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RESEARCH

Effect of an experimental desensitizing gel on bleaching-induced tooth sensitivity after in-office bleaching—a double-blind, randomized controlled trial

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Abstract

Objectives To evaluate the risk and intensity of tooth sensitivity (TS), and the efficacy of in-office bleaching after applying an experimental desensitizing gel composed of 10% calcium gluconate, 0.1% dexamethasone acetate, 10% potassium nitrate, and 5% glutaraldehyde.

Material and methods In a split-mouth, double-blind, placebo-controlled study, 50 participants had their upper hemiarches randomized into experimental and placebo groups. Desensitizing and placebo gels were applied for 10 min before in-office bleaching (35% hydrogen peroxide, 1 × 50 min; two bleaching sessions; 1-week interval). TS was recorded immediately after bleaching, 1, 24, and 48 h after each session, with a 0–10 visual analogue scale (VAS) and a five-point numerical rating scale (NRS). The color was recorded in all groups at baseline, 1 week after each session, and 1 month after the end of bleaching using shade guide units (ΔSGUs) and a spectrophotometer (ΔE_{ab}, ΔE_{00}, and ΔWI_D).

Results Most participants (96%) felt some discomfort during treatment regardless of the study group. The odds ratio for pain was 0.65 (95% CI 0.1 to 4.1; $p = 1.0$). The intensity of TS did not differ between groups ($p > 0.31$), and it was only 0.34 VAS units lower in the experimental group. A significant color change occurred in both groups regardless of the group.

Conclusions The desensitizing experimental gel applied before in-office bleaching did not reduce the risk and the intensity of TS and did not affect color change.

Clinical relevance Although the experimental desensitizing agent with varying mechanisms of action did not jeopardize the color change, it did not reduce the risk or intensity of in-office bleaching.

Clinical trial registration number RBR-7T7D4D.

Keywords Tooth bleaching · Dentin sensitivity · Dentin desensitizing agents · Hydrogen peroxide

Introduction

Some studies have shown that a large portion of the population is dissatisfied with the color of their teeth [1, 2]. This explains why clinicians have widely recommended and patients have widely accepted dental bleaching, either via the at-home or the in-office protocol, for obtaining esthetically pleasing smiles [3, 4].

Unlike at-home bleaching, in-office bleaching requires the use of high concentrations of hydrogen peroxide (HP) [5, 6]. However, the same HP that whitens teeth by oxidizing the dental structure's organic component can also quickly diffuse into the pulp chamber [7]. This can trigger an inflammatory process [8] with the release of several inflammatory chemical mediators [9, 10]. This process modifies the local microcirculation, generating pressure over the peripheral nerve fibers and activating nociceptors [11]. Most patients experience bleaching-induced tooth sensitivity (TS) as a clinical consequence. This pain is characterized as acute and

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transient pain, with patients commonly reporting it within the first 24 h after in-office dental bleaching [12].

The preventive effect of analgesics and opioids [13, 14], anti-inflammatories [15–18], antioxidants [19], and corticosteroids [20–22] has previously been investigated, and they could not mitigate bleaching-induced TS [23]. So far, the most successful approach to reducing TS has been the topical application of desensitizers, such as those containing glutaraldehyde [24, 25], potassium nitrate [26, 27], and calcium agents [28, 29].

These topical agents' mechanisms of action are different. Potassium nitrate prevents the repolarization of nerve fibers blocking the transmission of painful stimuli [26, 27, 30]. Meanwhile, glutaraldehyde was reported to coagulate proteins from enamel and dentinal tubules, reducing the easy passage of HP to the pulp [25, 31, 32]. Calcium-containing agents can also reduce the risk and intensity of TS mainly through the saturation of components on the enamel surface [33]. When calcium-containing products are applied, they interact with the dental surface [33]. They can be retained on the teeth, thus providing large amounts of calcium and phosphates for tissue interaction, which may reduce the passage of HP to the pulp [28, 29, 33–36]. Another possible agent is dexamethasone; this drug has already been tested orally [20, 22] but has not yet been investigated in topical form. This drug has primarily been used in dentistry via the oral route for oral surgeries [37–39] and endodontic treatments [40, 41], due to its potent anti-inflammatory effects. Although oral use of dexamethasone was not effective in reducing TS after dental bleaching [20, 22], its relatively smaller molar mass (392 g/mol^{-1}) suggests that it can penetrate enamel and dentin, which may justify its topical use. In addition, dexamethasone is known as inhibit the expression of several inflammatory mediators and cytokines [42], which could promote an anti-inflammatory and analgesic effect by its possible contact with the dental pulp, in an attempt to reduce TS in the present study.

The mechanism of bleaching-induced TS is not yet entirely known. We hypothesized that summing up some active agents' varying mechanisms of action could produce a more potent desensitizing effect than their individual use could. Therefore, we aimed to evaluate the impact of the topical application of this experimental desensitizing gel on the absolute risk and intensity of bleaching-induced TS and color change after in-office bleaching with 35% HP.

Material and methods

Ethics approval and protocol registration

This clinical investigation received approval (protocol 3.893.891) from the Ethics Committee of the State University of Ponta Grossa/PR/Brazil. This study was registered in the Brazilian Clinical Trials Registry under "RBR-7T7D4D." The preparation of this article followed the protocol established via the Consolidated Standards of Reporting Trials statement with extension for within-person designs [43].

Trial design, settings, and location of data collection

This study was a randomized, split-mouth, placebo-controlled, and double-blind controlled clinical trial. This study was performed from November 2019 to January 2020 in the clinics of the school of dentistry at the State University of Ponta Grossa/PR/Brazil.

Recruitment

Recruitment was performed by placing written advertisements on the university walls and using social media to obtain a convenient sample. The volunteers were informed about the study's objectives, and they all signed an informed consent form before being enrolled in the study.

Eligibility criteria

Participants included in this RCT were at least 18 years old, 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 periodontal disease. The canines had to be shade A_2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical, Vita Zahnfabrik). Participants with anterior restorations, dental prostheses, orthodontic apparatuses, and severe internal tooth discoloration (tetracycline stains, fluorosis, and pulpless teeth) were not included. In addition, pregnant or lactating women, smokers, participants who had bruxism and had undergone tooth-bleaching procedures, and any other condition that could cause sensitivity (such as recession, dentin exposure, or the presence of visible cracks in the teeth), and participants with continuous use of anti-inflammatory drugs or analgesics were also excluded.

Sample size estimation

This study's primary outcome was the absolute risk of TS. The absolute risk of TS was reported to be approximately 93% for the bleaching product Whiteness Automixx (FGM) [44]. For detecting an absolute risk difference of 25% between the control and experimental groups, a minimum sample size of 40 patients with a power of 80% and an alpha of 5% was required. Due to the high cost of the search for study participants during the follow-ups, we included 50 participants.

Randomization

We performed blocked randomization (block size of 2) to guarantee equal–sized groups with an equal allocation ratio at www.sealedenvelope.com. A third party not involved in the study implementation prepared consecutively numbered, opaque, and sealed envelopes containing information identifying the groups. The group identified in the envelope corresponded to the treatment performed on the right upper hemiarch, and the left hemiarch received the alternate treatment.

Blinding

This study was a double-blind study in which the patients and evaluators were blinded to the group assignment. As the gels differed slightly in the transparency, we could not blind the operator. The groups (experimental or placebo) were applied in the superior and inferior arches before the in-office dental bleaching.

Study intervention

We prepared an experimental desensitizing gel containing 10% calcium gluconate, 0.1% dexamethasone acetate, 10% potassium nitrate, and 5% glutaraldehyde. Also, it was used an excipient to prepare the experimental desensitizing (100 g). We used propylene glycol and hydroxyethylcellulose as thickening agents, and we used methylparaben as a preservative. The placebo gel was composed of the same thickening agents and preservative without the active components to maintain the same viscosity and appearance. Although all attempts were made to produce a placebo gel similar to the experimental gel, the final product showed a different transparency.

All participants underwent dental prophylaxis and oral hygiene guidance prior to the bleaching procedure. After a lip retractor (Arcfex, FGM, Joinville, SC, Brazil) was placed in the proper position, the gingival tissue was isolated with a light-cured resin dam (Topdam, FGM, Joinville, SC, Brazil). An extension of the barrier was created between the central incisors so that the products would not contact each other.

Before each bleaching session, the experimental or placebo gel was applied topically on the buccal surfaces of all of the teeth to be bleached. The gel was left undisturbed for 10 min and then activated for 10 s with a micro brush. The application of the gels was carried out in the upper and lower arches. After the application, the gels were removed with gauze and were washed with an air–water spray.

The 35% HP bleaching gel (Whiteness HP Automixx, FGM, Joinville, SC, Brazil) was applied in a 50-min session. At the end of the recommended time, the bleaching gel was removed with a disposable surgical saliva ejector, cleaned with gauze, and washed with an air–water spray. Two bleaching sessions were performed at a 1-week interval.

Evaluation of tooth sensitivity (TS)

Participants had to record their pain intensity in the following time intervals: (1) during the treatment; (2) up to 1 h after each bleaching session; (3) between 1 and 24 h after each bleaching session; and (4) between 24 and 48 h. After both bleaching sessions, these measurements were performed using the five-point numerical rating scale (NRS; 0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = severe) [21, 26, 44, 45] and 0–10 visual analog scale (VAS) [21, 26, 44, 45]. The VAS scale is a 10-cm horizontal line with scores of zero and 10 at their ends, in which zero means no sensitivity and 10 means severe tooth sensitivity. The patient 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 end was measured with the aid of a millimeter ruler.

The worst score (NRS) or numerical value (VAS) obtained from all-time recalls were considered for statistical purposes. A patient who was insensitive to bleaching needed to score zero (no TS) during all assessments from both bleaching sessions. Participants were supposed to have TS to the bleaching procedure in all other circumstances. This dichotomization made it possible to calculate the absolute risk of TS, which represented the percentage of participants who reported TS at least once during treatment.

Color change

Two calibrated operators performed color evaluation before the bleaching session, 1 week after the first bleaching session, 1 week after the second treatment, and 1 month after the bleaching treatment. The final color measurement was planned to be collected 30 days after bleaching. However, because the end of the present study was coincident with the rise of the COVID-19 pandemic, 23 patients had their final color changes evaluated within 2 to 6 months. The color evaluation was never performed immediately after each bleaching session so that the effect of dehydration and demineralization on color measures could be avoided. The color evaluation was performed with the value-oriented shade guide Vita Classical (Vita Zahnfabrik) and the Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik). In addition, an objective color evaluation was performed with the spectrophotometer Vita Easyshade (Vita Zahnfabrik).

The 16 shade guide tabs from the Vita Classical shade guide were arranged from the highest (B_1) to the lowest (C_4) value for the subjective examination. Although this scale is not linear in the truest sense, we treated the changes as

representing a continuous and approximately linear ranking for analysis as already performed in published studies [21, 25, 27, 44, 45]. The Vita Bleachedguide 3D-MASTER contains lighter shade tabs and is organized from the highest (0M1) to the lowest (5M3) value.

The middle third of the right upper canine 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 difference in the number of shade guide units (ΔSGUs), which occurred toward the lighter end of the value-oriented list of shade tabs. In the event of disagreement between the operators, the operators had to reach a consensus before the patient was dismissed.

For the objective evaluation, a preliminary impression of the maxillary arch was made with high-putty silicon paste (Cub Kit Profle, Vigodent) to serve as a standard guide for the tip of the spectrophotometer. A window was created on the buccal surface of the silicone guide toward the right maxillary canine, using a metal device approximately 6 mm in diameter (punch). A calibrated evaluator measured the color in all participants using a spectrophotometer (VITA Easyshade Advance, Vita Zahnfabrik) at the beginning of the first session and 30 days after the end of the bleaching treatment.

The objective color change was measured after the CIELab parameters of L^* (luminosity), a* (green to red axis), and b^* (blue to yellow axis) were obtained from the spectrophotometer. The difference between the baseline and 30 days after the end of the bleaching treatment was computed using the following CIELab formula [46]: $\Delta E_{ab} = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$. In addition, the color change was also calculated based on the CIEDE 2000 formula [47]: $\Delta E_{00} = [(\Delta L\ /\mathrm{kLSL})^2 + (\Delta \mathrm{C}/\ \mathrm{kCSC})^2 + (\Delta H/\mathrm{kHSH})^2 + \mathrm{RT}\ (\Delta C \times \Delta H/\mathrm{SC} \times \mathrm{SH})]^{1/2}$ and whiteness index [48]: $\Delta \mathrm{WI}_D = (0.511\mathrm{L}^*) - (2.3424\mathrm{a}^*) - (1.100\mathrm{b}^*)$.

Statistical analysis

The statistician was blinded to the groups. We performed both the intention-to-treat analysis (as planned a priori) and the per-protocol analysis. All randomized participants were incorporated into the data set in the intention-to-treat analysis. In contrast, in the per-protocol analysis, we excluded patients who did not perform the two bleaching sessions (Fig. 1).

The absolute risks of the TS of both groups were compared using McNemar's exact test ($\alpha = 0.05$, test for proportion of dependent data ratio). Then, the odds risk and the 95% confidence interval (CI) were calculated.

The assumptions of the normal distribution (Kolmogorov–Smirnov test) and equal variance (Barlett's test) of the continuous data sets were inspected. We used the Wilcoxon signed-rank test to compare the TS intensity in the NRS scale, and we used the paired *t*-test to compare data from the VAS scale. The subjective color assessment (ΔSGUs) and objective color assessment (ΔE_{ab}, ΔE_{00}, and $\Delta \mathrm{WI}_D$) were compared with a paired *t*-test. The mean difference and 95% CI were also calculated as the effect measures for the continuous outcomes.

We calculated Spearman's correlation between the two groups' TS risk paired data, and we also calculated the Pearson's correlation between the TS intensity data for both groups in the different dental arches. The statistical analysis was conducted in the software (SigmaPlot 14.0, Systat Software Inc. San Jose, CA, USA) with a significance level of 5%.

Results

Of the 50 participants, two did not return to recall evaluations after the first bleaching session, whereas five did not return after the second session. For the analysis of color change (intention-to-treat analysis), missing data from the color change were imputed using the last-outcome-carried-forward (LOCF) approach. These seven patients were excluded from the data set in the per-protocol analysis. Both analyses yielded similar conclusions (not shown data), and we presented data from the intention-to-treat analysis.

As for the risk and intensity of TS, a modified intention-to-treat analysis was performed, as we did not have any data from two participants, which prevented us from making any imputation. The exclusion of data was equal in the study, as it was a split-mouth study. Thus, it is unlikely that this procedure introduced biases to the study findings.

These seven participants returned to their home cities and reportedly lost interest in doing the bleaching protocol.

Demographic features of the participants

Fifty-nine participants were examined, and a total of 50 participants were included in the clinical study (Fig. 1). The baseline color of canines in the Vita Classical shade guide units was very similar for both groups (experimental gel: 9.7 ± 2.8; placebo: 9.8 ± 2.8). The participants were predominantly young adults with a mean age of 23.4 ± 7.5 years. Most participants were female (60.5%).

Risk of tooth sensitivity

The majority of the participants (96%) felt some discomfort during treatment. Forty-five participants reported pain on the experimental arch side, and all of them also reported pain on the placebo hemiarch side. Two participants did not report pain on either hemiarch side. In relative terms, the

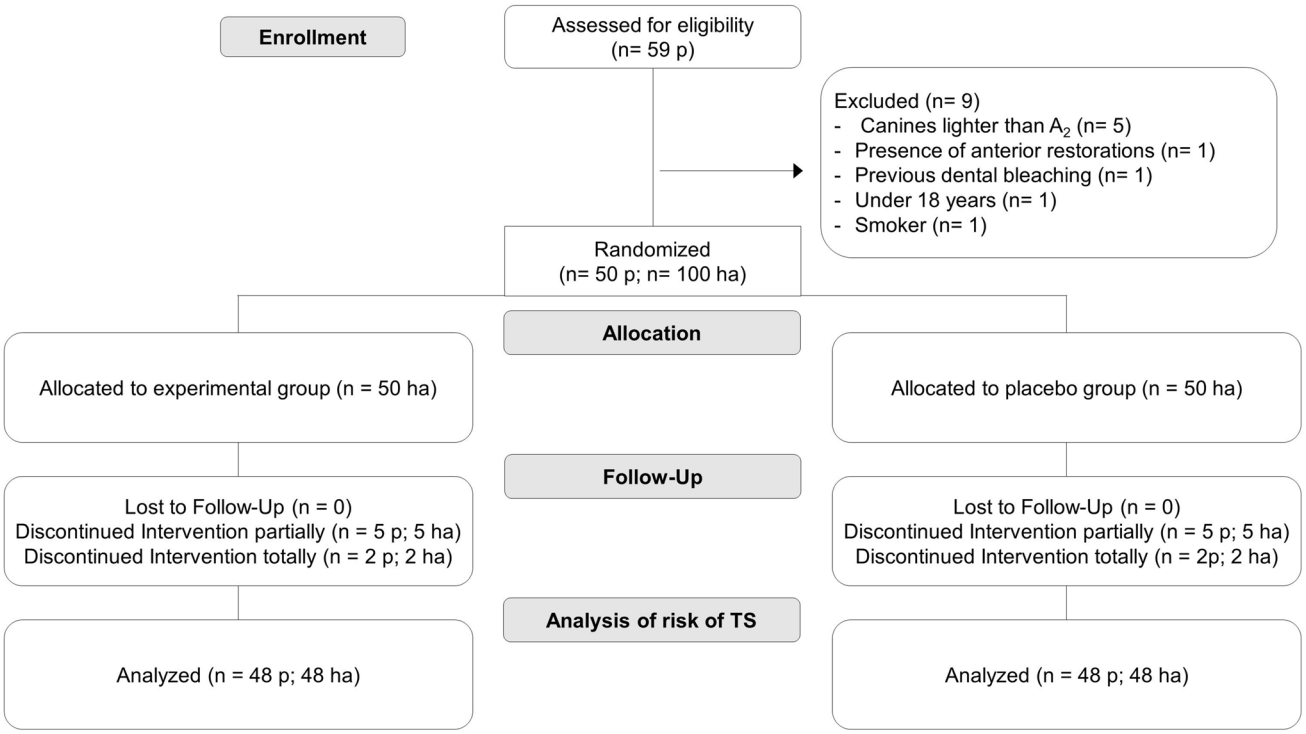

Fig. 1 Flow diagram of study design phases, including enrollment and allocation criteria for the analysis of the primary outcome. p, participants; ha, hemiarches

odds ratio for pain was 0.65 (0.1 to 4.1; $p=1.0$; Table 1). The Spearman correlation coefficient for the pairs of binary data was strong and significant ($r=0.80$; p-value <0.001).

Intensity of tooth sensitivity (TS)

The statistical analysis did not show any significant difference in the intensity of TS between the groups for any of the pain scales ($p=0.77$ for NRS, and $p=0.25$ for VAS; Table 2). The mean difference of the pain intensity on the VAS scale was, on average, 0.35 units lower, which is unlikely to be clinically important. The pain was positively correlated in both groups (Table 2). The correlation was strong and significant for both pain scales. For the NRS, the Spearman correlation was 0.76 ($p<0.001$), and for the VAS, the Pearson correlation was 0.77 ($p<0.001$).

Color evaluation

A significant color change occurred in all groups after bleaching, which was approximately, and on average, five units on the Vita Classical scale, five units on the Vita Bleachedguide, 15 units on the ΔE_{ab}, nine units on the ΔE_{00}, and nine units on the ΔWI_D (Table 3). No significant difference in color change was observed between the groups (Table 3; $p>0.32$).

Discussion

The conducting of this clinical trial was met with some challenges in the final phase of the data collection. The color change analysis performed 30 days after bleaching coincided

Table 1 Matched tabulation of the absolute risk of TS for both groups along with the odds ratio and 95% CI in a modified intention-to-treat analysis ($n=48$ hemiarches)

		Placebo			Odds ratio (95% CI)	p-value*
		Positive	Negative	Total		
Experimental	Positive	45	0	45	0.65 [0.10–4.09]	1.0
	Negative	1	2	3		
	Total	46	2	48		

*McNemar's test ($p=1.0$); Spearman correlation between paired data ($r=0.80$; p-value <0.001)

Table 2 Intensity of TS for both groups in medians, in the interquartile range (NRS scale), and in means and standard deviations (VAS scale), along with p-value and mean difference for VAS data (95% CI) in a modified intention-to-treat analysis ($n=48$ hemiarches)

Pain scales	Groups		Mean difference (95% CI)	*p*-value
	Experimental	Placebo		
NRS 0–4	2.0 (1.0–3.0)	2.0 (1.0–3.0)	–	0.80*
VAS 0–10	3.7 ± 2.8	4.1 ± 3.0	−0.34 (−1.0 to 0.3)	0.31**

*Wilcoxon signed-rank test. Spearman correlation between hemi arches for NRS scale ($r=0.71$; p-value < 0.001). **Paired t-test. Pearson correlation between hemi arches in VAS scale ($r=0.69$; p-value < 0.001)

with the emergent COVID-19 pandemic, which prevented us from evaluating the last color change in this specific time assessment period. Thus, the final color assessment had to be done 2 to 6 months after bleaching for some patients. Still, it is unlikely to have introduced bias because the comparison of the immediate results (approximately 30 days after bleaching) and those obtained 3 to 12 months after bleaching did not report any statistical and clinical differences between these assessment periods [49–53].

A total of seven patients decided to discontinue the bleaching protocol, and for two of them, no data were collected. Therefore, any imputation could be misleading. Because the missing data were balanced between groups (paired study design) and not at the randomization level, we excluded these two patients from the data analysis. These two exclusions explain why we performed a modified intention-to-treat analysis for the TS outcomes. In this modified approach, we used data only from the patients we could extract data from both bleaching sessions ($n=43$) or at least the first bleaching session ($n=5$).

Contrary to our expectations, the experimental desensitizing gel did not cause any reduction of the risk and intensity of TS. We believed that a synergic effect could be observed with the combination of the different agents used in experimental desensitizing gel. While there are no studies demonstrating efficacy of topical use of dexamethasone, previously studies have demonstrated a significant reduction in TS when the topical application of glutaraldehyde, potassium nitrate, and calcium agents were used [25, 28, 29, 34, 36]. Such agents are the most effective to date regarding the reduction of TS. Therefore, our hypothesis was that the association of these agents, with different mechanisms of action, could promote an increase in their effectiveness to reduction of TS.

However, it was not possible to predict how the dexamethasone used was able to penetrate through enamel and dentin and reach the pulp to produce the desired effect. Likewise, other agents, like calcium gluconate and potassium nitrate, could be able to deposit in the surface of enamel and dentin structure and prevent the penetration of hydrogen peroxide. This may have impaired the results in our study, and future in vitro studies need to be done to evaluate this hypothesis.

On the other hand, it is possible that the concentration of the agents used was not sufficient to produce the anti-inflammatory effects expected for dexamethasone, and the saturation and interaction with components on the enamel surface expect for the calcium-containing agents. Still, the use of nanotechnology for the formulation of the desensitizing agent could have promoted more satisfactory results regarding TS, as already demonstrated in previous studies [54, 55]. The use of nanotechnology provides advantages such as therapeutic efficacy, prolonged drug release, decreased toxicity, and longer action time [56] which could favoring drug penetration through the tooth structure. Therefore, the use of nanotechnology in the production of desensitizing and obliterating agents may promote more promising results. Future studies should be conducted to confirm this information.

Although the exact mechanism of bleaching-induced TS has not yet been explained, it is likely due to the damage that HP causes to living tissues from pulp tissue [9, 57]. In

Table 3 Means and standard deviations of ΔSGU (Classical and Bleachedguide), ΔEab, ΔE00, and ΔWID between baseline vs. final color evaluation for both groups along with the mean difference (95% CI) in the per protocol analysis* ($n=43$ hemi arches)

Color evaluation tool	Groups		*p*-value**	Mean difference (95% CI)
	Experimental	Placebo		
ΔSGU classical	5.3 ± 2.6	5.2 ± 2.9	0.32	0.1 (−0.1 to 0.4)
ΔSGU bleached guide	5.5 ± 2.7	5.5 ± 2.8	0.84	−0.0 (−0.3 to 0.2)
ΔE_{ab}	15.6 ± 7.0	15.0 ± 7.3	0.63	0.6 (−1.9 to 3.1)
ΔE_{00}	9.9 ± 4.6	9.4 ± 4.2	0.51	0.5 (−1.1 to 2.1)
ΔWI_D	9.2 ± 7.3	8.8 ± 6.2	0.76	0.3 (−2.0 to 2.7)

*The intention-to-treat analysis did not result in different conclusions. As this was a split-mouth design and randomization process was within patient, the exclusion of seven patients that discontinued treatment was balanced between groups and did not result in any type of imbalance

**Paired t-test

the case of injury, an acute inflammatory response begins to remove damaged tissue components to allow the body to begin the healing process. Due to increased blood flow, blood vessels dilate and eventually increase their permeability [8, 58], thus allowing fluid, proteins, and white blood cells to migrate from the circulation to the site of the tissue damage. A study found a higher density of macrophages and infiltrate inflammatory in the pulps that underwent in-office bleaching with 38% HP [59]. Macrophages are involved in the degradation of the extracellular matrix, the recruitment of leukocytes and pro-inflammatory cytokines, neovascularization, and fibroblast proliferation, among others [60, 61].

The edema within pulp tissue that occurs due to the release of inflammatory mediators and blood cells is different from what occurs in other connective tissues. Pulp tissue behaves differently because it is unique in that its soft tissues (pulp and pulp-dentin complex) are enclosed within mineralized hard tissues [62]. A rich neurovascular network that regulates various inflammatory mediators supplies the pulp tissue [63]. Thus, any minimal inflammatory signals and mediators may progress to pain.

It was already demonstrated that HP could reach the pulp tissue 15 min after being applied on the buccal enamel [55, 64]. This may occur because HP is a small molecule with a molecular mass of 35.01 g/mol^{-1}. The molecular mass of calcium gluconate (430.37 g/mol^{-1}), dexamethasone acetate (434.50 g/mol^{-1}), potassium nitrate (101.10 g/mol^{-1}), and glutaraldehyde (100.11 g/mol^{-1}) are higher than that of HP. They, therefore, may take longer to reach the pulp.

However, earlier clinical trials showed the beneficial effects of the desensitizing agents included in the experimental gel when used alone [24, 25, 28, 29, 65]. Most of these RCTs used low sample sizes (low study power) and a parallel design that did not control for intra-individual variability. The high correlation of the risk and TS intensity values between the dental hemiarches suggests that the split-mouth design can reduce the sample size while keeping the study power high enough to detect clinically meaningful differences.

When a total of 16 studies evaluating potassium-nitrate desensitizers were collected in a systematic review of the literature [26], a significant and positive effect in favor of the potassium nitrate was observed. Still, this effect was subtle and not clinically significant. Similarly, a recent RCT that evaluated the impact of the topical application of a corticoid-containing product did not find any significant reduction in the risk and intensity of TS [14, 21]. Similarly, the use of glutaraldehyde has not shown positive results in reducing TS when used alone [65]. However, the use of an experimental gel containing potassium nitrate and glutaraldehyde was able to reduce the risk and intensity of TS after in-office dental bleaching [25]. Thus, we can believe that the association of agents with different mechanisms of action could promote an increase in their effectiveness.

Altogether, this means that it is unlikely that the topical application of desensitizers can minimize bleaching-induced TS. More recently, another RCT showed promising results by associating topical bioactive desensitizers with intraoral drug prescription (acetaminophen/codeine) [34], but further studies should confirm these findings.

Another aspect of this study that we should not rule out is that the combination of these agents may impair each other's action via unknown mechanisms. However, the experimental gel was prepared and applied soon after preparation, thus reducing the likelihood of this hypothesis.

The color change was observed for both hemiarches irrespectively of the groups and color evaluation tools employed. In the present study, we measured color change using both subjective methods (color guide units) and objective methods (spectrophotometer). Shade guide units can provide a direct clinical indication of the degree of whitening [67], and therefore, they are widely employed in RCTs involving bleaching.

An objective evaluation is less clinically tangible but allows for the collection of more information. Using the same parameters of L^*, a^*, and b^* parameters, we could calculate color change using the conventional CIELab 76 system (ΔE_{ab}), the CIEDE2000 system (ΔE_{00}), and the whiteness index for dentistry (ΔWI_D) [46–48]. The CIEDE2000 system has been more recently employed, as it better estimates the visual perception of color [68]. The whiteness index provided more information on the direction of the bleaching effect [48] and has been added to recent RCTs about bleaching [21, 50, 53, 66].

To translate the ΔE values to the clinical scenario, clinicians should compare them with the 50:50 perceptibility (PT) and 50:50 acceptability (AT) thresholds [66]. The PT value is the minimal color difference that human eyes can distinguish. On the other hand, the AT value is more comprehensive, representing an existing difference acceptable for most people. The 50:50 PT and AT values for ΔE_{ab} were reported to be 1.2 and 2.7, respectively [66], whereas for ΔE_{00}, the values were 0.8 and 1.8, respectively [66]. By looking at Table 3, one can see that the difference in the means between the study groups did not reach these thresholds, so they are clinically unimportant. On the other hand, these thresholds were exceeded in all of the time assessment periods, which is evidence of effective whitening.

Finally, in relation to the limiting factors of this study, we need to mention the fact that most of the participants were young adults, which may affect the generalization of the results for the general population. In addition, the subjectivity at the time of reporting pain may lead to changes in the observed results. Also, it is not known whether the concentration of the agents used was sufficient to produce the expected effect, which also leads to the need for further studies.

Conclusions

The application of an experimental desensitizer (calcium gluconate, dexamethasone acetate, potassium nitrate, and glutaraldehyde) before in-office bleaching did not reduce the risk and the intensity of tooth sensitivity and did not affect color change.

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Author contributions **Conceptualization** [Laína Vochikovski, Marcia Rezende, Paulo Vitor Farago, Alessandro Dourado Loguercio, Alessandra Reis]; **Methodology** [Laína Vochikovski, Michael Willian Favoreto, Marcia Rezende, Renata Maria Olenki Terra, Karine Letícia da Silva, Alessandra Reis]; **Investigation** [Laína Vochikovski, Michael Willian Favoreto, Marcia Rezende, Renata Maria Olenki Terra, Karine Letícia da Silva, Alessandra Reis]; **Resources** [Alessandro Dourado Loguercio, Alessandra Reis]; **Data Curation** [Laína Vochikovski, Michael Willian Favoreto, Marcia Rezende, Renata Maria Olenki Terra, Karine Letícia da Silva, Alessandra Reis]; **Formal analysis** [Michael Willian Favoreto, Paulo Vitor Farago, Alessandro Dourado Loguercio, Alessandra Reis]; **Writing –Original Draft** [Laína Vochikovski, Michael Willian Favoreto, Marcia Rezende, Renata Maria Olenki Terra, Karine Letícia da Silva]; **Writing –Review & Editing** [Paulo Vitor Farago, Alessandro Dourado Loguercio, Alessandra Reis]; **Supervision** [Alessandro Dourado Loguercio, Alessandra Reis]; **Project administration** [Alessandra Reis].

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Declarations

Ethical approval The clinical investigation was approved (protocol 3.893.891) by the scientific review committee and by the committee for the protection of human participants of the State University of Ponta Grossa/PR/Brasil.

Competing interests The authors declare no competing interests.

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

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