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Clinical Research

Preventive Use of a Resin-based Desensitizer Containing Glutaraldehyde on Tooth Sensitivity Caused by In-office Bleaching: A Randomized, Single-blind Clinical Trial

ACS Diniz • SNL Lima • RRdJ Tavarez • AH Borges • SCS Pinto
MR Tonetto • AD Loguercio • MC Bandéca

Clinical Relevance

Application of Gluma Desensitizer prior to bleaching provides no significant decrease in sensitivity.

SUMMARY

Objective: To evaluate the risk and intensity of bleaching-induced tooth sensitivity (TS) after in-office bleaching following topical application of a resin-based glutaraldehyde desensitizer.

Methods: Thirty-three patients were randomly assigned to the experimental (Gluma Desensitizer Liquid, Heraeus Kulzer, Hanau, Germany) and placebo groups. The placebo or Gluma Desensitizer Liquid was applied for one minute prior to application of an in-office bleach-

Ana Carolina Soares Diniz, MSc student, Department of Postgraduate Program in Dentistry, CEUMA University, São Luis, MA, Brazil

Suellen Nogueira Linares Lima, MSc student, Department of Postgraduate Program in Dentistry, CEUMA University, São Luis, MA, Brazil

Rudys Rodolfo de Jesus Tavarez, professor, Department of Postgraduate Program in Dentistry, CEUMA University, São Luis, MA, Brazil

Alvaro Henrique Borges, professor, Department of Postgraduate Program in Integrated Dental Science, University of Cuiaba, Cuiaba, MT, Brazil

Shelon Cristina Souza Pinto, professor, Department of Restorative Dentistry, School of Dentistry, State University of Ponta Grossa, Parana, Brazil

Mateus Rodrigues Tonetto, professor, Department of Postgraduate Program in Integrated Dental Science, University of Cuiaba, Cuiaba, MT, Brazil

*Alessandro Dourado Loguércio, professor, Department of Restorative Dentistry, School of Dentistry, State University of Ponta Grossa, Parana, Brazil

Matheus Coelho Bandéca, professor, Department of Postgraduate Program in Dentistry, CEUMA University, São Luis, MA, Brazil

*Corresponding author: Avenida Carlos Cavalcanti, 4748–Uvaranas, Ponta Grossa, Paraná, Brazil, CEP 84030-900; e-mail: aloguercio@hotmail.com

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ing gel. Bleaching was performed with 35% hydrogen peroxide gel (three applications × 15 minutes each) over two sessions, one week apart. The color of the anterior teeth was evaluated before and 21 days after treatment using the VITA Classical shade guide, Bleachedguide 3D, and Easyshade spectrophotometer. TS during and after the bleaching was recorded according to the visual analog (VAS) and numerical rating (NRS) scales. All data were submitted to statistical analysis (α=0.05).

Results: There was no significant difference in absolute risk or intensity of TS between the two groups (risk and VAS, p=0.93 and 0.31, respectively; NRS, $p \geq 0.45$). At the end of the bleaching protocol, tooth whitening was observed in both groups, as evident from color change in shade guide units (ΔSGU, 4.1-7.1; both guides) and overall color change (ΔE, 7.4-9.3 units); however, there were no significant differences in whitening between the two groups ($p > 0.11$).

Conclusion: Gluma Desensitizer Liquid was not able to reduce the risk or intensity of TS. Bleaching efficacy was not affected by application of the desensitizer.

INTRODUCTION

Dental bleaching is a popular procedure for treatment of discolored teeth.[1-8] It is a very conservative, simple, and low-cost procedure.[8] Unfortunately, tooth sensitivity (TS) is a common side effect of bleaching, particularly with in-office bleaching protocols that employ relatively high concentrations of hydrogen peroxide.[4-6]

The incidence of TS after in-office bleaching has been reported to be relatively high.[1,3,8-11] In addition, while the intensity of TS after in-office bleaching has been reported as usually being moderate,[7,12,13] in some cases it is severe and irritating enough to cause patients to withdraw from treatment.[14] Although the mechanism of bleaching-induced TS is not well understood,[15] it seems to result from the passage of hydrogen peroxide through hard tissues to the pulp, where it induces a reversible inflammatory process[16,17] and might also directly stimulate nerves, leading to pain.[18]

Several approaches have been proposed to minimize this side effect caused by bleaching products. As reported in a recent systematic literature review, preemptive administration of oral drugs such as analgesics, anti-inflammatories, antioxidants, and corticosteroids[3,9,19,20] has been found to be ineffective in minimizing the risk or intensity of bleaching-induced TS.[21] Similarly, reports on the effect of topical application of potassium nitrate, fluorides, and remineralizing agents on in-office bleaching-induced TS are conflicting.[22-26]

Glutaraldehyde-based products exhibit satisfactory performance as desensitizing agents in treatment of dentin hypersensitivity as well as upon prior application in restorative procedures.[27-29] A recent study on the effect of prior application of a resin-based glutaraldehyde desensitizer gel (Gluma Desensitizer Power Gel, Heraeus Kulzer, Hanau, Germany) on in-office bleaching-induced TS[11] reported significant reduction of bleaching-induced TS during and after in-office whitening.[11]

In contrast, in a study on the effect of prior application of different desensitizing agents—including a fluoride varnish, sealant, and resin-based glutaraldehyde desensitizer (Gluma Desensitizer Liquid, Heraeus Kulzer)—on in-office bleaching-induced TS in patients with dentinal hypersensitivity, Ibrahim and Banna[30] reported no significant differences in performance between the resin-based glutaraldehyde desensitizer and resin-based adhesive without glutaraldehyde (sealant). Although different types of TS have been evaluated in both studies, these conflicting results[11,30] indicate the necessity of more clinical studies for evaluating whether the presence of glutaraldehyde in desensitizers helps minimize in-office bleaching-induced TS. In addition, it is not clear whether application of different glutaraldehyde-containing substances influences the efficacy of tooth whitening, because only one study to date has presented relevant data in terms of color change.[11] Therefore, this randomized clinical study aimed to evaluate the risk of bleaching-induced TS (primary outcome) after in-office bleaching following topical application of a resin-based glutaraldehyde desensitizer when compared with a placebo group. In addition, the intensity of bleaching-induced TS and efficacy of in-office bleaching were evaluated as secondary outcomes.

The null hypotheses of the present study were 1) the use of resin-based glutaraldehyde desensitizer liquid and placebo groups will yield similar risks to bleaching-induced TS, 2) both groups will have a similar intensity of bleaching-induced TS, and 3) both groups will have the same bleaching effectiveness.

METHODS AND MATERIALS

The ethics committee of the local university approved this clinical investigation (Protocol No.

1.422.841). The research protocol was registered in the Brazilian clinical trials registry (No. RBR-7YRR3S). The experimental design was planned in accordance with the Consolidated Standards of Reporting Trials statement.[31] Based on pre-established criteria, 33 volunteers from São Luís, Maranhão, Brazil, were selected for this study. Two weeks prior to bleaching, all volunteers received dental screening and dental prophylaxis with pumice and water in a rubber cup and signed informed consent forms.

Study Design

This was a randomized, single-blind, split-mouth clinical trial, with equal probability of a participant receiving either of two treatments. The study was conducted between March and June 2016 at the clinic of the School of Dentistry, Ceuma University, São Luis, Brazil.

Inclusion and Exclusion Criteria

Patients included in this clinical trial were at least 18 years old and had good general and oral health. Participants were recruited by means of local advertisement. A total of 33 participants were examined for fulfillment of the inclusion and exclusion criteria while seated in a dental chair (Figure 1). The inclusion criteria were as follows: caries-free maxillary and mandibular anterior teeth without restorations on the labial surfaces and central incisors of shade A2 or darker, as judged by comparison with a value-oriented shade guide (VITA Lumin, VITA Zahnfabrik, Bad Sackingen, Germany). The exclusion criteria were as follows: history of tooth whitening, presence of anterior restorations, pregnancy or lactation, and severe internal tooth discoloration (eg, tetracycline stains, fluorosis, or pulpless teeth), bruxism, or any other pathology (eg, recession or dentin exposure) that could cause sensitivity. These criteria were so stipulated because the participants would not be immediately eligible for cosmetic treatment such as bleaching if they had other restorative needs that required immediate attention. A week prior to bleaching, the participants were questioned about previous TS according to the criteria described in the TS Evaluation section. Patients with preexisting TS were excluded from the study.

Sample Size Calculation

The primary outcome of this study was absolute risk of TS. It was determined that 33 patients would be required to ensure an 80% probability of detecting a decrease in mean absolute risk of TS from 85% in the control group[12,23,25,26] to 55% in the experimental group (α=0.05). Also, determination of sample size for a second outcome, TS intensity, was performed. For TS intensity, it was determined that 22 patients would be required to exclude a mean difference of 2 in the visual analog scale (VAS) scores with 80% power and 5% alpha, considering that the standard deviation of VAS score is approximately 2. The limit of equivalence (difference of means) was considered based on the results of the VAS score in clinical trials that evaluated in-office bleaching.[3,9,20,26] The sample size was calculated on the website www.sealedenvelope.com. This study was powered to detect a significant effect.

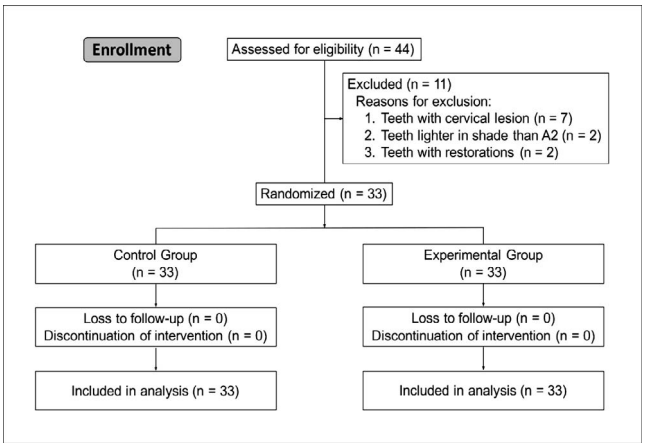

Figure 1. *Flow diagram of the clinical trial, including detailed information on excluded participants.*

Intervention

Randomization was performed using computer-generated tables prepared by a third party not involved in the study protocol. Details of group allocation were recorded on cards contained in sequentially numbered, opaque, sealed envelopes, prepared by a third party not involved in any phase of this clinical trial. To avoid disclosure of the randomization scheme, these envelopes were opened on the day of restorative intervention. Participants as well as the operator were blinded to group allocation and the study protocol.

The gingival tissue of teeth meant to be bleached was isolated using a light-polymerized resin dam (Top Dam, FGM Dental Products, Joinville, Brazil). For all patients, the left side received the treatment described first in the randomization list, while the right side received the treatment mentioned second. Either the placebo or experimental agent was applied to the buccal tooth surfaces and left

Table 1: *Products, Composition, and Application Regimens*

Product	Composition[a]	Application Regimen[a]
Gluma Desensitizer Liquid	2-hydroxyethyl methacrylate, glutaraldehyde, and purified water	1.Insert the lip retractor. 2.Apply the light-cured gingival barrier and perform light curing. 3.Actively apply the desensitizer on the labial surfaces of teeth with the aid of a micro-brush (10 seconds for each tooth). 4.Leave the product in contact with the labial surface for 60 seconds. 5.Dry the surface carefully by applying a stream of compressed air until the fluid film has disappeared and the surface is no longer shiny. 6.Rinse with water (10 seconds).
Whiteness HP Maxx 35%	35% hydrogen peroxide	1.Mix the two gel phases in a 3:1 ratio (drops) of peroxide to thickener. 2.With the aid of a nozzle, spread the gel on the buccal surfaces of teeth, forming a 0.5- to 1-mm-thick layer. 3.Leave the gel in for 15 min, and stir the product every 5 minutes to release bubbles. 4.Aspirate excess gel, wash the teeth, and repeat the application two more times (a total of three applications, amounting to 45 min of contact with teeth). 5.Aspirate excess gel, wash the teeth, and remove the gingival barrier.

[a] *According to the manufacturer's indications.*

undisturbed for 60 seconds. Teeth were then lightly air-dried until the fluid film disappeared and the surface was no longer shiny. During application of the placebo or experimental agent, the contralateral side was covered with gauze to avoid contact and mutual influence of the two treatments.

The experimental group was treated with Gluma Desensitizer Liquid (Heraeus Kulzer). Details regarding composition and mode of application are described in Table 1. The placebo had the same composition as the desensitizing agent, except for the absence of the active ingredients (ie, resin monomers and glutaraldehyde). The desensitizing and placebo agents were provided in bottles marked only with numbered codes that neither the clinicians nor patients could identify. Unfortunately, because of the peculiar smell of glutaraldehyde, the clinicians and patients were able to differentiate between the two treatments over the course of the study.

All participants received bleaching with 35% hydrogen peroxide gel (Whiteness HP 35, FGM Dental Products) according to the manufacturer's instructions (Table 1). Bleaching was performed over two sessions, a week apart. Participants were instructed to brush teeth regularly using toothpaste without desensitizing or bleaching agents.

Shade Evaluation

The 16 tabs of the VITA Classical shade guide were arranged from the highest (B1) to the lowest (C4) value. Although this scale is not linear in the truest sense, the shades were treated as representing a continuous and approximately linear ranking for the purpose of analysis. Change in tooth shade was calculated from the start of treatment to individual recall times according to the change in shade guide units (ΔSGU) from the darker toward the lighter end of the value-oriented list. Color was recorded at baseline, a week after the first and second bleaching sessions, and 21 days after the first bleaching session, using the VITA Classical shade guide, Bleachedguide 3D, and Easyshade Advance 4.0 spectrophotometer. Color evaluation was performed in a room under artificial lighting conditions, without interference from outside light. According to the American Dental Association guidelines, the mid-third of the labial surface of anterior teeth (central incisors) was considered as the area of interest for shade matching.[32]

A preliminary impression of the maxillary arch was acquired using high-putty Coltoflax silicone putty (Vigodent S/A Ind. Com., Rio de Janeiro, RJ, Brazil) to serve as a standard guide for the spectrophotometer probe. A window of 3-mm radius was created at the mid-third of the labial surface of the molded silicone guide using a metallic device with well-formed borders. A single calibrated operator evaluated tooth color in all participants using the VITA Easyshade spectrophotometer (Easyshade, Vident, Brea, CA, USA) before and 21 days after bleaching. The L*, a*, and b* measurements were recorded, with L* representing a value from 0 (black) to 100 (white) and a* and b* representing the shade, where a* was measured along the red-green axis and b* along the yellow-blue axis. Variation in color between the two assessment periods (ΔE) was determined using the following formula:

Table 2: *Number of Patients Who Experienced TS at Least Once During the Bleaching Regimen in Both Groups Along With Absolute Risk and Risk Ratio*

Treatment		No. of Participants With TS		Absolute Risk[a] (95% CI)	Risk Ratio (95% CI)
		Yes	No		
HP 35%	Gluma	24	9	68 (52-81)	1.20 (0.92-1.58)
	Placebo	29	4	82 (67-92)	

Abbreviations: CI, confidence interval; HP, hydrogen peroxide; TS, tooth sensitivity.
[a] *McNemar test (p=0.93).*

Table 3: *Intensity of Tooth Sensitivity According to the VAS[a] and NRS[b] in Both Study Groups*

Time Assessment	VAS[a]		NRS	
	Gluma	Placebo	Gluma	Placebo
Up to 1 h	1.66 ± 2.5	1.67 ± 2.3	1 (0/1)	1 (0/2)
1-24 h	2.48 ± 2.9	2.50 ± 2.9	1 (0/2)	1 (0/2)
24-48 h	0.54 ± 1.3	0.65 ± 1.6	0 (0/0)	0 (0/1)

Abbreviations: NRS, numerical rating scale; VAS, visual analog scale.
[a] *Mean ± standard deviation: two-way repeated-measures analysis of variance and Tukey test (p>0.31).*
[b] *Median (interquartile range): Kruskal-Wallis and Mann-Whitney tests (p≥0.45). There were no statistically significant differences in values between the two measurement scales.*

$$DE = \left[(DL*)^2 + (Da*)^2 + (Db*)^2\right]^{1/2}.$$

Evaluation of TS

Patients were asked to record any perception of TS immediately, 1 hour, 24 hours, and up to 48 hours after each session using a five-point verbal rating scale (0 = *none*, 1 = *mild*, 2 = *moderate*, 3 = *considerable*, and 4 = *severe TS*) and a 10-cm VAS with *no pain* and *worst pain* at opposite ends. Given that bleaching was performed over two sessions, the worst scores reported in the two sessions were considered for statistical analysis. The data were arranged into two categories: overall percentage of patients who reported TS at least once during treatment (absolute risk of TS) and TS intensity at each assessment point.

Statistical Analysis

Statistical analysis involved all randomly assigned participants and was performed according to the intention-to-treat protocol.[31] Absolute risk of TS was compared between the two groups by McNemar's test (α=0.05). Relative risk of TS and the confidence interval for effect size were also calculated.

Because the data exhibited normal distribution, bleaching-induced TS intensity measured by VAS scores was compared between the two groups by two-way repeated-measures analysis of variance and Tukey test. However, TS intensity measured by numerical rating scale (NRS) scores did not exhibit normal distribution and was therefore compared between the two groups at each assessment point by the Kruskal-Wallis and Mann-Whitney tests.

Color changes (ΔSGU according to both guides and ΔE between baseline and 21 months after bleaching) were compared between the two groups by the Student *t*-test. The significance level for all statistical tests was set at 0.05. All analyses were performed with SigmaPlot version 11.0 (Systat Software Inc, San Jose, CA, USA).

RESULTS

Participant Characteristics

A total of 44 participants were examined for verification of eligibility for the present study (Figure 1). There was no significant difference in baseline tooth color between the two treatment groups (placebo, 5.90 ± 2.6; experimental, 6.4 ± 2.7). The mean age of the participants was 23 ± 4 years (range, 18-40 years), and 55% of the patients were female.

Adherence to Protocol and Loss to Follow-up

All participants attended the recall visit 21 days after bleaching. Figure 1 presents the flow diagram for participant selection in different phases of the study.

Tooth Sensitivity

There was no significant difference in absolute risk of TS between the two groups (p=0.93; Table 2). With regard to intensity of TS, there was no significant difference between the two groups at any of the time points (VAS, p=0.31; NRS, $p\geq$0.45; Table 3).

Color Evaluation

The results of subjective and objective evaluation revealed significant whitening in both study groups. At the end of the bleaching protocol, both groups exhibited tooth whitening corresponding to 4.1 to 7.1 SGU (according to both guides), with ΔE ranging from 7.4 to 9.3 units (Table 4). The results of

Table 4: *Color Change in SGU (ΔSGU) and Overall Color Change (ΔE) From Baseline to 21 Days After Bleaching in the Two Treatment Groups*[a]

Color Evaluation Tool	Gluma	Placebo	*p* Value[b]
ΔSGU (Vita Classical)	5.0 ± 2.7	4.1 ± 2.5	0.12
ΔSGU (Vita Bleachedguide 3D)	7.1 ± 3.2	6.6 ± 3.6	0.55
ΔE	7.4 ± 3.6	9.3 ± 4.5	0.11

Abbreviation: SGU, shade guide units (Vita Classical and Vita Bleachedguide).
[a] *Values are presented as mean ± standard deviations.*
[b] *Student* t*-test paired.*

subjective (VITA Classical shade guide, $p=0.12$; VITA Bleachedguide 3D, $p=0.55$) and objective (spectrophotometry, $p=0.11$) evaluation supported the hypothesis of equivalence in treatment outcomes between the two groups after bleaching.

DISCUSSION

As mentioned in the introduction, topical application of several chemical agents has produced conflicting results in terms of its effect on TS due to in-office bleaching.[22-26] Therefore, it is important to evaluate alternative desensitizer agents that can reduce in-office bleaching-induced TS. Thus, the main purpose of this study was to evaluate if preventive application of a resin-based desensitizer liquid containing glutaraldehyde and hydrophilic monomers (Gluma Desensitizer Liquid) could reduce TS induced by bleaching.

Glutaraldehyde is a well-known biological fixative. There are several theories on the mechanism by which glutaraldehyde decreases dentin hypersensitivity.[33-36] The most accepted mechanism of action was elucidated by Schüpbach and others,[37] who suggested that, upon topical application of glutaraldehyde on the dentin surface, the reaction between glutaraldehyde and plasma proteins in dentin leads to precipitation of the latter. The results of a subsequent spectroscopic study confirmed that glutaraldehyde reacts with plasma proteins such as albumins and causes proteins to precipitate.[38] Another study demonstrated a reaction between glutaraldehyde–cross-linked albumin and the hydrophilic monomer (HEMA) present in the Gluma Desensitizer Liquid, resulting in the formation of a mixture of polyHEMA molecules.[38] These precipitates occlude open dentinal tubules beneath the surface, thus interfering with the hydrodynamics of dentinal fluid and preventing dentin sensitivity.[27-29]

However, it is necessary that glutaraldehyde and HEMA be able to penetrate through enamel and dentin along the same pathway as peroxide radicals.[39,40] Unfortunately, to the best of our knowledge, no study to date has evaluated transenamel penetration of glutaraldehyde or HEMA; this aspect deserves to be addressed in future studies. A tentative explanation is that the molecular sizes of glutaraldehyde (molar mass, 100 $gmol^{-1}$) and HEMA (molar mass, 130.14 $gmol^{-1}$) are lower compared with those of other high-molecular-size substances that have been proven to penetrate through enamel and dentin.[41,42] Also, because Gluma Desensitizer is used as a liquid, the solubility and diffusion coefficient of the molecule, as measured by Fick's second law, facilitate its penetration inside the pulp.[43-45] Therefore, it is reasonable to conclude that both substances can reach the dentin-pulp complex.

Unfortunately, the results of the present clinical trial demonstrated that, in comparison with teeth submitted for placebo treatment, prior application of Gluma Desensitizing Liquid for one minute reduced bleaching-induced TS by only 15%; however, this difference was not statistically significant. Also, no significant difference was observed in the intensity of TS, leading us to accept the first and second null hypotheses.

This result is contradictory to that of a previous study that employed a very similar product (Gluma Desensitizer Power Gel) for pretreatment before in-office bleaching. The compositions of Gluma Desensitizer Power Gel and Gluma Desensitizer Liquid are very similar, with the exception of the presence of pyrogenic silicic acid in the former.[46,47] Several studies have demonstrated that, upon application on the dentin surface, the gel reduces dentin permeability as effectively as the liquid desensitizer,[48,49] especially upon application at the same time. Similar results were observed in the present study as well as in the study by Mehta and others.[11] However, there are substantial differences in the in-office bleaching protocol between the two studies: although Mehta and others[11] performed in-office bleaching for only 15 minutes, in-office bleaching in the present study was performed with three 15-minute applications. Unfortunately, comparison of the results of TS observed in the present study with the results of the previous study[30] is not possible, mainly because Ibrahim and El Banna[30] evaluated subjects with existing dentin sensitivity and applied the desensitizers on the dentin surface.

Previous studies have demonstrated that the higher the number of applications or the longer the application of in-office bleaching agents on enamel, the greater the extent of hydrogen peroxide pene-

tration to the pulp chamber[39,40] and the more intense the adverse effects on pulp cells,[16,17] with the consequence being increased TS. This was confirmed in a recent randomized clinical trial, where the authors compared the effects of different durations of in-office bleaching on bleaching-induced TS. The results revealed that the proportion of patients with TS upon a single 15-minute application of in-office bleaching gel (60%) was lower compared with that upon two to three 15-minute applications of the gel in the same session (80%-95%).[50] This leads us to conclude that at shorter durations of application of in-office bleaching gel—as that in the study by Mehta and others[11]—application of Gluma Desensitizer for only one minute is enough to reduce bleaching-induced TS. However, these application times are inadequate for bringing about a decrease in TS when relatively high concentrations of hydrogen peroxide are applied, as observed in the 3×15-minute application protocol.

Several studies have demonstrated that application of glutaraldehyde only slightly increases the mechanical properties of dentin at shorter application times (eg, one minute).[51,52] However, upon application for longer durations, the cross-linking effect of glutaraldehyde increases significantly.[53,54] Since application of Gluma Desensitizer results in closure of dentinal tubules because of cross-linking, thus hindering the easy passage of peroxide radicals into the pulp chamber,[37] increasing the application time of the desensitizer will further impair the passage of hydrogen peroxide, thus minimizing bleaching-induced TS. However, this hypothesis has yet to be proven, and further studies are required to evaluate the effect of longer application times of Gluma Desensitizer Liquid or Gel on reducing bleaching-induced TS.

The results of evaluation of color change in the present study indicated that prior application of the Gluma desensitizing agent or placebo had no effect on tooth whitening, leading us to also accept the third null hypothesis. This is a common finding when at-home or in-office bleaching are evaluated,[55-60] and it can be explained by the fact that, usually, the desensitizer agents used did not contain any colorants in their composition.

Both study groups exhibited significant degrees of tooth whitening, ranging from 4.1 to 7.1 units in terms of ΔSGU and 7.4 to 9.3 units in terms of ΔE. These results correspond with those of previous randomized clinical trials that employed relatively high concentrations of hydrogen peroxide, applied three times for 15 minutes each.[7,20,50]

CONCLUSION

Prior application of Gluma Desensitizer Liquid for one minute did not significantly reduce the risk or intensity of in-office bleaching-induced TS, although a slight reduction in risk of TS was observed. Prior application of Gluma Desensitizer Liquid did not jeopardize the whitening effect of in-house bleaching.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of Ceuma University. The approval code for this study is Protocol No. 1.422.841.

Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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