Pre-operative use of dexamethasone does not reduce incidence or intensity of bleaching-induced tooth sensitivity. A triple-blind, parallel-design, randomized clinical trial

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Abstract

Objectives This study evaluated the effect of the administration of pre-operative dexamethasone on tooth sensitivity stemming from in-office bleaching.

Materials and methods A triple-blind, parallel-design, randomized clinical trial was conducted on 70 volunteers who received dexamethasone or placebo capsules. The drugs were administered in a protocol of three daily 8-mg doses of the drug, starting 48 h before the in-office bleaching treatment. Two bleaching sessions with 37.5% hydrogen peroxide gel were performed with a 1-week interval. Tooth sensitivity (TS) was recorded on visual analog scales (VAS) and numeric rating scales (NRS) in different periods up to 48 h after bleaching. The color evaluations were also performed. The absolute risk of TS and its intensity were evaluated by using Fisher’s exact test. Comparisons of the TS intensity (NRS and VAS data) were performed by using the Mann-Whitney U test and a two-way repeated measures ANOVA and Tukey’s test, respectively.

Results In both groups, a high risk of TS (Dexa 80% x Placebo 94%) was detected. No significant difference was observed in terms of TS intensity. A whitening of approximately 3 shade guide units of the VITA Classical was detected in both groups, which were statistically similar.

Conclusions It was concluded that the administration pre-operatively of dexamethasone, in the proposed protocol, does not reduce the incidence or intensity of bleaching-induced tooth sensitivity.

Clinical relevance The use of dexamethasone drug before in-office bleaching treatment does not reduce incidence or intensity of tooth sensitivity.

Clinical trial registration number NCT02956070

Keywords Dentin sensitivity · Dental bleaching · Hydrogen peroxide · Dexamethasone
Introduction

Currently, dental bleaching is one of the most requested dental procedures by patients who want more pleasant smiles, which the media demands as a model of health and beauty [1, 2]. Dental bleaching has been the treatment of choice for teeth with shade alterations, as it is a safe, effective, and conservative technique [3–8]. This procedure is performed with the application of hydrogen or carbamide peroxide gels on the surface of the teeth and can be done at home, with or without the supervision of the dentist, or in office [9, 10]. Although the home bleaching technique is most suitable for vital teeth [11], some patients do not get used to the at-home technique, as they do not get used to the bleaching trays, or want (or need) more fasten results [7, 8, 11, 12]. For these patients, in-office bleaching is an excellent alternative, as the results can be observed after one or two bleaching sessions, and the professional executes and controls the whole process [11–15], avoiding gel ingestion and exposure to soft tissues, reducing the percentage of patients with gingival irritation and reducing total bleeding time [6, 8, 14, 16–18].

Despite the effectiveness of the techniques in achieving desired tooth whitening, adverse effects are evidenced [6, 11], with tooth sensitivity (TS) highlighted as the most widely reported effect in the literature [19–23]. This bleaching-induced TS appears to result from an inflammatory process in the dental pulp in different magnitudes, stemming from the action of hydrogen peroxide (H₂O₂) applied during the bleaching treatment [24, 25]. Hydrogen peroxide increases the permeability of the enamel, diffuses through the dentin [10], and penetrates the pulp chamber [11, 12]. Tooth sensitivity associated with a dental bleaching technique may result from the action of chemicals resulting from the degradation of hydrogen peroxide, which penetrate the pulp chamber and lead to the activation of nociceptive sensors [13] and transient inflammatory reactions [14], and can last for up to 48 h after bleaching [22, 26, 27]. When it happens during or after the first bleaching session, this TS can spur discontinuation of the bleaching treatment [28].

Many attempts to reduce bleaching-induced TS were already done, with changes in the techniques or in the concentrations of bleaching gels [26, 27], and also with the use of topical desensitizing agents (fluorides, potassium nitrate, glutaraldehyde) before or after dental bleaching [11, 22, 28–34]. Some of them have shown promising results, but usually, TS was still observed during the bleaching treatment by many patients. In other studies, non-steroidal anti-inflammatory drugs [20, 35], or even more selective anti-inflammatory drugs [21] were used to reduce the TS, but in general, although it was observed some reduction in the immediate bleaching-induced TS [20, 35], the pain was still present within the next 48 h after bleaching.

Recently, a study [36] tried to reduce TS using dexamethasone, in a protocol where 8 mg of the drug was used 1 h before the dental bleaching session, and then, the patient received extra doses of 4 mg every 6 h for 48 h after the dental bleaching session. It is known that corticosteroids prevent or suppress inflammation response via multiple mechanisms when compared with non-steroid anti-inflammatory drugs. Inasmuch, dexamethasone, a synthetic corticosteroid, represses inducible cyclooxygenase 2 (COX-2) synthesis and blocks the entire arachidonic acid pathway. As a consequence, eicosanoid production (prostaglandins and leukotrienes) on macrophages/monocytes is limited [37]. In addition, dexamethasone reduces the release of cytokines, including IL-1, IL-6, IL-2, IL-3, and TNF-alfa on lymphocytes. Less postoperative edema is either related to the diminished secretion of vasoactive proteins (intercellular adhesion molecule, ICAM-1) on endothelial cells or the decrease of leukocytes extravasation in the injured area [38]. On the other hand, as time is required to modulate gene expression and protein synthesis, most of the anti-inflammatory effects of corticosteroids are not immediate but become apparent after several hours or even days. Indeed, dexamethasone after binding to an intracellular glucocorticoid receptor provides specificity to the induction or the repression of gene transcription that participates in the inflammatory response. This fact is of clinical significance, as a delay generally is seen, before the beneficial anti-inflammatory effects of dexamethasone become manifest [39]. In oral surgeries, for example, dexamethasone is used in a protocol where the patient starts using the drug 48 h before the surgical procedure, and takes additional doses until the moment of the surgery, so that, its effects can be clinically observed in the surgery day, decreasing pain and edema [40]. In the study where dexamethasone was used to reduce bleaching-induced TS [36], it was used only 1 h before the bleaching session, and this could be the reason for the negative results that made the authors conclude that dexamethasone was not able to reduce bleaching-induced TS.

Taken this, we hypothesized that a different pretreatment protocol using oral dexamethasone would prevent bleaching-induced TS. To test this hypothesis, we designed a randomized, triple-blinded, parallel-group clinical trial quantifying TS in patients who received three doses of dexamethasone beginning 48 h prior to each bleaching procedure.

Materials and methods

Study design The description of the experimental design followed the Consolidated Standards of Reporting Trials (CONSORT). The Fluminense Federal University—Nova Friburgo (protocol number 1.376.881) Ethics Committees reviewed and approved the protocol and issued a consent form for this study. Written informed consent was obtained from all participants prior to starting the treatment. This clinical trial was registered in clinicaltrial.gov clinical registry.
(#NCT02956070). All participants were informed about the nature and objectives of the study, but they were not aware of which group they were allocated.

This was a randomized, triple-blinded, parallel-group clinical trial in which the volunteer, operator, and evaluator were blinded to the group assignment. The study was carried out in the clinics of the School of Dentistry of Fluminense Federal University (Nova Friburgo, RJ, Brazil) from February 15, 2016, to July 12, 2016. Patients were recruited as they seek for treatment in the clinics of Dentistry of the University. No advertisement was made for participant recruitment. Patients were recruited in the order in which they reported for the screening session, thus forming a sample of convenience.

Inclusion and exclusion criteria A total of 123 participants were examined by two calibrated investigators (SM and CG) to check if they met the inclusion and exclusion criteria (Fig. 1). The evaluations were performed using a mouth mirror, an explorer, and a periodontal probe. Participants had to be in good general health, be at least 18 years old, have an acceptable oral hygiene level, and could not report any type of TS. Participants were required to have eight caries-free maxillary anterior teeth without restorations, and free of periodontal disease. The central incisors had to be shade A1 or darker as judged by comparison with a shade guide (VITA Classical, VITA Zahnfabrik). The two examiners evaluated the teeth color against the shade guide at baseline and were required to have an agreement of at least 85% (Kappa statistic test) before beginning the study evaluation.

Volunteers with severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth) or with anterior orthodontic apparatuses were not included in the study. In addition, pregnant and lactating women, participants with any other pathology that could cause sensitivity (such as gingival recession, dental exposure, visible cracks in teeth), those taking anti-inflammatory or analgesic drugs, those who smoked, or volunteers who had undergone dental bleaching procedures were excluded. Those who reported past or present health problems in the stomach, heart, kidneys or liver; those patients with diabetes, hypertension or the use of antihypertensive drugs; or patients who reported allergies to dexamethasone and lactose were also excluded from the study. After the screening sessions, 70 patients were selected and were randomized into two different groups.

Sample size calculation and randomization The absolute risk of TS (that is, the number of participants percent) who reported pain at some point during dental bleaching was reported to be approximately 90% for a similar 35% hydrogen peroxide bleaching product [20, 21, 36]. With an α of 0.05, a power of 90%, and a two-sided test, the minimal sample size was 35 patients in each group in order to detect a decrease in the primary outcome measure from 90% in the control group to 60% in the experimental group.

The randomization was done using blocked randomization (block sizes of 2 and 4) with an equal allocation ration. These randomization schemes were performed using software available at http://www.sealedenvelope.com. A staff member not involved in the research protocol performed the randomization process with computer-generated tables. Opaque and sealed envelopes containing the identification of the groups were prepared.

Blinding The operators, who performed the bleaching procedures, were blinded to the group assignment. Patients were also blinded to group assignment. And the evaluators, who evaluated tooth sensitivity and color changes, were also blinded, in a triple-blind randomized clinical trial design. A different researcher, not involved in the evaluation or in the bleaching procedures, was responsible for the administration of the drugs.

Study intervention We divided volunteers into the dexamethasone group, who received the anti-inflammatory (dexamethasone, capsule—8 mg) and application of a placebo gel, and the control group, who received placebo capsules and the application of desensitizing gel containing 6% potassium nitrate and 0.10% fluoride sodium (Sootho, SDI, Victoria, Australia). All volunteers received the same bleaching treatment, which four experienced operators (LP, FC, WA, ED) performed. One week before the in-office bleaching session, volunteers received individual pots containing six capsules in total, with the dexamethasone (handled by Bem Viver laboratory Ltda.), or placebo, in identical capsules depending on their allocation group, which contained the same components of the dexamethasone drug except for the active ingredient (Table 1).

Volunteers were treated in two clinical sessions with an interval of 7 days between them. The protocol for use of the product was as follows: the volunteers in the experimental group received six capsules of dexamethasone 8 mg each, which was administered orally, initially 2 days before the 1st bleaching query (8 mg, 9 AM, 2 days before the bleaching session; 8 mg, 9 AM, 1 day before the bleaching session; 8 mg, 9 AM, on the day of the bleaching session) [40]. This same scheme was performed for the 2nd bleaching session. The operators instructed the volunteers to increase adherence to the protocol, and the researchers made telephone calls and sent cell phone text messages to remind the volunteers of every capsule to be taken.

Before the dental bleaching, gingival tissue was isolated from teeth using a light-cured resin (Gingival Barrier, SDI), and each tooth was light-cured for 10 s using a light curing unit with 1200 mW/cm² light intensity (Radii-cal, SDI). After the placement of a lip retractor (OptraGate – Ivoclar Vivadent), the operator used the 37.5% hydrogen peroxide gel (polaoffice+, SDI) in three 8-min applications in accordance with the manufacturer’s directions. The bleaching agent...
was refreshed every 8 min during the 24-min application period. At the end of each session, a single researcher responsible for the blinding (MB) delivered a single syringe to the operator, which would contain desensitizing gel if the patient was in the control group, or placebo gel containing only carbopol (no active ingredient) if the patient was in the dexamethasone group. The gel was applied with a brush on the labial surface of the whitened teeth for 2 to 3 min as the manufacturer (Soothe SDI Dental Limited) directed.

**TS evaluation** TS was evaluated in four different times, during bleaching, up to 1, 24, and 48 h postbleaching. The volunteers were asked to indicate the TS in two different scales. In the first one, they ranked TS using a numeric value of the degree of sensitivity for each of the periods above, using a 5-point numeric rating scale (NRS) in which 0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = severe [6, 11, 13, 20]. In the second one, they recorded the pain intensity using a visual analogic scale (VAS) [15, 19–22]. This scale is a 100-milimeter horizontal line with scores of 0 and 100 at their ends, in which 0 = no sensitivity and 100 = severe sensitivity. The volunteer had to mark 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. The worst score or numeric value obtained in both bleaching sessions was considered for statistical purposes and the determination of the overall risk and intensity of TS. The absolute risk of TS represented the percentage of volunteers who reported TS at least once during treatment, in the first or in the second session.
**Table 1** Dexamethasone or placebo in identical capsules depending on their allocation group

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pola Office + SDI*</td>
<td>• 37.5% hydrogen peroxide</td>
</tr>
<tr>
<td></td>
<td>• Potassium nitrate</td>
</tr>
<tr>
<td>Soothe SDI*</td>
<td>• Potassium nitrate 6.0%</td>
</tr>
<tr>
<td></td>
<td>• Fluoride ions 0.10%</td>
</tr>
<tr>
<td></td>
<td>• Water 89.60%</td>
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<tr>
<td></td>
<td>• Thickener 4.20%</td>
</tr>
<tr>
<td></td>
<td>• Sodium benzoate 0.10%</td>
</tr>
<tr>
<td>Dexamethasone capsules**</td>
<td>• Dexamethasone base 8 mg</td>
</tr>
<tr>
<td></td>
<td>• Starch 50%</td>
</tr>
<tr>
<td></td>
<td>• Lactose monohydrate 35%</td>
</tr>
<tr>
<td></td>
<td>• Dibasic calcium phosphate 14%</td>
</tr>
<tr>
<td></td>
<td>• Magnesium stearate 1%</td>
</tr>
<tr>
<td>Placebo capsules**</td>
<td>• Starch 50%</td>
</tr>
<tr>
<td></td>
<td>• Lactose monohydrate 35%</td>
</tr>
<tr>
<td></td>
<td>• Dibasic calcium phosphate 14%</td>
</tr>
<tr>
<td></td>
<td>• Magnesium stearate 1%</td>
</tr>
<tr>
<td>Placebo gel**</td>
<td>• Carbopol</td>
</tr>
</tbody>
</table>

*SDI, Victoria, Australia

**Handled by Bem Viver laboratory Ltda., registration number 09047030/0001-28, located at Santa Rosa street, Icarai-Niteroi, RJ, Brazil. Batch of the product: 189155

**Color evaluation** Shade evaluation was performed 1 week after the 1st bleaching session, but before the 2nd session, and 1 week after the 2nd bleaching session. Color evaluation was not performed immediately after each bleaching session because of dehydration and demineralization that occurs after every bleaching in-office session. Then, any interference on color measures could be avoided. We performed the color evaluation using the shade guides VITA Classical and the VITA Bleachedguide 3D-MASTER (VITA Zahnfabrik).

For the color evaluation, the VITA Classical shade guide’s 16 tabs were arranged in order of values from the highest one (B1) to the lowest one (C4), and each tab received a rank from 1 to 16. The VITA Bleachedguide 3D-MASTER’s 24 tabs are already organized from the highest (0M1) to lowest (5M3) value [41]. The tabs were also ranked from 1 to 24. The color changes were treated as representing a continuous and approximately linear ranking for the purpose of analysis, as already performed in several published studies [6, 13, 15, 21, 34]. The measurement area of interest for shade matching was the middle 1/3 of the facial surface of the central incisor, according to the American Dental Association guidelines [11, 26, 34].

The two examiners, blinded to the allocation assignment, evaluated the patient’s teeth against the shade guide at the different time assessments. Color changes were calculated by calculating the change in the number of shade guide units (ΔSGU). Both examiners evaluated the color once and independently. When disagreements occurred during the evaluations, they had to reach a consensus before the participant was dismissed.

**Statistical analysis** The statistical analyses followed the intention-to-treat protocol according to CONSORT (Consolidated Standards of Reporting Trials) suggestion. All participants who were randomly assigned were involved. The statistician was blinded to the study groups.

The absolute risk of TS was evaluated by using Fisher’s exact test. (α = 0.05). The relative risk and the confidence interval for the effect size were calculated. Comparison of the TS intensity (NRS data) of the two groups at the two different assessment points were performed by using the Mann-Whitney U test, and comparisons between times within each group were performed using the Friedman test. Comparison of the TS intensity (VAS data) of the two groups at the two different assessment points were performed by using a two-way repeated measures ANOVA and Tukey’s test.

Color changes between groups (ASGU between base line versus 1 week after the 2nd bleaching session) were compared by using a t test, and the shade changes were evaluated by using Student’s t test.

The statistical analyses were performed by using the SPSS for windows version 20.0 (IBM) software. In all statistical tests, we pre-set the level of significance to 5%.

**Results**

The bleaching procedures were implemented exactly as planned, and no modification was performed. Fifty-three out of 123 patients examined for eligibility were not enrolled in the study because they did not fulfill the inclusion criteria. Thus, a total of 70 subjects (20 men and 50 women) were selected (Fig. 1). The baseline color of the volunteers was similar (control group, 5.9 [1.9]; dexamethasone, 5.6 [2.1]); the mean age (SD) between volunteers was similar between the groups (control, 22.5 [2.1] and dexamethasone, 22.3 [2.7]), ranging from 19 to 29 years. Thirty-four percent of the volunteers from the control group, and 23% of the volunteers from the dexamethasone group were men. No discontinuity in both treatment groups was found in the clinical investigation. All volunteers attended the recall visit 1 week postbleaching.

**Tooth sensitivity** Two volunteers, 1 from each group, took an analgesic to alleviate the bleaching-induced TS (Tylenol, Janssen Cilag Farmacêutica) in the period from 5 to 7 h after the 2nd and last clinical bleachings.

Table 2 shows the number of participants who experienced TS during the bleaching regimen in the control group and dexamethasone group. In this table, it is shown that no significant difference was observed between groups (P = 0.075). The relative risk, along with the 95% confidence interval, is also evidence that the use of the experimental drug protocol had no effect on the reduction of TS.
Tables 3 and 4 show that the TS was similar in both groups, at different assessment points, in both sessions, using both pain scales. It is also seen that the bleaching-induced TS did not last longer than 48 h after the bleaching protocol (Tables 3 and 4).

Color evaluation The bleaching gel used in this study was able to promote significant whitening in both groups (P < .001). The descriptive data from bleaching obtained after the bleaching sessions can be seen in Table 5. At the end of the bleaching treatment, a whitening of approximately 3 shade guide units was detected for both groups.

The results of the subjective shade evaluation (VITA Classical, P = 0.27; VITA Bleachedguide 3D-MASTER, P = 0.68) matched the hypothesis of equality between the groups after bleaching. The effect size and the confidence interval for the overall mean difference is also shown in Table 5 and is evidence of no statistical difference between groups.

Adverse effects In this study, no reports of adverse effects by volunteers were received.

Discussion

Dental bleaching is a conservative cosmetic treatment, increasingly recommended for darkened vital teeth, with very favorable and safe results. However, some patients cannot tolerate the use of trays or wish for a faster result. In this case, the in-office bleaching technique using high concentrations of hydrogen peroxide (30–35%) becomes an appropriate alternative. The effectiveness of this whitening technique is well documented in the literature, with a change in the color scale ranging from 5 to 8 shade guide units (SGUs) after two clinical bleaching sessions [6, 11, 12, 26]. Nonetheless, several studies have shown that a frequent problem associated with this technique is increased TS, which often leads to patient withdrawal from treatment [13, 20, 21, 23, 34, 36, 42].

In this study, two calibrated researchers used two visual methods of color choice (kappa = 85%). The colors were analyzed with reference to the VITA Classical and Vita Bleachedguide 3D-MASTER scales. Although it does not have a linear correlation of value, the Vita Classical scale is frequently used in bleaching studies [6, 13, 15, 36, 41]. The VITA Bleachedguide 3D-MASTER scale is younger and has been organized to encompass color variations to characterize the shadows and to facilitate the recording of the tooth whitening color by having a subtle and gradual distribution from the lowest to highest value [43]. Based on the VITA Classical scale, this study showed an effective whitening of approximately 3 SGUs for both groups, which shows that the product used (Pola Office Plus, SDI—37% hydrogen peroxide) was effective with the bleaching protocol used. Although these mean values are lower than the 5 to 8 mean values found in the literature [6, 11, 12, 26, 36], it must be said that many patients in this study had the initial color close to A1, which means that they would not bleach many units, and probably, this is the reason for the lower mean values.

Currently, the mechanism responsible for TS after a tooth bleaching procedure is unclear. Literature explains this condition with the hydrodynamic theory [44]. According to this theory, fluid movement inside dentin tubules is responsible for stimulating receptors in the pulpal dentin area, resulting in pain. However, Markowitz [28] noted that the mechanism

| Table 3 | Medians and interquartile (1 and 3 interquartile) ranges of the tooth sensitivity at different assessment points using the numeric rating scale (NRS) |
|---|---|---|---|---|---|---|---|---|
| Assessment times | First session | | | | Second session | | | |
| | Control | Dexamethasone | Comparison group | | Control | Dexamethasone | Comparison group |
| During bleaching | 0 (0–1)A | 0 (0–1)A | NS† | | 0 (0–1)A | 0 (0–1)A | NS |
| Up to 1 h after bleaching | 0 (0–1)A | 0 (0–1)A | NS | | 0 (0–1)A | 1 (0–1)A | NS |
| Up to 24 h after bleaching | 0 (0–1)A | 0 (0–1)A | NS | | 0 (0–2)A | 0 (0–1)A | NS |
| Up to 48 h after bleaching | 0 (0–0)B | 0 (0–0)B | NS | | 0 (0–0)B | 0 (0–0)B | NS |

Within each column, significant differences are represented by different uppercase letters
†NS, no significant difference between groups
of TS stemming from tooth bleaching, which occurs in healthy teeth with no other provoking stimulus, differs from the mechanisms of other forms of TS, which usually occur when stimuli (cold or tactile) contact the surface of exposed dentin. It has been hypothesized that TS resulting from tooth bleaching occurs because peroxide penetrates the tooth structure and directly activates a neuronal receptor and not because of hydrodynamic effects. In addition, alteration stemming from bleaching agents on the morphological enamel surface (increased surface porosity, depressions, and superficial irregularities) [45, 46] could leave the dentin less protected. Although the mechanism of bleaching-induced TS is not well understood, it seems to result from a reversible inflammatory process due to damage resulting from hydrogen peroxide in the pulp [28]. This pain is usually mild and resolves within 48 h after the protocol [22, 26, 27]. Nevertheless, in some cases, the bleaching-induced TS can be severe and responsible for patients’ withdrawal from treatment [28].

In a recent systematic review where the mean percentage of sensitivity in home and in-office bleaching techniques was compared, a significant increase in dental sensitivity in the in-office bleaching technique compared with the home technique was found [47]. In another recent systematic review and meta-analysis, the risk and intensity of TS during home and in-office tooth bleaching in adult patients were assessed, and no significant differences in risk/intensity between the techniques were found [48]. In this study, in the control group, where the bleaching product was used in association with the desensitizer with potassium nitrate and sodium fluoride, according to the manufacturer’s instructions, a sensitivity risk of 94% was observed, with an average value of sensitivity intensity of 8.09 (17.06) during the 1st whitening session, reaching 11.14 (20.08) in the 1st hour after bleaching but dropping to close to 0 within the 1st 48 h. In the 2nd session, these values were slightly higher (although no statistically significant difference was found when the results of the 2 weeks were compared with each other), also reaching values close to 0 in the 1st 48 h. This same trend of decreasing sensitivity values reaching values close to 0 in the 1st 48 h was observed in the experimental group, as well as the trend of higher values in the 2nd bleaching session (Table 4). In this experimental group, the sensitivity risk was of 80%, which was lower than that of the control group but without a statistically significant difference ($P = 0.075$). It should be noted, however, that the median sensitivity intensity in both groups was between 0 and 1 (absent or mild) in the 2 weeks (Table 3), which means that although the sensitivity was present, it was considered mild and did not prevent the continuity of bleaching treatment. These values showed that this work is in agreement with

<table>
<thead>
<tr>
<th>Assessment times</th>
<th>Color evaluation tool</th>
<th>Groups</th>
<th>$P$ value</th>
<th>Mean difference (95% confidence interval)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During bleaching</td>
<td>VITA Classical</td>
<td>2.14 (1.52)</td>
<td>1.89 (1.37)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>VITA Bleachedguide</td>
<td>1.91 (0.95)</td>
<td>1.86 (0.97)</td>
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</tr>
<tr>
<td></td>
<td>VITA Classical</td>
<td>0.74 (1.15)</td>
<td>0.71 (1.49)</td>
<td>0.93</td>
</tr>
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<td></td>
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<td>2nd session versus 1st Session</td>
<td>VITA Classical</td>
<td>2.54 (2.39)</td>
<td>2.91 (1.96)</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>VITA Bleachedguide</td>
<td>3.00 (1.19)</td>
<td>3.2 (1.35)</td>
<td>0.51</td>
</tr>
<tr>
<td>Baseline versus 2nd Session</td>
<td>VITA Classical</td>
<td>2.77 (1.96)</td>
<td>2.26 (1.87)</td>
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</tr>
<tr>
<td></td>
<td>VITA Bleachedguide</td>
<td>3.20 (1.13)</td>
<td>3.09 (1.17)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Within each column, significant differences are represented by different uppercase letters
†NS, no significant difference between groups

Table 5 Means (standard deviations) of the change in shade guide units obtained with the VITAL Classical and VITA Bleachedguide 3D-Master at baseline versus each bleaching session and 1 week postbleaching

<table>
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<th>Time interval</th>
<th>Color evaluation tool</th>
<th>Groups</th>
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<th>Mean difference (95% confidence interval)</th>
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<td>Dexamethasone</td>
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<td>3.2 (1.35)</td>
<td>0.51</td>
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<tr>
<td>Baseline versus 1 week after 2nd Session</td>
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<td>2.77 (1.96)</td>
<td>2.26 (1.87)</td>
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empirical. Therapeutic principals, such as the disease states of corticoid levels, the use of corticosteroids is largely benefits for each patient, are considered to design corticosteroid severity, side effects, and a careful consideration of the risks/

leading to a decrease in levels of proinflammatory chemical pollutants are generally attributed to the suppression of endogenous cortisol that the adrenal gland secretes. Its therapeutic effects are generally attributed to the suppression of constitutive cyclooxygenase-1 (COX-1) negative control group was really unnecessary. This meta-analysis was already done in other studies [11, 22, 29, 33, 34], and other studies [49–51] comparing other treatments using this same sodium fluoride/potassium nitrate association as a control group have shown the same tendency. Considering that our objective was to compare the dexamethasone experimental protocol with this “gold standard” treatment (sodium fluoride/potassium nitrate), this negative control group was really unnecessary.

Non-steroidal anti-inflammatory drugs (NSAIDs) are known to act by suppressing constitutive cyclooxygenase-1 (COX-1) and induced cyclooxygenase-2 (COX-2). Its use for the prevention of bleaching-induced sensitivity has been tried in some studies, and the results of the preventive use of non-steroidal anti-inflammatory drugs for the treatment of dental sensitivity resulting from a bleaching treatment were compared in a systematic review with a meta-analysis [42]. This meta-analysis showed no significant effect of preventive analgesia with the use of NSAIDs for dental sensitivity after dental bleaching, suggesting the need for further studies in this area [42].

One recent study [36] has evaluated the use of steroidal anti-inflammatory drugs, also known as corticosteroids, which are defined as synthetic hormones that mimic the actions of endogenous cortisol that the adrenal gland secretes. Its therapeutic effects are generally attributed to the suppression of multiple mechanisms involved in the inflammatory response, leading to a decrease in levels of proinflammatory chemical mediators at the site of injury [52].

Except for the replacement therapy of patients with deficiency states of corticoid levels, the use of corticosteroids is largely empirical [53, 54]. Therapeutic principals, such as the disease severity, side effects, and a careful consideration of the risks/benefits for each patient, are considered to design corticosteroid’s protocols [55]. The rationale behind the protocol used in this study is 1st because pretreatment with dexamethasone would reduce the production of several inflammatory mediators, known to sensitize nociceptors. Second, the maximal daily dose of dexamethasone (15 mg by oral route or 20 mg intravenously) in a short course therapy (up to a week) is unlikely to be harmful [56].

Taken this, we expected that three single doses of 8 mg, administered 48, 24, and 1 h prior to each bleaching section would inhibit the synthesis of most inflammatory mediators, which are regularly released after teeth whitening. Therefore, TS would be prevented via dexamethasone’s anti-inflammatory effects [57]. So far, posttreatment using steroidal, non-steroidal, or selective non-steroidal anti-inflammatory drugs did not completely attenuate bleaching-induced TS [36, 42].

Likewise, pretreatment with dexamethasone did not reduce the bleaching-induced TS. This fact strongly suggests that other mechanisms rather than the ordinary release of inflammatory mediators or cytokines contribute to TS. As it is well known, dental bleaching causes a chemical-inciting event within the pulp tissue, which leads to the nerve excitation resulting in pain. Recent reviews suggested that tooth pain occurs in response to the excitation of a transient receptor potential cation channel called TRPA1 [58–60]. Although TRPA1 plays a role in TS, it is regulated by TNF-alfa [61], a transcription factor whose activation should also have been attenuated by our dexamethasone pretreatment protocol.

TRPA1 is a classical thermosensory channel belonging to a subfamily of the transient receptor potential (TRP) channel family, which is activated by several reactive agents, such as hydrogen peroxide [62], and changes in the environmental temperature [63]. During this study, we noticed that TS scored higher on cold days, even with patients who do not normally feel pain (data not shown). Further analyses would be important to clarify a possible relationship between cold/hot and the hydrogen peroxide threshold activation of pulp TRPA1 receptors.

Hydrogen peroxide most likely directly activates TRPA1 and thereby contributes to its hyperalgesia responses, augmenting the perception of pain. Arachidonic acid metabolites do not appear to involve direct binding to TRPA1. This is an argument that explains dexamethasone failure in either preventing or treating TS. Although dental bleaching causes a reversible inflammatory response, bleaching-induced sensitivity seems to be more related to direct TRPA1 receptor activation. New approaches should focus on using TRPA1 antagonist substances or analgesics for treatment soon after bleach-induced TS occurs.

Conclusions

The administration pre-operatively of dexamethasone, in a protocol of three daily doses 8 mg of the drug, starting 48 h before an in-office bleaching treatment, does not reduce the incidence or intensity of bleaching-induced TS.
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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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