©Operative Dentistry, 2018, **43-2,** E53-E63

Clinical Research

Combination of Acetaminophen/ Codeine Analgesics Does Not Avoid Bleaching-Induced Tooth Sensitivity: A Randomized, Triple-Blind Two-Center Clinical Trial

FM Coppla • M Rezende • E de Paula • PV Farago • AD Loguercio • S Kossatz • A Reis

Clinical Relevance

The use of an opioid analgesic drug was not capable of preventing tooth sensitivity arising from in-office dental bleaching.

SUMMARY

Bleaching-induced tooth sensitivity (TS) is highly prevalent. Objective: This study aimed to determine if the combination of opioids and nonopioids analgesics (Tylex) may provide a better analgesic effect. Method: A triple-blind, parallel, randomized two-center clinical trial was conducted with 105 healthy patients who received either a placebo or a combination of acetaminophen/codeine. The first dose of Tylex 30 mg (acetaminophen 500 mg/codeine 30 mg) or placebo was administered one hour before the in-office bleaching (35% hydrogen peroxide), and extra doses were administered every six hours for 48 hours. The TS was recorded using a visual analog scale of 0 to 10 and a numeric rating scale of 0 to 4 in different periods: during bleaching, one hour up to 24 hours, and 24 hours up to 48 hours postbleaching. The color was measured before and one month after dental bleaching with a visual shade guide (Vita Classical), Vita Bleached-

Fabiana Madalozzo Coppla, DDS, MS, PhD, Department of Restorative Dentistry, University Estadual de Ponta Grossa, Ponta Grossa, Brazil

Márcia Rezende, MS, PhD, postdoctoral student, Department of Restorative Dentistry, University Estadual de Ponta Grossa, Ponta Grossa, Brazil, and Professor, Paulo Picanço School of Dentistry, Fortaleza, Brazil

Eloisa de Paula, MS, DDS, PhD, postdoctoral student, Department of Restorative Dentistry, University of Oeste of Paraná, Cascavel, Brazil

Paulo Vitor Farago, MS, PhD, professor, School of Pharmacy, State University of Ponta Grossa, Ponta Grossa, Brazil

*Alessandro Dourado Loguercio, DDS, MS, PhD, professor, School of Dentistry, State University of Ponta Grossa, Ponta Grossa, Brazil

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

Alessandra Reis, DDS, PhD, professor, School of Dentistry, Department of Restorative Dentistry, University Estadual de Ponta Grossa, Ponta Grossa, Brazil

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

DOI: 10.2341/17-092-C

guide 3D-MASTER, and the spectrophotometer Vita Easyshade. The absolute risk of TS was evaluated using the Fisher exact test. Data of TS intensity with numeric rating scale of the two groups were compared with the Mann-Whitney *U*-test and the Friedman test, while data from the visual analog scale were evaluated by two-way repeated measures analysis of variance and the Tukey test for pairwise comparison. The color changes between groups were compared using the Student *t*-test (α=0.05). Results: No significant differences between the groups were observed in the risk and intensity of TS. The overall absolute risk of TS was approximately 96%. No significant differences between groups were observed in terms of color change ($p>0.05$) for any scale. Conclusion: The use of an acetaminophen/codeine combination prior to in-office bleaching does not reduce the risk and intensity of bleaching-induced TS.

INTRODUCTION

In-office bleaching is an alternative to the popular at-home bleaching, and a dental professional can perform it on the same day the patient walks into the dental office.[1] The in-office bleaching protocol has some advantages, as it allows close dentist control, avoids soft tissue exposure to peroxides, avoids the risk of material ingestion, and reduces total treatment time. However, in-office bleaching using 35% hydrogen peroxide (HP) has a long history of tooth sensitivity (TS),[2-4] producing TS intensity that is, on average, four times higher than that produced by at-home bleaching.[5] In recent clinical trials, authors reported an absolute risk of TS varying from 67% to 100%,[5-9] meaning that under the best conditions, six patients in every 10 will experience pain during treatment.

The high variability of pain induced by bleaching can be explained by variables such as age, gender, baseline tooth color, and bleaching technique (at-home or in-office bleaching, a single bleaching session or even shorter application times of 10 to 20 minutes, or variations in the concentrations and composition of the products). Rezende and others[10] showed an association between baseline tooth color and bleaching-induced TS: every 1-shade-guide-unit (SGU) increase in baseline color reduces the odds of TS by 17% and the intensity by 13%. Baseline color can predict TS; in other words, the darker the teeth, the lower the intensity and risk of TS.

To the extent of the authors' knowledge, the reasons for bleaching-induced TS are not clear. TS seems to result from the easy passage of HP through the enamel and dentin to the pulp,[11] causing pulp damage and a reversible inflammation process.[12] Since 2009, some authors have investigated the use of anti-inflammatory drugs to reduce this adverse effect.[5,6,13-15] In their studies, the use of ibuprofen, a nonsteroidal anti-inflammatory, reduced TS immediately up to one hour after bleaching.[14,15] The administration of other medicines, such as a selective anti-inflammatory drug (etoricoxib, 60 mg) or a steroidal anti-inflammatory drug (dexamethasone, 4 mg), was not capable of reducing this side effect.[5,14]

Another medicine that can be used per the oral route but not yet investigated could be an alternative approach. Nonopioid analgesics produce analgesia through peripheral action consisting of the inhibition of the cyclooxygenase enzyme system.[16] This class of analgesics comprises commonly used drugs for pain control due to their low toxicity, with rare side effects in cardiovascular and respiratory systems.[16] However, compared to opioid analgesics, they have a limited analgesic effect.[16] Opioid analgesics act on specific sites in the central nervous system. At the cellular level, they promote the closing of voltage-gated calcium channels, a reduction in the production of cyclic adenosine monophosphate, and the stimulation of potassium efflux resulting in cell hyperpolarization. This, in turn, reduces the neuronal excitability and nociceptive impulses of pain.[17] They are used successfully for the relief of acute pain.[18,19]

Perhaps combining an opioid (codeine) and a nonopioid analgesic (acetaminophen) can induce analgesia through both peripheral and central mechanisms[17] at a higher level than that possible by using either drug alone. This could help reduce the risk and intensity of bleaching-induced TS. Indeed, some studies in the dental field that used this combination for treatment of irreversible pulpitis have shown good results in terms of pain prevention.[20,21]

Therefore, this parallel, triple-masked, randomized clinical trial aimed to evaluate the effect of an acetaminophen/codeine analgesic, administered perioperatively for 48 hours, on the risk and intensity of bleaching-induced TS. The color change was also evaluated as a secondary outcome. The null hypothesis of this study was that combined acetaminophen/codeine administered perioperatively for 48 hours does not reduce the risk and intensity of bleaching-induced TS.

METHODS AND MATERIALS

Ethics Approval

This clinical investigation was approved (protocol number 890.207) by the scientific review committee and by the committee for the protection of human subjects of the State University of Ponta Grossa (Ponta Grossa, Brazil). This study was registered in the Brazilian clinical trials registry under the identification number RBR-4jsgbc (http://www.ensaiosclinicos.gov.br). This clinical report follows the protocol established by the Consolidated Standards of Reporting Trials statement.[22]

Trial Design, Settings, and Locations of Data Collection

This was a randomized, parallel, placebo-controlled, triple-mask clinical trial in which the patient, operator, and evaluator were masked to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the randomization process and delivery and guidance on the administration of the drugs. This study was performed from July to December 2015 in Ponta Grossa and Cascavel, Brazil. All bleaching procedures were carried out within the Clinics of the Dental School of the State University of Ponta Grossa, Ponta Grossa, and at Paranaense University, Cascavel, Brazil. Both centers are located in the state of Paraná, Brazil.

Recruitment

Two weeks before the bleaching procedures, all the volunteers, who were patients in search of treatment in the clinics of the respective dental schools, signed an informed consent form and received a dental prophylaxis with pumice and water in a rubber cup.

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 without restorations and no periodontal disease and must have reviewed and signed the informed consent form. The central incisors were shade A2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical, Vita Zahnfabrik, Bad Säckingen, Germany).

Two calibrated investigators in each dental school independently performed the color evaluation with a value-oriented shade guide. The two examiners, masked to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at baseline and one month after the procedure. The two examiners were required to have an agreement of at least 85% (kappa statistic) before beginning the study evaluation. For this purpose, the evaluators independently registered the color of 10 patients before and after bleaching to record the interexaminer agreement by kappa statistics. After reaching this level of agreement, they were considered trained to start the color measurements in the present clinical trial.

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

Patients who reported some earlier or present stomach, heart, kidney, or liver problems and participants reporting continuous use of anti-inflammatory and/or analgesic drugs were excluded. Additionally, patients with diabetes, hypertension, or known allergies 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 was reported to be approximately 87%[14,23] for the bleaching product Whiteness HP Maxx (FGM Prod. Odont. Ltda, Joinville, Brazil). Thus, a minimum sample size of 92 patients was required to have an 80% chance of detecting, as significant at the two-sided 5% level, a decrease in the primary outcome measure from 86% in the control group to 61% in the experimental group (which represents a difference of 25% in the absolute risk of TS). Sample size was increased by approximately 15% to compensate for the eventual loss of patients.

Random Sequence Generation and Allocation Concealment

We used blocked randomization (block sizes of 2 and 4) with an equal allocation ratio. The randomization process was performed using software freely available on the Internet (http://www.sealedenvelope.com). Opaque and sealed envelopes containing the

identification of the groups were prepared by a third party not involved in the study intervention. This third researcher, not involved in the evaluation process, was responsible for the randomization process, delivery, and guidance on the administration of the drugs. A single random sequence was performed for both centers.

Study Intervention

Patients were divided into acetaminophen/codeine and placebo groups. All patients received the same bleaching treatment, which was performed by a single operator in each dental school. One hour before in-office bleaching, patients received either the acetaminophen (500 mg)/codeine (30 mg) (Tylex, 30 mg; Janssen-Cilag Farmacêutica Ltda, São José dos Campos, Brazil) or the placebo in identical capsules. The operator administered the first dose of drug one hour before the protocol, and extra doses were administered every six hours for 48 hours to keep a safe maximum daily dosage of 240 mg of codeine and 4000 mg of acetaminophen.[24]

The tablets of Tylex (combination of acetaminophen and codeine) were removed from their original packaging and inserted whole into empty capsules (identified by green and white color). We stored the capsules in individual vials containing eight capsules that would be required for each bleaching session. We prepared the placebo capsules in the same way described above. The capsules contained the same components of the Tylex 30-mg drug (starch, cellulose, sodium dioctyl sulfosuccinate/sodium benzoate, and magnesium stearate) except for the active ingredient.

One hour before starting the bleaching application, the masked researcher responsible for drug administration gave the first dose to the patient. Then they isolated the gingival tissue of the teeth to be bleached using a light-cured resin dam (Top Dam, FGM), and each tooth was light cured for 10 seconds (Radii-cal, SDI, Victoria, Australia). After placement of a lip retractor (Arcflex, FGM), the researcher used the 35% HP gel (Whiteness HP Maxx, FGM) in three 15-minute applications for both groups in accordance with the manufacturer's directions. The researcher refreshed the in-office bleaching agent every 15 minutes during the 45-minute application period. Two bleaching sessions were performed one week apart. All participants were instructed to brush their teeth regularly using fluoridated toothpaste.

TS Evaluation

TS was evaluated during bleaching up to one hour, from one hour up to 24 hours, and from 24 hours up to 48 hours postbleaching in both sessions. The patient was asked to indicate the numerical value of the degree of sensitivity for each one of the periods above using a five-point numeric rating scale (NRS) where 0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = severe.[4,6,13,14,23,25,26]

Additionally, the participants were instructed to record the pain intensity using the visual analog scale (VAS).[1,27,28] This scale is a 10-cm horizontal line with scores of 0 and 10 at their ends, where 0 = no sensitivity and 10 = severe sensitivity. The patient marked with a vertical line across the horizontal line of the scale the intensity of the TS. Then the distance in millimeters from the zero ends was measured with the aid of a millimeter ruler.

First, the data of TS from both bleaching sessions were merged. For this purpose, the worst score (NRS) and numerical value (VAS) obtained in both bleaching sessions in each assessment period was considered for statistical purposes and for the determination of the overall risk and intensity of TS.

If a 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. This dichotomization allowed us to calculate the absolute risk of TS, which represented the percentage of patients who reported TS at least once during treatment. We also calculated the overall TS intensity.

Color Evaluation

Color evaluation was recorded before and one month after dental bleaching. Color evaluation was never performed immediately after each bleaching session so that the effect of dehydration and demineralization on color measures could be prevented. The measurement area of interest for shade matching was the middle one-third of the facial surface of the anterior central incisor, according to the American Dental Association guidelines.[3,23,29] The color evaluation was performed with the value-oriented shade guide Vita Classical (Vita Zahnfabrik) and the Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik). Additionally, an objective color evaluation was performed with the spectrophotometer Vita Easyshade (Vita Zahnfabrik).

For the subjective examination, with shade guide Vita Classical, the shade guide's 16 tabs were arranged from the highest (B1) to the lowest (C4) value. Although this scale is not linear in the truest sense, we treated the changes as representing a continuous and approximately linear ranking for the purpose of analysis, as already performed in several published studies.[1,4,14,25,26,28-30] The Vita Bleached-guide 3D-MASTER contains lighter shade tabs and is already organized from the highest (0M1) to the lowest (5M3) value.[5,30,31]

The two examiners, masked to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at the different time assessments. Color changes were calculated from the beginning of the active phase through to the individual recall times by calculating the change in the number of SGU (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs. In the event of disagreements between the examiners during shade evaluation, a consensus was reached.

For the objective examination, before the spectrophotometer measurement, an impression of the maxillary arch was taken with dense silicone paste (Zetaplus and Oranwash Kit, Zhermack, Italy). The impression was extended to the maxillary canine and served as a standard color measurement guide for the spectrophotometer. For each dental component to be evaluated, a window was created on the labial surface of the molded silicone guide using a metal device with a radius of 3 mm and well-formed borders.[25] The shade was determined using the parameters of the Easyshade device where it 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 color comparison before and after treatment is given by differences between the two colors (ΔE), calculated using the formula $\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.[32]

Blinding

This was a triple-mask study in which the patient, operator, and evaluator were blinded to the group assignment.

Statistical Analysis

The analysis followed the intention-to-treat protocol and involved all participants who were randomly assigned.[22] In case of missing data, the last observation was carried forward. A preliminary statistical analysis was conducted to evaluate if the study center had any influence on the results. The absolute risk of pain of each group in both centers was compared by using the Fisher exact test. We also compared the TS intensity of both centers (within group) at each assessment time using the Mann-Whitney *U*-test. As we did not observe any statistical difference between study centers ($p>0.05$ for any comparison), the data from both centers (that come from the same population of the state of Paraná, Brazil) were merged and evaluated together.

The absolute risk of TS (including data from both centers) of both groups was compared using the Fisher exact test ($\alpha=0.05$). The relative risk as well as the confidence interval for the effect size were calculated.

Comparison of the TS intensity (NRS data) of the two groups (from the two centers) at the two different assessment points was performed using the Mann-Whitney *U*-test. Comparisons between times within each group were performed using the Friedman test. The comparison of the TS intensity obtained with the VAS was performed with two-way repeated measures analysis of variance and the Tukey test for pairwise comparison. The color changes between groups (ΔSGU and ΔE between baseline vs one month postbleaching) were compared using a Student *t*-test. In all statistical tests, the significance level was 5%. We performed all analyses by using the software SigmaPlot version 11.0 (Systat Software, San Jose, CA, USA).

RESULTS

Baseline Data and Characteristics of Included Participants

A total of 200 participants were examined in a dental chair to check whether they met the inclusion and exclusion criteria (Figure 1). In-office bleaching was performed in 105 patients out of these 200 examined participants. The baseline color (mean±standard deviation) of the participants was similar (placebo=6.2±2.0 and acetaminophen/codeine=6.0±2.0). Similarly, the mean age (years) of participants from both groups was equivalent (placebo=22.5±5.0 and acetaminophen/codeine: 22.3±6.3), ranging from 18 to 46 years old. Nineteen participants (37%) from the placebo group and nine participants (17%) from the acetaminophen/codeine group were male.

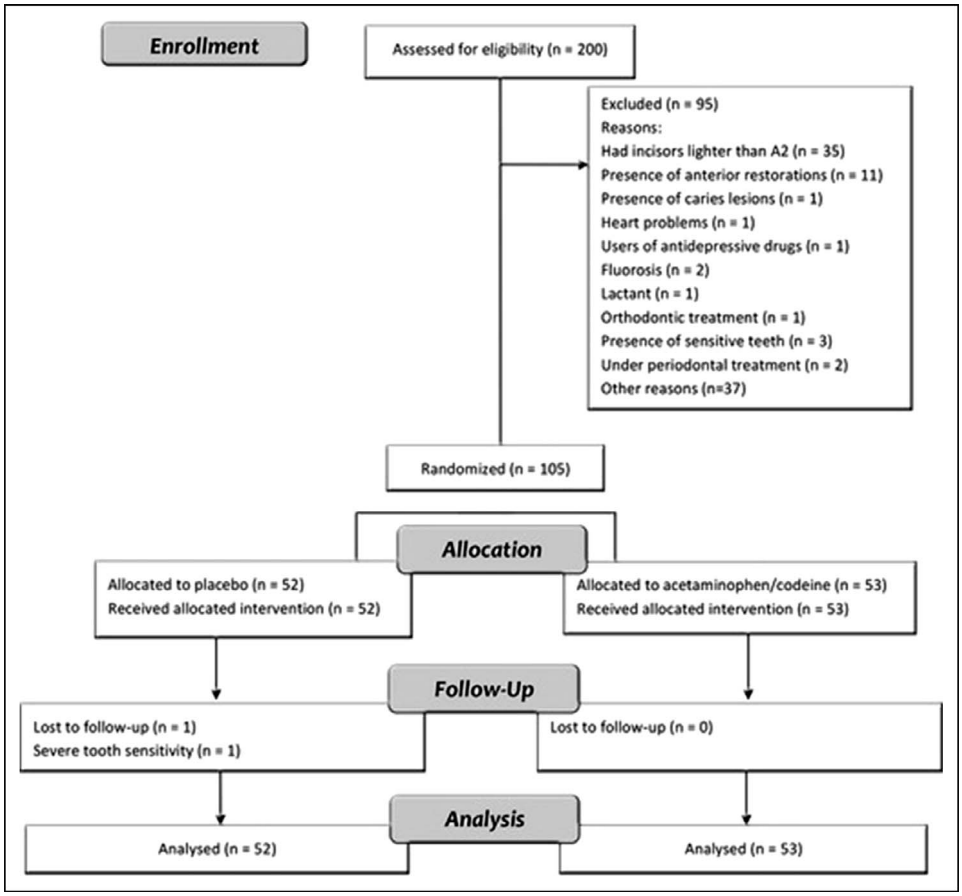

Figure 1. *Flow diagram of the clinical trial including detailed information on the excluded participants.*

Adherence to the Protocol and Dropouts

One patient from the placebo group discontinued intervention in this clinical investigation due to intense pain. This patient performed only the first bleaching session. All participants attended the recall visits one month postbleaching, except the participant from the placebo group who discontinued treatment. For this participant, the last observation was carried forward for statistical purposes to keep the intention-to-treat analysis.[22]

Two patients from the placebo group reported not taking one and six capsules after the first bleaching session: one forgot how to take it, and the other presented adverse effects (described later). Three patients from the acetaminophen/codeine group did not take three, five, and six capsules after the first bleaching session due to the development of adverse effects. Figure 1 depicts the participant flow diagram in the different phases of the study design.

TS

Three patients from the placebo group and one from the acetaminophen/codeine group took an analgesic (rescue medication) to alleviate the bleaching-induced TS (Tylenol, Janssen-Cilag Farmacêutica Ltda, São José dos Campos, Brazil). The data of these patients were included in the data analysis following the intention-to-treat protocol.

In regard to the absolute risk of TS, no significant difference was observed between groups as seen in Table 1 ($p=0.61$). The relative risk, along with the 95% confidence interval, is also evidence that the use of the acetaminophen/codeine drug had no effect on the reduction of TS. In regard to TS intensity (Tables 2 and 3), the groups did not differ statistically under the two pain scales used in this study ($p>0.05$). The very low mean difference between the two groups also shows that the observed difference is not clinically important (Table 3). But we could clearly observe that bleaching-induced TS was significantly more severe in the first 24 hours ($p<0.05$) and that it reduced considerably 48 hours after bleaching (Tables 2 and 3).

Color Evaluation

Significant whitening was observed in both study groups under the subjective and objective evaluation

Table 1: *Comparison of the Number of Patients Who Experienced Tooth Sensitivity (TS) During the Bleaching Regimen in Both Groups Along With Absolute Risk and Risk Ratio*[a]

Treatment	TS (Number of Participants)		Absolute Risk (95% Confidence Interval)	Risk Ratio (95% Confidence Interval)
	Yes	No		
Placebo	52	1	96.2 (87.2 to 98.9)	1.0 (0.92 to 1.07)
Acetaminophen/codeine	50	2	96.2 (87.0 to 98.4)	

[a] *Fisher's exact test (p = 0.61).*

methods ($p<0.05$). At the end of the bleaching protocol, a whitening of approximately 4 to 6 SGU was detected for both groups, and the ΔE varied by approximately 4.0 units (Table 4). The statistical analysis of the subjective (Vita Classical and Vita Bleachedguide) and the objective evaluation with the spectrophotometer matched the hypothesis of equality between the groups after bleaching ($p>0.05$). The very low mean difference between color change for each color measurement instrument highlights the lack of clinical importance of the observed difference (Table 4).

Adverse Effects

Five patients from the acetaminophen/codeine group and one patient from the placebo group presented nausea, vomiting, and malaise after the first bleaching session. For this reason, medication was discontinued, but the patient finished the bleaching protocol. In one patient from the placebo group and two patients from the acetaminophen/codeine group, symptoms disappeared with the discontinuation of the drugs. However, another patient from the acetaminophen/codeine group had to have the support of a physician who prescribed him an antiemetic drug.

DISCUSSION

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 is quite difficult due to different bleaching products and protocols,[33] studies that performed two in-office bleaching sessions with 35% HP yielded similar results.[3,23,34,35]

The Vita Classical shade guide is the most frequently used subjective tool for evaluation of color changes in bleaching studies,[5,33,36] but it presents a nonlinear arrangement of colors, as it was not designed for whitening evaluation. For this reason, we also employed the Bleachedguide VITA 3D-MASTER shade guide and an objective tool, the Easyshade spectrophotometer.

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,[37] and it is already organized from low to high value. It has the disadvantage of being rarely employed,[5,31,38-42] preventing authors from comparing these results with the literature. In the light of that, the authors of this study discourage the sole use of this tool.

Regardless of the instrument used for color measurement, all were convergent in the findings that groups were statistically similar, meaning that the perioperative use of acetaminophen/codeine did not jeopardize the whitening efficacy of the bleaching procedures. Intraoral 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 intraoral drugs did not affect whitening efficacy.[5,13-15]

Table 2: *Comparison of Tooth Sensitivity Intensity Experienced by Patients From the Treatment Groups at Different Assessment Points Using the Numeric Rating Scale (NRS)*[a]

Time Assessments	NRS[b]		Number of Scores 0/1/2/3/4	
	Placebo	Acetaminophen/Codeine	Placebo	Acetaminophen/Codeine
Up to 1 h	2 (1/3) Aa	2 (1/3) Xa	1/12/18/18/5	5/13/17/12/5
Up to 24 h	1 (0/2) Bb	1 (0/2) Yb	14/18/11/10/0	20/10/11/8/3
Up to 48 h	0 (0/0) Cc	0 (0/0) Zc	45/6/2/0/0	43/8/1/0/0

[a] *At each period, differences are represented by different lowercase letters (Mann-Whitney U-test for the NRS scale). For each treatment, different uppercase letters represent statistically significant means (Friedman test for the NRS scale).*
[b] *Medians (interquartile range).*

Table 3: *Comparison of Tooth Sensitivity Intensity Experienced by Patients From the Treatment Groups at Different Assessment Points Using the Visual Analog Scale (VAS)*[a]

Time Assessments	VAS[b]		Mean Difference (95% Confidence Interval)
	Placebo	Acetaminophen/Codeine	
Up to 1 h	3.8 ± 2.8 Aa	3.6 ± 2.7 Xa	0.2 (−0.9 to 1.3)
Up to 24 h	2.3 ± 2.4 Bb	2.6 ± 2.9 Yb	−0.3 (−1.3 to 0.8)
Up to 48 h	0.2 ± 0.7 Cc	0.3 ± 0.8 Zc	−0.1 (−0.4 to 0.2)

[a] *At each period, differences are represented by different lowercase letters (two-way analysis of variance for the VAS scale). For each treatment, different uppercase letters represent statistically significant means (repeated measures one-way analysis of variance for the VAS scale).*
[b] *Means and standard deviations.*

It is believed that TS that originates from bleaching is an inflammatory response of the dental pulp after the application of HP[12,43] with the liberation of bradykinin[44] and substance P, which are involved in the process of inflammation and pulp pain.[45,46] The release of substance P sends the nociceptive pain signals that indicate to the central nervous system a local proinflammatory action.[47]

The majority of the common opioids are agonists and work by stimulating the different opioid receptors (MOP, KOP, DOP, and so on), all of which are G-protein–coupled receptors. Within the central nervous system, activation of MOP receptors in the midbrain is thought to play the most important role on the opioid-induced analgesia.[48] Thus, theoretically, the net effect is the reduction of neuronal excitability, resulting in decreased neurotransmission of nociceptive impulses.[49] This could have been reinforced by the peripheral action of the acetaminophen, which acts by inhibiting cyclooxygenase release.[47]

We administered the medicines one hour before starting the bleaching procedure, as the drug takes around 30 to 60 minutes after ingestion to reach pharmacological plasmatic levels.[24] Extra doses of the medicine were administered every six hours up to 48 hours. Although the combination of codeine and acetaminophen (Tylex, 30 mg) is used in cases of severe pain, this combination reduced neither the risk nor the intensity of TS experienced by these patients. A high risk of TS was observed for both groups, corroborating the findings of previous studies.[5,7,13,14,28] Approximately 96% of participants in both groups reported TS at some stage of bleaching.

The ineffectiveness of this drug combination suggests that there are other mechanisms involved in the development of bleaching-induced TS. Previous studies that tested drugs with other mechanisms of action, such as nonsteroidal anti-inflammatory drugs,[13,15] selective anti-inflammatory medicine,[14] and even corticosteroids,[5] have also reached the same conclusion that they are not capable of preventing bleaching-induced TS. As wisely described by de Paula,[6] several factors may modulate the amount of drug that reaches the plasma and extracellular fluid and in the pulp chamber when administered per the oral route, such as the presence of the immune system, lymphatic drainage, urinary excretion, and morphological characteristics of the dentin substrate.[6]

Another factor that may explain the lack of effectiveness of this medicine combination is that codeine, which is the prototype of the weak opioid analgesics, has a weak affinity to MOP opioid receptors. Additionally, and contrary to other opioids, codeine needs to first be metabolized to morphine for production of its analgesic effect.[48] Between 5% and 10% of the population is estimated to lack the ability to perform this conversion, limiting the pain relief produced by such a drug.[48]

Table 4: *Means ± Standard Deviations of Differences Between Colors (ΔE) and Change in the Number of Shade Guide Units (ΔSGU) Obtained With the Vita Classical and Vita Bleached Guides Between Baseline and One Month Postbleaching*

Color Instruments	Groups		Mean Difference (95% Confidence Interval)	*p*-Value[a]
	Placebo	Acetaminophen/Codeine		
ΔSGU Vita Classical	5.0 ± 1.8	4.6 ± 2.0	0.4 (−0.3 to 1.1)	0.29
ΔSGU Vita Bleached	6.0 ± 3.1	5.7 ± 3.3	0.3 (−0.9 to 1.5)	0.70
ΔE	4.1 ± 1.7	4.1 ± 1.6	0.0 (−0.6 to 0.6)	0.94

[a] *Unpaired* t*-test.*

So far, minimization of the bleaching-induced TS was successfully observed only when desensitizing agents were applied topically.[7,23,28] This may suggest that perhaps these medicines are not reaching the plasmatic tissue of the pulp at the time that bleaching is performed. More basic studies should be performed to elucidate the mechanism of pain generated during bleaching and yield more appropriate approaches for the management of such an undesirable side effect.

Finally, the limitations of this study should be reported. Although our sample size was larger than most studies that evaluate anti-inflammatory drugs for the reduction of TS, the sample size was calculated only for the detection of high effect sizes for the risk of TS. Therefore, we cannot rule out the fact that smaller effect sizes might exist. The use of the same experimental design to conduct studies with larger sample sizes should be encouraged to rule out this hypothesis.

CONCLUSION

The use of an acetaminophen/codeine combination (Tylex, 30 mg) is not recommended because it does not decrease the risk and intensity of bleaching-induced TS and also causes a high number of adverse effects.

Acknowledgements

This study was partially supported by the National Council for Scientific and Technological Development (CNPq) under grants 301937/2009-5 and 301891/2010-9 as well as the Araucária Foundation. The authors are also grateful for FGM Dental Products for the donation of the bleaching agents employed in this study.

Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of the State University of Ponta Grossa. The approval code for this study is 890.207.

Conflict of Interest

The authors of this article 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.

(Accepted 14 August 2017)

REFERENCES

1. Gurgan S, Cakir FY, & Yazici E (2010) Different light-activated in-office bleaching systems: A clinical evaluation *Lasers in Medical Science* **25(6)** 817-822.
2. Haywood VB (2005) Treating sensitivity during tooth whitening *Compendium of Continuing Education in Dentistry* **26(9)** 11-20.
3. Reis A, Dalanhol AP, Cunha TS, Kossatz S, & Loguercio AD (2011) Assessment of tooth sensitivity using a desensitizer before light-activated bleaching *Operative Dentistry* **36(1)** 12-17.
4. 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 *Operative Dentistry* **38(4)** 386-393.
5. Rezende M, Bonafe 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 *Journal of the American Dental Association* **147(1)** 41-49.
6. de Paula EA, Kossatz S, Fernandes D, Loguercio AD, & Reis A (2014) Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: A randomized triple-blind clinical trial *Operative Dentistry* **39(2)** 128-135.
7. Bonafe E, Bacovis CL, Iensen S, Loguercio AD, Reis A, & Kossatz S (2013) Tooth sensitivity and efficacy of in-office bleaching in restored teeth *Journal of Dentistry* **41(4)** 363-369.
8. Basting RT, Amaral FL, Franca FM, & Florio FM (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 *Operative Dentistry* **37(5)** 464-473.
9. Santana MA, Nahsan FP, Oliveira AH, Loguercio AD, & Faria-e-Silva AL (2014) Randomized controlled trial of sealed in-office bleaching effectiveness *Brazilian Dental Journal* **25(3)** 207-211.
10. Rezende M, Loguercio AD, Kossatz S, & Reis A (2016) Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis *Journal of Dentistry* **45(1)** 1-6.
11. Palo RMI, Bonetti-Filho, Valera MC, Camargo CH, Camargo S, Moura-Netto C, & Pameijer C (2012) Quantification of peroxide ion passage in dentin, enamel, and cementum after internal bleaching with hydrogen peroxide *Operative Dentistry* **37(6)** 660-664.
12. Costa CA, Riehl H, Kina JF, Sacono NT, & Hebling J (2010) Human pulp responses to in-office tooth bleaching *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **109(4)** e59-e64.
13. Paula EA, Loguercio D, Fernandes D, Kossatz S, & Reis A (2013) The effect of perioperative ibuprofen use on tooth sensitivity caused by in-office bleaching *Operative Dentistry* **38(6)** 601-608.
14. de Paula EA, Loguercio D, 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 *Clinical Oral Investigations* **17(9)** 2091-2097.
15. Charakorn P, Cabanilla LL, Wagner WC, Foong WC, Shaheen J, Pregitzer R, & Schneider D (2009) The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching *Operative Dentistry* **34(2)** 131-135.

16. Hamza M, & Dionne RA (2009) Mechanisms of non-opioid analgesics beyond cyclooxygenase enzyme inhibition *Current Molecular Pharmacology* **2(1)** 1-14.

17. Hutchinson MRY, Shavit Y, Grace PM, Rice KC, Maier SF, & Watkins LR (2011) Exploring the neuroimmunopharmacology of opioids: An integrative review of mechanisms of central immune signaling and their implications for opioid analgesia *Pharmacological Reviews* **63(3)** 772-810.

18. Becker DE, & Phero JC (2005) Drug therapy in dental practice: nonopioid and opioid analgesics *Anesthesia Progress* **52(4)** 140-149.

19. Coulthard P, Patel N, Bailey E, & Armstrong D (2014) Barriers to the use of morphine for the management of severe postoperative pain—A before and after study *International Journal of Surgery* **12(2)** 150-155.

20. Modaresi J, Dianat O, & Mozayeni MA (2006) The efficacy comparison of ibuprofen, acetaminophen-codeine, and placebo premedication therapy on the depth of anesthesia during treatment of inflamed teeth *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **102(3)** 399-403.

21. Henry M, Reader A, & Beck M (2001) Effect of penicillin on postoperative endodontic pain and swelling in symptomatic necrotic teeth *Journal of Endodontics* **27(2)** 117-123.

22. Schulz KF, Altman DG, & Moher CD (2011) Group CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials *International Journal of Surgery* **9(8)** 672-677.

23. Tay LY, Kose C, Loguercio AD, & Reis A (2009) Assessing the effect of a desensitizing agent used before in-office tooth bleaching *Journal of the American Dental Association* **140(10)** 1245-1251.

24. Vuilleumier PH, Stamer UM, & Landau R (2012) Pharmacogenomic considerations in opioid analgesia *Pharmacogenomics and Personalized Medicine* **5** 73-87.

25. Bernardon JK, Sartori N, Ballarin A, Perdigao J, Lopes GC, & Baratieri LN (2010) Clinical performance of vital bleaching techniques *Operative Dentistry* **35(1)** 3-10.

26. Meireles SS, Heckmann SS, Leida FL, dos Santos Ida S, Della Bona A, & Demarco FF (2008) Efficacy and safety of 10% and 16% carbamide peroxide tooth-whitening gels: A randomized clinical trial *Operative Dentistry* **33(6)** 606-612.

27. 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 *Journal of Dentistry* **40(8)** 644-653.

28. Mehta D, Venkata S, Naganath M, LingaReddy U, Ishihata H, & Finger WJ (2013) Clinical trial of tooth desensitization prior to in-office bleaching *European Journal of Oral Science* **121(5)** 477-481.

29. Kossatz S, Martins G, Loguercio AD, & Reis A (2012) Tooth sensitivity and bleaching effectiveness associated with use of a calcium-containing in-office bleaching gel *Journal of the American Dental Association* **143(12)** 81-87.

30. Paravina RD (2008) New shade guide for tooth whitening monitoring: Visual assessment *Journal of Prosthetic Dentistry* **99(3)** 178-184.

31. de Geus JL, Rezende M, Margraf LS, Bortoluzzi MC, Fernandez E, Loguercio AD, Reis A, & Kossatz S (2015) Evaluation of genotoxicity and efficacy of at-home bleaching in smokers: A single-blind controlled clinical trial *Operative Dentistry* **40(1)** 47-55.

32. l'Eclairage CId (1978) Recommendations on uniform color spaces, color difference equations, psychometric color terms **(Supplement 2)** to *CIE publication* **15** (E2-31.1) 1971 (TC-1.3) Bureau Central de la CIE.

33. de Geus JL, Wambier LM, Kossatz S, Loguercio AD, & Reis A (2016) At-home vs in-office bleaching: A systematic review and meta-analysis *Operative Dentistry* **41(4)** 341-356.

34. Papathanasiou A, Kastali S, Perry RD, & Kugel G (2002) Clinical evaluation of a 35% hydrogen peroxide in-office whitening system *Compendium of Continuing Education in Dentistry* **23(4)** 335-338.

35. Onwudiwe UV, Umesi DC, Orenuga OO, & Shaba OP (2013) Clinical evaluation of 16% and 35% carbamide peroxide as in-office vital tooth whitening agents *Nigerian Quarterly Journal of Hospital Medicine* **23(2)** 80-84.

36. Luque-Martinez I, Reis A, Schroeder M, Munoz 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 *Clinical Oral Investigations* **20(7)** 1419-1433.

37. Paravina RD, Johnston WM, & Powers JM (2007) New shade guide for evaluation of tooth whitening—Colorimetric study *Journal of Esthetic and Restorative Dentistry* **19(5)** 276-283.

38. Da Costa J, Lubisich E, Ferracane J, & Hilton T (2011) Comparison of efficacy of an in-office whitening system used with and without a whitening priming agent *Journal of Esthetic and Restorative Dentistry* **23(2)** 97-104.

39. Ontiveros JC, Eldiwany MS, & Paravina R (2012) Clinical effectiveness and sensitivity with overnight use of 22% carbamide peroxide gel *Journal of Dentistry* **40** e17-e24.

40. Ontiveros JC, & Paravina RD (2009) Color change of vital teeth exposed to bleaching performed with and without supplementary light *Journal of Dentistry* **37(11)** 840-847.

41. de Geus JL, de Lara MB, Hanzen TA, Fernandez E, Loguercio AD, Kossatz S, & Reis A (2015) One-year follow-up of at-home bleaching in smokers before and after dental prophylaxis *Journal of Dentistry* **43(11)** 1346-1351.

42. Correa AC, Santana TR, Nahsan FP, Loguercio AD, & Faria ESAL (2016) The impact of a customized tray on in-office bleaching tooth sensitivity: A randomized clinical trial *Operative Dentistry* **41(1)** 15-22.

43. Cooper JS, Bokmeyer TJ, & Bowles WH (1992) Penetration of the pulp chamber by carbamide peroxide bleaching agents *Journal of Endodontics* **18(7)** 315-317.

44. Lepinski AM, Hargreaves KM, Goodis HE, & Bowles WR (2000) Bradykinin levels in dental pulp by microdialysis *Journal of Endodontics* **26(12)** 744-747.

45. Caviedes-Bucheli J, Ariza-Garcia G, Restrepo-Mendez S, Rios-Osorio N, Lombana N, & Munoz HR (2008) The effect of tooth bleaching on substance P expression in human dental pulp *Journal of Endodontics* **34(12)** 1462-1465.

46. Rodd HD, & Boissonade FM (2000) Substance P expression in human tooth pulp in relation to caries and pain experience *European Journal of Oral Science* **108(6)** 467-474.

47. Laskin DM (2013) Application of current pain management concepts to the prevention and management of postoperative pain *Journal of the American Dental Association* **144(3)** 284-286.

48. Pathan H, & Williams J (2012) Basic opioid pharmacology: An update *British Journal of Pain* **6(1)** 11-16.

49. Trescot AM, Datta S, Lee M, & Hansen H (2008) Opioid pharmacology *Pain Physician* **11(Supplement 2)** S133-S153.