching-induced TS. The intensity of bleaching-induced TS and color change was also evaluated as secondary outcome.

2 METHODS AND MATERIALS

Ethics approval and Protocol registration

This clinical investigation was approved (protocol number 45733615.6.0000.0109) by the Scientific Review Committee and by the Committee for the Protection of Human Subjects of the University of Paraná – UNIPAR (Cascavel, PR, Brazil). It was registered in clinical trials registry (REBEC) under identification number RBR-9GXBG6.The study protocol was registered in the clinicaltrial.gov under protocol number NCT03343392. This clinical report follows the protocol established by the Consolidated Standards of Reporting Trials statement with extension for within-person designs (Schulz et al. 2003) and followed the methodology used by de Paula and others (De Paula et al. 2014), (De paula et al 2013) , (Rezende et al. 2016), (Coppla et al 2018).

Brazilian Journal of Development

Trial design, settings and locations of data collection

This was a randomized, parallel, placebo-controlled, triple-mask, superiority clinical trial, in which the patient, operator and evaluator were masked to the group assignment. This study was performed from 12/2017 to 12/2018 in the city of Cascavel (Paraná, Brazil). All bleaching procedures were carried out within the Clinics of the Dental School of the State University of Oeste do Paraná (Cascavel, Paraná, Brazil).

Recruitment

Participants were recruited through written advertisements placed on the university walls.All participants signed an informed consent form before being enrolled in the study.Each eligible volunteer was registered in a form especially created for this study in the public domain statistical software Epi Info™ (Center for Disease Control and Prevention –CDC, Atlanta, Georgia, USA).

Eligibility criteria

Patients included in this clinical trial were at least 18 years old and had good general and oral health and did not report any type of TS. The participants were required to have six caries-free maxillary anterior teeth and without restorations, absence of periodontal disease and must reviewed and signed the informed consent form. The central incisors should be shade A2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical A1-D4® shade guide, Vita Zahnfabrik, Bad Säckingen, Germany).

Participants with anterior restorations or dental prosthesis, with orthodontics apparatus, with severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth) were not included in the study. Additionally, pregnant/lactating women, participants with any other pathology that could cause sensitivity (such as recession, dentine exposure, presence of visible cracks in teeth), taking anti-inflammatory and/or analgesic drugs, bruxists or participants that had undergone tooth-whitening procedures were also excluded.

Patients that reported some earlier or present health problems in stomach, heart, kidney and liver, participants reporting continuous use of anti-inflammatory and/or analgesic drugs were excluded. Additionally, diabetics, hypertensive or patients with known allergy to acetaminophen/codeine and lactose were excluded from the study.

Sample size calculation

The primary outcome of this study was the absolute risk of TS. The absolute risk of TS (that is, the percentage of patients who reported pain at some point during dental bleaching) was reported to be approximately 86% (De Paula, 2013a) (Tay et al. 2009), for the bleaching product Whiteness HP AutoMixx (FGM Dental Products, Joinville, SC, Brazil). Using an alpha of 0.05, 90% power and a two-sided test, the minimum sample size in this superiority trial was 114 patients to detect a 26% difference in the risk of TSbetween groups.

Random sequence generation and allocation concealment

A third person who was not involved in implementation and evaluation steps performed blocked randomization (block sizes of 2 and 4) in the website www.sealedenvelope.com. Details of the allocated groups were recorded on cards contained in sequentially numbered, opaque, sealed envelopes. The information contained in the envelope determined the treatment to be assigned for each patient. Once the participant was eligible for the procedure and completed all baseline assessments, the allocation assignment was revealed by opening this envelope at the moment of treatment implementation.

Blinding

This was a triple-mask study, in which the patient, operator and evaluator were blinded to the group assignment. A third researcher who was not involved in the implementation and evaluation processes was responsible for the randomization, delivery of and guidance on the administration of the drugs.

Both the drugs and placebo pills were similar in appearance, consistency. They were delivered in identical vials coded as “A” and “B”. Only the research coordinator knew the coding system.

Study intervention

Patients were divided into acetaminophen/ketorolac and placebo groups. All patients received the same bleaching treatment, which was performed by five calibrated operators. One hour before in-office bleaching patients received either the acetaminophen 750 mg (Paracetamol 750 mg, Bioativa compounding pharmacy, Cascavel, PR, Brazil) along with ketorolac tromethamine oral 10 mg (Toragesic® 10 mg, EMS Sigma Farma, Hortolândia, SP, Brazil) or placebo pills of both medicines in identical tablets or capsules. The placebo tablets acetomynophen contained starch lactose free (Placebo tablets, Bioativa compounding pharmacy,

Cascavel, PR, Brazil) and the placebo capsules for ketorolac tromethamine contained base past, lactose free (Oro-tab®, Bioativa compounding pharmacy, Cascavel, PR, Brazil).

We stored the capsules in a vial containing 6 capsules of acetomynophen and 6 capsules of ketorolac tromethamine required for each bleaching session. The operator administered the first dose of the drug one hour before the protocol, and extra doses were administered every eight hours for a period of 48 h to keep a safe maximum daily dosage of 4000 mg of acetaminophen and 40 mg of ketorolac tromethamine (Wannmacher and Ferreira. 1995).

One hour after drug administration, the operator placed a lip retractor (Arcflex, FGM Dental Products, Joinville, SC, Brazil) and isolated the gingival tissue of the teeth to be bleached using a light-cured resin dam (Top Dam, FGM Dental Products, Joinville, SC, Brazil), being each tooth was light-cured for 10 s (Radii-cal, SDI, Melbourne, VIC, Australia). The 35% hydrogen peroxide gel (Whiteness HP AutoMixx, FGM Dental Products, Joinville, SC, Brazil) was applied in a single 50-minute application for both groups in accordance with the manufacturer's directions. Two bleaching sessions were performed with one-week interval. All participants were instructed to brush their teeth regularly using fluoridated toothpaste.

Outcomes

Tooth sensitivity (TS) evaluation.

Before the implementation, patients were instructed to record the bleaching induced TS, using the 5-point numeric rating scale (NRS) and 0-10 visual analogue scale (VAS), in six times assessments: 1) during bleaching and up to 1 h, 2) 1 h up to 6 h; 3) 6 h up to 12 h and 4) 12 h up to 18 h, 5) 18 h up to 24 h, and 6) from 24 h up to 48 h post-bleaching.

For the NRS scale, the patient was asked to record the degree of TS in a zero to 4 scores, where 0 means no sensitivity, 1 mild tooth sensitivity, 2 moderate tooth sensitivity, 3 considerable tooth sensitivity, and 4 severe tooth sensitivity (De Paula et al. 2013a) (Tay et al. 2009) (Reis et al. 2013) (Bernardon et al. 2010) (De Paula et al. 2014). For the VAS scale (Gurgan et al. 2010) (He et al. 2012) (Mehta et al. 2013), the patient should mark with a vertical line across a 10-cm horizontal line the intensity of the TS. In the extremes of this horizontal line there was numbers 0 and 10, with 0 meaning no sensitivity and 10 = severe sensitivity. Then, the distance in mm from the zero ends was measured with the aid of a millimeter ruler.

The patients were also instructed to record in a paper form, that contained a mouth drawn with the teeth of the upper and lower arch, the painful teeth. They were explained how to fill out the forms and we also explained to them that if they did not feel any TS, their intensity would be zero. These forms were returned to the researchers during the next schedule appointment (1 week

later).

The data from both bleaching sessions were merged for statistical purposes, as they did not show any different patterns (data not shown). For this purpose, the worst score (NRS scale) and the highest numerical value (VAS) from the two bleaching sessions in all time assessment periods were used to analyze the bleaching-induced TS.

If the patient scored zero (no sensitivity) in all time assessments from both bleaching sessions, this patient was considered to be insensitive to the bleaching protocol. In all other circumstances, the patients were considered to have sensitivity to the bleaching procedure.

Color evaluation.

Two experienced and calibrated dentists (kappa statistics higher than 80% after previous calibration), who were not involved in the randomization procedures, performed clinical assessments at baseline, 1 week after the first bleaching session and 1 month after the end of the bleaching treatment. We never evaluated color immediately after each bleaching session to avoid the effects of dehydration and demineralization on the color measures. We evaluated color using the VITA Classical and VITA Bleachedguide 3D-MASTERshade guides (Vita Zahnfabrik, Bad Säckingen, Germany). In addition, we performed an objective color evaluation with a VITA Easyshade spectrophotometer (Vita Zahnfabrik, Bad Säckingen, Germany).

The Vita Classical scale is arranged in 16 tabs from the highest value (B1) to the lowest (C4): B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4, C4. Although this scale is not linear in the truest sense, color changes have been considered continuous and linear in several clinical studies on tooth whitening (De Paula et al. 2014) (Alomari and El Daraa 2010) (Bernardon et al. 2016) (De Geus et al. 2015) (Tay et al. 2009). The VITA Bleachedguide 3D-MASTER contains lighter shade tabs and is organized from the highest value (0M1) to the lowest (5M3).

The middle third of the buccal surfaces of the upper anterior central incisor was used as the tooth-matching area. Color changes were calculated from the beginning of the active phase up 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. In case of disagreement between the operators, they reached a consensus.

To measure color with the spectrophotometer, the examiner took an impression of the maxillary arch with dense silicone paste (Zetaplus and Oranwash® Kit, Zhermack, Italy). The impression was extended to the maxillary canines and served as a standard color measurement guide for the spectrophotometer. To evaluate each central incisor, we created a window on the

buccal surface of the silicone guide using a metal device with a radius of three mm, which is exactly the diameter of the tip of the spectrophotometer (Tay et al. 2009) (Rezende et al. 2019). We then inserted the tip of the device into the silicone guide and obtained the L*, a*, and b* parameters of color from the spectrophotometer. The L* value represents the luminosity (value from 0 [black] to 100 [white]), the a* value represents the measurement along the red-green axis, and the b* value represents the measurement along the yellow-blue axis. The color change (ΔE) before (baseline) and after each treatment (in each assessment period) was given by the differences between the two colors measured with the spectrophotometer, calculated using the following formula: $\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.

Statistical analysis

The analysis followed the intention-to-treat protocol and involved all participants (Fig. 1). The statistician was also blinded to the group assignment. The risks of bleaching-induced TS and the proportion of teeth from both groups that reported TS at least once in the central incisors, lateral incisors, canines and premolars from both arches were calculated and compared by Chi-square test ($\alpha = 0.05$, test for proportion of dependent data ratio). The risk ratio and the confidence interval (CI) for the effect size were also calculated.

The TS intensity data set for both the VAS and NRS scales were plotted in histograms and inspected for normal distributions. As data did not have normal distribution, the groups were compared using Mann-Whitney. Comparisons between times within each group were performed with the Friedman test ($\alpha = 0.05$).

The means and standard deviations of color change in ΔSGU and ΔE between baseline and 30 days after bleaching were calculated. In order to assess whether the bleaching therapies were effective, data from both groups were compared using paired Student t-test. The level of significance of all tests was set at 5%.

The proportion of patients from both groups that reported TS at least once in the central incisors, lateral incisors, canines and premolars from both arches were calculated and compared by chi-square test.

3 RESULTS

Characteristics of included participants

A total of 204 participants were examined according to inclusion and exclusion criteria (Fig. 1), but only 115 participants remained for the clinical trial.Table 1 describes the baseline color of the participants and their gender distribution. No hypothesis testing was performed for

the baseline features, as any difference between these features were due to chance alone.

Adherence to the protocol

In the placebo group, one patient was pregnant and the bleaching treatment was not performed. One patient from placebo group discontinued intervention in this clinical investigation after the first bleaching session due to intense pain, this patient performed only one session. Five participants did not attend the recall visits one-month post-bleaching, including the participant from the placebo group that discontinued treatment. For these participants, the last observation was carried forward for statistical purposes to keep the intention-to-treat analysis (Schulz et al. 2010). Figure 1 depicts the participant flow diagram in the different phases of the study design.

Risk of tooth sensitivity

A total of 45 patients presented pain in the placebo group (79%; 95% confidence interval [CI] 68 to 89) and forty-twopatients reported pain in the acetaminophen/ketorolac group (72%; 95% CI 60 to 82). In comparative terms, the risk ratio for pain was 0.9 (95% CI 0.7 to 1.1; Table 2). As the 95% CI does not exclude benefit or harm (it crosses the null value of 1), no significant differences between groups were detected (Table 2; chi-square test; $p = 0.414$).

Intensity of tooth sensitivity

Both NRS and VAS scales detected the differences between groups at the different time assessments (Table 3; $p < 0.05$). Lower pain intensity was observed for the acetaminophen/ketorolac group in the period 12 to 24 h ($p < 0.04$), and in the period 24 h to 48 h for NRS ($p = 0.03$) and VAS ($p = 0.03$) scales. For the VAS scale, the mean difference was -0.3 (95% CI -0.71 to -0.03) in the period of 12 to 24 h and -0.7 (95% CI 1.52 to 0.02) at 12 to 24 h and -0.2 (-0.53 to -0.01) and -0.4 (-0.86 to 0.03) at 24 h to 48 h after bleaching (Table 4).

Only one participant in the acetaminophen/ketorolac and in placebo group experienced pain after 48 h.

Painful teeth

A total of 1824 teeth were bleached in this research in both groups and from these 254 teeth presented sensitivity symptoms during and immediately post bleaching (14%; 95% [CI] 12% to 15%). The proportion of teeth from both groups that reported TS at least once in the central incisors, lateral incisors, canines and premolars from both arches are in Table 5. The teeth

less cited with sensitivity symptoms were the upper and lower premolars and the most painful teeth were the central and lateral lower incisors (Table 5).

Color evaluation

Significant whitening was detected by the three different tools. A bleaching of approximately 4 units of color in the Vita Classical scale, 6 units in the Vita Bleachedguide, and 7 units in the ΔE was observed. No significant difference of color change was observed between groups (Table 6; p > 0 .05).

Adverse effects

One patient from the acetaminophen/ketorolac tromethamine group presented nausea after the first bleaching session due to intense pain, but the patient finished the bleaching protocol and took a rescue medication (Ibuprofen 400 mg; Uniprofen, União Química Farm Nacional S/A, Embu-Guaçu, SP, Brasil) to alleviate the bleaching-induced TS. The same procedure was done for other four patients from the placebo group.

4 DISCUSSION

Though tooth whitening is one of the most sought after procedures in dental offices, dental sensitivity remains the most common adverse effect reported by patients, often leading to discontinuation of treatment (Basting et al. 2012) (Reis et al. 2013) heless, this study demonstrated that approximately 78% of patients in both groups reported TS at some stage of bleaching, confirming the high risk of TS shown by previous studies (Bonafé et al. 2013) (De Paula et al. 2013a) (De Paula et al. 2013b) (Mehta et al. 2013).

The pain caused by mechanical, thermal and chemical stimuli release pro-nociceptive mediators (ATP, glutamate, kinins, cytokines), that activate nociceptors (Fried et al. 2011) (Gibbs et al. 2011) of primary afferent neurons (A and C nerve fibers) and non- neural cells that reside or infiltrate into the injured area (as mast cells, platelets, macrophages, neutrophils and fibroblasts) (Basbaum, et al. 2009) releasing endogenous factors, making an inflammatory soup, to enhance nociceptive signal transmission to the central nervous system, so-called “peripheral sensitization” (Amaya et al. 2013). The soup is represented for signaling molecules, including neuropeptides (substance P), aracdonic acid metabolites (prostaglandins, thromboxanes, leukotrienes and lipoxins), bradykinin, vasoactive amines (histamine and serotonin), cytokines and chemokines (Basbaum, et al. 2009) and the nociceptors express one or more cell surface receptors, as the G protein coupled receptors (GPCR), the TRP channels, the acid-sensitive ion

channels (ASIC), the two-pore potassium channels (K2P), and the receptor tyrosine kinases (RTK), which recognize and respond for all these pro-inflammatory or pro-algesic agents (Laskin 2013).

Unquestionably, the most common approach to reduce nociception process and inflammatory pain involves inhibiting the components of the inflammatory soup (Basbaum, et al. 2009) or to act on any of the channels cited. Therefore a single drug not always is able to avoid pain or avoid the bleaching-induced TS, as demonstrated in the clinical trials that administered nonsteroidal anti-inflammatory drugs, (Charakorn et al. 2009) (De Paula et al. 2013b) selective anti-inflammatory drugs (De Paula et al. 2013a), corticosteroids (Rezende et al. 2016) and even codeine, an opioid (Coppla et al. 2018). A second approach, as the one used in this research, is the administration of two drugs of different analgesic classes concomitantly, acting at different pathophysiological mechanisms involved in pain (Hyllested et al. 2002). Ketorolac tromethamine work through the inhibition of cyclooxygenase (COX), and by producing a regulatory effect at the opioid receptors and in the nitric oxide synthase (Parke et al. 1995). Acetaminophen work through the inhibition of bradykinin and by antagonizing the substance P (Jacqz-Aigrain and Anderson 2006). However, they were not capable to reduce the absolute risk of TS experienced by these patients.

This research and others (, have shown that it is not possible yet to act in the pro-inflammatory and pro-algesic agents specific involved in bleaching-induced TS. De Souza Costa et al. 2010) (Cartagena et al. 2015) (Jacqz- Aigrain et al. 2006) (Haywood et al. 2005) (Reis et al. 2011) (Rezende et al. 2016) (Bonafé et al. 2013).

Although in the dental pain nociceptive endings become sensitized, this theory is problematic (Fried et al. 2011). Fried et al. also, propose that many dentinal afferents are not nociceptors at all, but rather low-threshold mechanoreceptors (LTM). The bleached patients can testify intense pain caused for weak mechanical stimuli such as air-puffs and cold water when directed at teeth. As these stimuli do not activate nociceptors or evoke pain on skin or gingiva, there must be something different about teeth, as an afferent with low-threshold peripheral characteristics having pain provoking CNS connectivity (peripheral neuropathic pain). Due to “central sensitization”, A-fiber LTM afferents can evoke tactile allodynia (“Aβ pain”) and the drugs the most frequently indicated to treat this kind of pain are tricyclic antidepressants and the anticonvulsants gabapentin and pregabalin (Gibbs, et al. 2011).

However, to take drugs to prevent or relieve TS because of bleaching should not be taken as a protocol. The authors this research recommend the bleaching protocol must be changed, maybe a second appointment should not be performed, must be reduced the concentration of HP,

the application time (Basbaum et al. 2009), to apply products with other components and additives (with desensitizing agents and higher pH) and to use different brands of the bleaching agent (Amaya et al. 2013). If patients report tooth sensitivity, it might signalize that bleaching should not endure.

First of all, the drugs researched did not avoid the bleaching-induced TS and second, the drugs cause side effects. The reported adverse reactions for APAP have include nausea, vomiting, constipation and for KT may include redness and itching of the skin, swelling in the face and around the eyes, breathing problems, fever, bleeding or bruising, yellowish skin or eyes, decreased urination, stomach pain, vomiting, feces with bright or darkened blood, nausea, diarrhea, drowsiness, headache or swelling in the feet.

However, it is worth mentioning, that the intensity of TS in the acetaminophen/ketorolac group was lower after 12 h post bleaching in the present investigation. In the pulp, the nociceptors transmit their input centrally via two different types of axons: myelinated AΔ and unmyelinated C fibers (Jain and Gupta et al. 2013). The initial pain sensed in the first phase of the bleaching process is extremely sharp, and it could be associated with the fast-conducting AΔ fibers (Jain and Gupta et al. 2013) and the drugs administered in this study were not capable to prevent de-sensitization this kind of fiber, causing TS during and up to 12 h after tooth bleaching. After 12 h, with development of the moderate inflammatory process,[51] the characteristics of pain are different: being more slow, dull, poorly localized and mediated by C fiber axons (Jain and Gupta et al. 2013) (Figdor 1994) (Narhi et al. 1992) (Walton and Nair 1995). Therefore, this type of pain could have been modulated by the medicines used in this research; especially the acetaminophen that is antagonizing of substance P (Jacqz Aigrain and Anderson 2006) which is released mainly by C fiber (Sacerdote and Levrini 2012). However, it is worth mentioning that the mean difference in pain intensity from both groups was very low and not clinically important. It is still necessary the conduction of further studies to reduce the bleaching-induced TS.

In a literature review, Haywood 2005 and Bonafe et al. 2013 reported that TS from bleaching usually affects the smaller teeth, such as the maxillary lateral incisors and the mandibular incisors. The present clinical study found all teeth presented tooth sensitivity symptoms during and immediately post bleaching by the risk of TS varied from tooth to tooth. Indeed, the lower central incisors were most painful teeth and the the premolars were less cited as painful by patients, which indicates that teeth with less dental structure are more likely to have tooth sensitivity. Moncada and others (Moncada et al. 2013), determined by cone beam computed tomography (CBCT) that the tooth thickness are not correlated with tooth sensitivity immediately after dental bleaching, however they only evaluated central incisors and they have not taken into

consideration the whole volume of the dental structure.

Our study used 3 methods for color evaluation. Although the spectrophotometer provides an objective color assessment, previous studies reported that shade guides showed more accurate visual correlation and allowed more accurate monitoring, and consistent and reliable color of teeth (Paravina 2008).VITA Classical is frequently used in dental bleaching studies (Rezende et al. 2016) (De Geus et al. 2016) Luque-Martinez et al. 2016), however, it has a nonlinear color arrangement, as it was not primarily designed for evaluation of dental bleaching. This was the reason we also used the shade guide VITA Bleachedguide 3D-MASTER.

According to the Vita Classical shade guide, the degree of whitening observed in this study, for both groups, was approximately 5 SGU. Although comparison with other studies are quite difficult due to different bleaching products and protocols (De Geus et al. 2016), studies that performed two in-office bleaching sessions with 35% hydrogen peroxide yielded similar results (Reis et al. 2011) (Tay et al. 2009) (Papathanasiou et al. 2002) (Onwudiwe et al. 2013).

The Bleachedguide VITA 3D-MASTER shade guide was developed for evaluation of color changes in bleaching studies; it presents more uniform color distribution compared to Vita Classical (Paravina 2008) and it is already organized from low-to-high value. It has the disadvantage of being rarely employed (Rezende et al. 2016) (De Geus et al. 2016) (De Geus et al. 2015) (Correa et al. 2016) preventing authors from comparing these results with the literature. In face of that, the authors of this study discourage the sole use of this tool.

Regardless of the instrument used for color measurement, they were all convergent in the findings that groups were statistically similar, which means that the perioperative use of the tromethamine/acetaminophen association did not jeopardize the whitening efficacy of the bleaching procedures. Intra-oral use of different drugs has been used to prevent bleaching-induced TS, but based on the present study and on the findings from earlier studies we reached the overall conclusion that the use of intra-oral drugs did not affect the whitening efficacy (Rezende et al. 2016) Charakorn et al. 2009) (De Paula et al. 2013b).

The use of acetaminophen/ketorolac tromethamine association prior to in-office bleaching does not reduce the risk but it reduced the tooth intensity 12 hours after bleaching, although this reduction was not clinically significant.

Compliance with ethical standards

It was conducted in accordance with the protocol established by the Consolidated Standards of Reporting Trials statement with extension for within-person designs.

Conflicts 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.

Funding

The authors do not have any financial interest in the companies whose materials are included in this article. This study was not funded by any sponsoring company.

This study was performed by Eloisa Andrade de Paula as partial fulfillment of his Post-Doctoral at the State University of Oeste do Paraná (UNIOESTE), Cascavel, PR, Brazil, with scholarship supported by the Coordination for the Improvement of Higher Education Personnel (CAPES) under grants PNPD20132394.

Ethical approval

This clinical investigation was approved (protocol number 45733615.6.0000.0109) by the Scientific Review Committee and by the Committee for the Protection of Human Subjects of the University of Paraná – UNIPAR (Cascavel, PR, Brazil). It was registered in clinical trials registry (REBEC) under identification number RBR-9GXBG6. All persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study were omitted.

Informed consent

Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. DE SOUZA COSTA CA, RIEHL H, KINA JF, SACONO NT & HEBLING J. 2010 Human pulp responses to in-office tooth bleaching. Oral Surg. Oral Med. Oral Pathol. Oral Radiol 109(4) e59-e64.
2. CARTAGENA AF, PARREIRAS SO, LOGUERCIO AD, REIS A & CAMPANHA NH. 2015. In-office bleaching effects on the pulp flow and tooth sensitivity–case. Braz Oral Res 29(1) 1-6.
3. JACQZ-AIGRAIN E, ANDERSON BJ. 2006. Pain control: non-steroidal anti-inflammatory agents. Semin Fetal Neonat M 11(4) 251-259.
4. HAYWOOD VB. 2005. Treating sensitivity during tooth. Compend Contin Educ Dent Suppl. (Jamesburg, NJ: 1995) 26(9 Suppl 3) 11-20.
5. REIS A, DALANHOL A, CUNHA T, KOSSATZ S & LOGUERCIO A. 2011. Assessment of tooth sensitivity using a desensitizer before light-activated bleaching. Oper. Dent 36(1) 12-17.
6. REZENDE M, BONAFÉ E, VOCHIKOVSKI L, FARAGO PV, LOGUERCIO AD, REIS A

& KOSSATZ S. 2016. Pre-and postoperative dexamethasone does not reduce bleaching-induced tooth sensitivity: a randomized, triple-masked clinical trial. J Am Dent Assoc 147(1) 41-49.
7. BONAFÉ E, BACOVIS CL, IENSEN S, LOGUERCIO AD, REIS A & KOSSATZ S. 2013. Tooth sensitivity and efficacy of in-office bleaching in restored teeth. J Dent 41(4) 363-369.
8. DE PAULA E, KOSSATZ S, FERNANDES D, LOGUERCIO A & REIS A. 2014. Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: a randomized triple-blind clinical trial. Oper. Dent 39(2) 128-135.
9. SANTANA MAP, NAHSAN FPS, OLIVEIRA AHDA, LOGUÉRCIO AD & FARIA-E-SILVA AL. 2014. Randomized controlled trial of sealed in-office bleaching effectiveness Braz. Dent. J. 25(3) 207-211.
10. CHARAKORN P, CABANILLA L, WAGNER W, FOONG W, SHAHEEN J, PREGITZER R & SCHNEIDER D. 2009. The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching. Oper. Dent. 34(2) 131-135.
11. DE PAULA EA, LOGUERCIO AD, FERNANDES D, KOSSATZ S & REIS A. 2013. Perioperative use of an anti-inflammatory drug on tooth sensitivity caused by in-office bleaching: a randomized, triple-blind clinical trial Clin. Oral Investig. 17(9) 2091-2097.
12. DA COSTA POUBEL LA, DE GOUVEA CVD, CALAZANS FS, DIP EC, ALVES WV, MARINS SS, BARCELOS R, BARCELEIRO MO. 2019. Pre-operative use of dexamethasone does not reduce incidence or intensity of bleaching-induced tooth sensitivity. A triple-blind, parallel-design, randomized clinical trial. Clin. Oral Investig.23(1) 435-444.
13. VAEZ SC, FARIA-E-SILVA AL, LOGUÉRCIO AD, FERNANDES MTG, NAHSAN FPS. 2018. Preemptive use of etodolac on tooth sensitivity after in-office bleaching: a randomized clinical trial. J APPL ORAL SCI. 26 e20160473.
14. FERNANDES M, VAEZ S, LIMA C, NAHSAN F, LOGUÉRCIO A & FARIA-E-SILVA A. 2017. Preemptive use of naproxen on tooth sensitivity caused by in-office bleaching: a triple-blind, crossover, randomized clinical trial. Oper. Dent. 42(5) 486-496.
15. LEPINSKI AM, HARGREAVES KM, GOODIS HE & BOWLES WR. 2000. Bradykinin levels in dental pulp by microdialysis. J. Endod. 26(12) 744-747.
16. RODD HD & BOISSONADE FM. 2000. Substance P expression in human tooth pulp in relation to caries and pain experience. Eur J Oral Sci. 108(6) 467-474.
17. CAVIEDES-BUCHELI J, ARIZA-GARCÍA G, RESTREPO-MÉNDEZ S, RÍOS-OSORIO N, LOMBANA N & MUÑOZ HR. 2008. The effect of tooth bleaching on substance P expression in human dental pulp. J. Endod. 34(12) 1462-1465.
18. GRAHAM GG, DAVIES MJ, DAY RO, MOHAMUDALLY A & SCOTT KF. 2013. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings Inflammopharmacology 21(3) 201-232.
19. BOTTING RM. 2000. Mechanism of action of acetaminophen: is there a cyclooxygenase 3? Clin. Infect. Dis. 31(Supplement_5) S202-S210.
20. HYLLESTED M, JONES S, PEDERSEN J & KEHLET H. 2002. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review Br. J. Anaesth. 88(2) 199-214.
21. ROOKS 2ND W, MALONEY P, SHOTT L, SCHULER M, SEVELIUS H, STROSBERG A, TANENBAUM L, TOMOLONIS A, WALLACH M & WATERBURY D. 1985. The analgesic and anti-inflammatory profile of ketorolac and its tromethamine salt Drugs Exp Clin Res 11(8) 479-492.
22. MCALEER SD, MAJID O, VENABLES E, POLACK T & SHEIKH MS. 2007. Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. Br J Clin Pharmacol. 47(1) 13-18.
23. SCHULZ KF, ALTMAN DG & MOHER D. 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials Ann Intern Med 152(11) 726-732.

24. COPPLA F, REZENDE M, DE PAULA E, FARAGO P, LOGUERCIO A, KOSSATZ S & REIS A. 2018. Combination of acetaminophen/codeine analgesics does not avoid bleaching-induced tooth sensitivity: A randomized, triple-blind two-center clinical trial. Oper. Dent. 43(2) E53-E63.
25. TAY LY, KOSE C, LOGUERCIO AD & REIS A. 2009. Assessing the effect of a desensitizing agent used before in-office tooth bleaching. J Am Dent Assoc. 140(10) 1245-1251.
26. WANNMACHER L & FERREIRA MBC. 1995. Farmacologia clínica para dentistas Farmacologia clínica para dentistas Guanabara Koogan.
27. REIS A, KOSSATZ S, MARTINS GC & LOGUERCIO AD. 2013. Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: a randomized clinical trial Oper. Dent. 38(4) 386-393.
28. BERNARDON JK, SARTORI N, BALLARIN A, PERDIGAO J, LOPES G & BARATIERI LN. 2010. Clinical performance of vital bleaching techniques Oper. Dent. 35(1) 3-10.
29. DE PAULA EA, KOSSATZ S, FERNANDES D, LOGUERCIO AD & REIS A. 2014. Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: a randomized tripleblind clinical trial Oper. Dent. 39(2) 128-135.
30. MEIRELES SS, HECKMANN SS, SANTOS IS, DELLA BONA A & DEMARCO FF. 2008. double blind randomized clinical trial of at-home tooth bleaching using two carbamide peroxide concentrations: 6-month follow-up. J Dent. 36(11) 878-884.
31. GURGAN S, CAKIR FY & YAZICI E. 2010. Different light-activated in-office bleaching systems: a clinical evaluation. Laser Med Sci. 25(6) 817-822.
32. HE LB, SHAO MY, TAN K, XU X & LI JY. 2012. The effects of light on bleaching and tooth sensitivity during in-office vital bleaching: A systematic review and meta-analysis. J Dent. 40(8) 644-653.
33. MEHTA D, VENKATA S, NAGANATH M, LINGAREDDY U, ISHIHATA H & FINGER WJ 2013. Clinical trial of tooth desensitization prior to in-office bleaching. Eur J Oral Sci. 121(5) 477-481.
34. ALOMARI Q, EL DARAA E. 2010. A randomized clinical trial of in-office dental bleaching with or without light activation. J Contemp Dent Pract. 11(1) e17-e24.
35. BERNARDON JK, MARTINS MV, RAUBER GB, JUNIOR SM & BARATIERI LN. 2016. Clinical evaluation of different desensitizing agents in home-bleaching gels. J Prosthet Dent. 115(6) 692-696.
36. DE GEUS JL, DE LARA M, HANZEN T, FERNÁNDEZ E, LOGUERCIO A, KOSSATZ S & REIS A. 2015. One-year follow-up of at-home bleaching in smokers before and after dental prophylaxis. J Dent. 43(11) 1346-1351.
37. TAY LY, KOSE C, LOGUERCIO AD & REIS A. 2009. Assessing the effect of a desensitizing agent used before in-office tooth bleaching. J Am Dent Assoc. 140(10) 1245-1251.
38. REZENDE M, COPPLA FM, CHEMIN K, CHIBINSKI AC, LOGUERCIO AD, REIS A. 2019. Tooth sensitivity after dental bleaching with a desensitizing-containing and a desensitizing-free bleaching gel: a systematic review and meta-analysis. Oper. Dent. 44(2) e58-e74.
39. BASTING RT, AMARAL F, FRANÇA F & FLÓRIO F. 2012. Clinical comparative study of the effectiveness of and tooth sensitivity to 10% and 20% carbamide peroxide home-use and 35% and 38% hydrogen peroxide in-office bleaching materials containing desensitizing agents Oper. Dent. 37(5) 464-473.
40. REIS A, KOSSATZ S, MARTINS G & LOGUERCIO A. 2013. Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: a randomized clinical trial Oper. Dent. 38(4) 386-393.
41. DE PAULA E, KOSSATZ S, FERNANDES D, LOGUERCIO A & REIS A. 2013. The effect of perioperative ibuprofen use on tooth sensitivity caused by in-office bleaching. Oper. Dent.

38(6) 601-608.
42. MEHTA D, VENKATA S, NAGANATH M, LINGAREDDY U, ISHIHATA H & FINGER WJ. 2013. Clinical trial of tooth desensitization prior to in-office. Eur J Oral Sci. 121(5) 477-481.
43. FRIED K, SESSLE BJ & DEVOR M. 2011. The paradox of pain from the tooth-pulp: Low-threshold "algoneurons"?. Pain. 152(12) 2685.
44. GIBBS J, MELNYK J & BASBAUM A. 2011. Differential TRPV1 and TRPV2 channel expression in dental pulp. Saudi J Dent Res. 90(6) 765-770.
45. BASBAUM AI, BAUTISTA DM, SCHERRER G & JULIUS D. 2009. Cellular and molecular mechanisms of pain. Cell J. 139(2) 267-284.
46. AMAYA F, IZUMI Y, MATSUDA M & SASAKI M. 2013. Tissue injury and related mediators of pain exacerbation. Curr. Neuropharmacol. 11(6) 592-597.
47. LASKIN DM. 2013. Application of current pain management concepts to the prevention and management of postoperative pain. J Am Dent Assoc. 144(3) 284-286.
48. PARKE TJ, MILLETT S, OLD S, GOODWIN AP & RICE AS. 1995. Ketorolac for early postoperative analgesia J. Clin. Anesth. 7(6) 465-469.
49. TAY LY, KOSE C, LOGUERCIO AD & REIS A. 2009. Assessing the effect of a desensitizing agent used before in-office tooth bleaching . J Am Dent Assoc. 140(10) 1245-1251.
50. JAIN N & GUPTA A. 2013. An insight into neurophysiology of pulpal pain: facts and hypotheses. Korean J Pain. 26(4) 347-355.
51. RODERJAN DA, STANISLAWCZUK R, HEBLING J, COSTA CADS, REIS A & LOGUERCIO AD. 2015. Response of human pulps to different in-office bleaching techniques: preliminary findings. Braz. Dent. J. 26(3) 242-248.
52. FIGDOR D. 1994.Aspects of dentinal and Pulpal Pain. Pain of dentinal and pulpal origin--a review for the clinician. Ann R Australas Coll Dent Surg. 12 131-142.
53. NÄRHI M, JYVÄSJÄRVI E, VIRTANEN A, HUOPANIEMI T, NGASSAPA D & HIRVONEN T. 1992. Role of intradental A-and C-type nerve fibres in dental pain mechanisms Proc Finn Dent Soc 88(Suppl 1) 507-516.
54. WALTON RE & NAIR PR. 1995. Neural elements in dental pulp and dentin. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 80(6) 710-719.
55. SACERDOTE P & LEVRINI L. 2012. Peripheral mechanisms of dental pain: the role of substance P. Mediators Inflamm. 2012 951920.
56. MONCADA G, SEPÚLVEDA D, ELPHICK K, CONTENTE M, ESTAY J, BAHAMONDES V, FERNANDEZ E, OLIVEIRA O & MARTIN J. 2013. Effects of light activation, agent concentration, and tooth thickness on dental sensitivity after bleaching. Oper. Dent. 38(5) 467-476.
57. PARAVINA RD. 2008. New shade guide for tooth whitening monitoring: visual assessment. J Prosthet Dent. 99(3) 178-184.
58. REZENDE M, DE GEUS J, LOGUERCIO A, REIS A & KOSSATZ D. 2016. Clinical Evaluation of Genotoxicity of In-office Bleaching. Oper. Dent. 41(6) 578-586.
59. DE GEUS J, WAMBIER L, KOSSATZ S, LOGUERCIO A & REIS A. 2016. At-home vs in-office bleaching: a systematic review and Meta-analysis. Oper. Dent. 41(4) 341-356.
60. LUQUE-MARTINEZ I, REIS A, SCHROEDER M, MUÑOZ MA, LOGUERCIO AD, MASTERSON D & MAIA LC. 2016. Comparison of efficacy of tray-delivered carbamide and hydrogen peroxide for at-home bleaching: a systematic review and meta-analysis Clin. Oral Investig. 20(7) 1419-1433.
61. PAPATHANASIOU A, KASTALI S, PERRY RD & KUGEL G. 2002. Clinical evaluation of a 35% hydrogen peroxide in-office whitening system. Compend Contin Educ Dent. 23(4) 335-338.
62. ONWUDIWE U, UMESI D, ORENUGA O & SHABA O. 2013. Clinical evaluation of 16%

and 35% carbamide peroxide as in-office vital tooth whitening agents. Nig Q J Hosp Med. 23(2) 80-84.[i]
63. DE GEUS JL, DE LARA M, HANZEN T, FERNÁNDEZ E, LOGUERCIO A, KOSSATZ S & REIS A. 2015. One-year follow-up of at-home bleaching in smokers before and after dental prophylaxis. J Dent. 43(11) 1346-1351.
64. CORREA A, SANTANA T, NAHSAN F, LOGUERCIO A & FARIA-E-SILVA A. 2016. The impact of a customized tray on in-office bleaching tooth sensitivity: A randomized clinical trial Oper. Dent. 41(1) 15-22.

Table 1. Baseline Characteristics of the Participants.

Characteristic		**Acetaminophen/Ketorolac (n=58)**	**Placeb (n=57)**
Baseline color (SGU*; mean ± SD)		6.2 ± 1.5	6.1 ± 1.8
Age (years; mean ± SD)		22.3 ± 3.5	23.0 ± 4.3
Gender (female; %)		63.8	65.0
Race	White (%)	91.4	89.5
	Black (%)	0	0
	Mulatto (%)	8.6	8.8
	Yellow (%)	0	1.7
Smoker		0	2
Patients that used whitening toothpaste		0	0

* Abbreviations: SGU, shade guide unit measured by Vita Classical; SD, standard deviation.

Table II. Comparison of absolute risk of tooth sensitivity (percentage, 95% confidence interval) along with the risk ratio (*).

Treatment	**Absolute risk (95% CI)**	**Risk ratio (95% CI)**
Acetaminophen/ ketorolac (n=58)	72 (60 - 82)	0.9 (0.7 to 1.1)
Placebo (n = 56)	79 (68 - 89)	

(*) chi-square test (p-value = 0.414).

Table III. Medians and interquartile ranges of the tooth sensitivity intensity at different assessment points using the NRS and VAS scale.

Time assessment periods	**NRS scale**			**VAS scale**		
	Acetaminophen/ ketorolac	**Placebo**	**p-value**	**Acetaminophen/ ketorolac**	**Placebo**	**p-value**
During bleaching	1 (0-2) A	1 (0-2) A	0.60	1.0 (0-4) A	1.0 (0-4) A	0.77
Up to 1 h	1 (0-3) B	2 (0-3) B	0.28	2.5 (0-5) B	3.5 (0-6) B	0.20
1 h to 6 h	1 (0-2) C	2 (0-3) C	0.18	2.8 (0-5) C	4.0 (0-6) C	0.06
6 h to 12 h	1 (0-2) D	1 (0-2) D	0.07	1.0 (0-3) D	2.0 (0-5) D	0.17
12 h to 24 h	0 (0-1) E	1 (0-1) E	**0.04**	0.0 (0-1) E	1.0 (0-3) E	**0.03**
24 h to 48 h	0 (0-0) F	0 (0-1) F	**0.03**	0.0 (0-0) F	0.0 (0-1) F	**0.03**

Brazilian Journal of Development

Table IV – Means and standard deviations of the TS intensity at the different time assessment periods along with the effect size and the 95% confidence interval with VAS scale.			
Time assessement periods	**Acetaminophen/ ketorolac**	**Placebo**	**Mean difference (95% CI)**
During bleaching	2.1 ± 2.4	2.2 ± 2.9	-0.1 (-1.16 to 0.86)
Up to 1 h	2.9 ± 3.0	3.6 ± 3.1	-0.7 (-1.87 to 0.40)
1 h to 6 h	2.9 ± 2.9	4.0 ± 3.2	-1.0 (-2.22 to 0.08)
6 h to 12 h	2.0 ± 2.7	2.7 ± 2.7	-0.6 (-1.68 to 0.31)
12 h to 24 h	1.0 ± 1.9	1.8 ± 2.2	-0.7 (-1.52 to 0.02)
24 h to 48 h	0.2 ± 0.8	0.6 ± 1.4	-0.4 (-0.86 to 0.03)

Table V. The proportion of teeth from both groups that reported TS at least once in the central incisors, lateral incisors, canines and premolars from both arches (percentage, 95% confidence interval).		
Kind of Teeth	% (95% CI) (n= 254 painful teeth)	
	Upper arch	**Lower arch**
Central incisor	9.4 (6 to 13)	29.9 (16 to 26)
Lateral incisor	8.7 (5 to 12)	18.5 (14 to 23)
Canines	13.8 (10 to 18)	13.8 (13 to 22)
Premolars	4.3 (2 to 7)	6.7 (4 to 10)
(*) chi-square test (p-value p < 0.001).		

Table VI. Means and standard deviations of ΔSGU obtained with the Vita Classical and Vita Bleachedguide and ΔE obtained by spectrophotometer between baseline vs. 1-month post bleaching along with the p-value of the pairwise comparison as well as the effect size (95% confidence interval).				
Color evaluation tool	**Groups**		**p-value**	**Mean difference (95% CI)**
	Acetaminophen/ ketorolac	**Placebo**		
Vita Classical	4.7 ± 1.6	4.7 ± 1.7	0.83	-0.06 (-0.6 to 0.5)
Vita Bleached	7.1 ± 3.3	6.3 ± 2.8	0.18	0.2 (-0.2 to 0.8)
ΔE	7.0 ± 3.4	7.4 ± 3.8	0.83	0.4 (-0.9 to 1.7)

Brazilian Journal of Development

Figure captions:

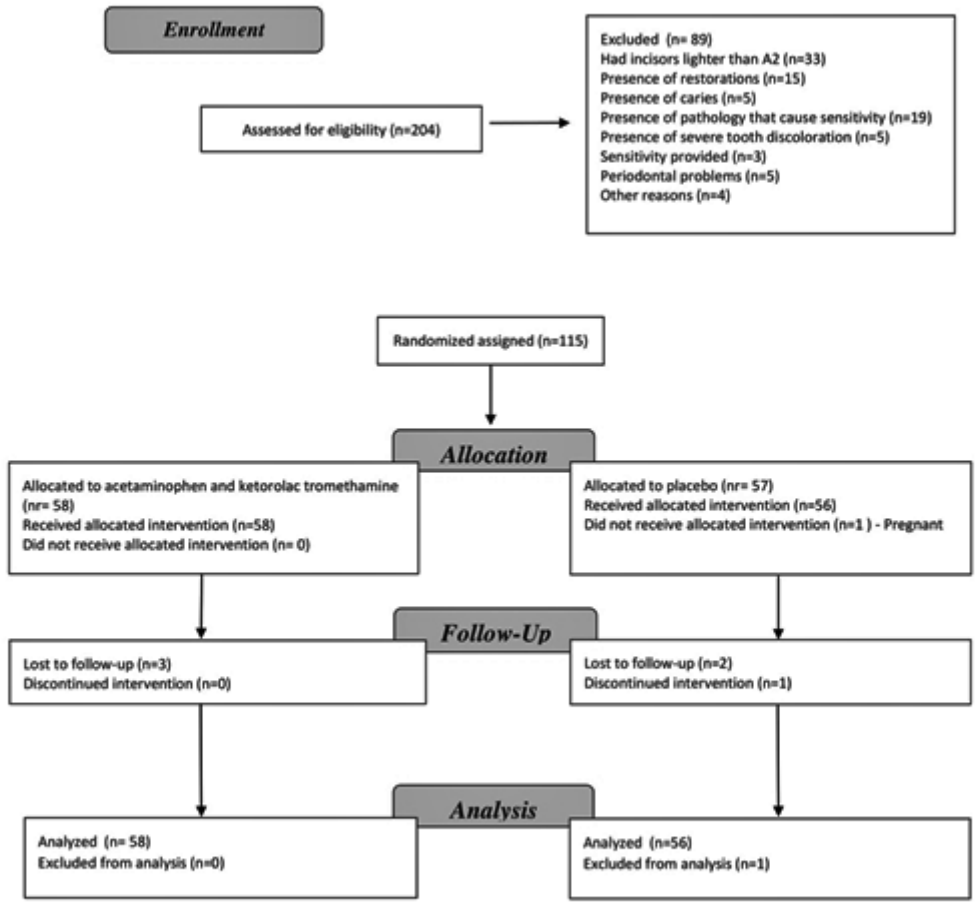

Fig. 1. Flow diagram of the clinical trial including detailed information on the excluded participants.