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WILSON DA SILVA JÚNIOR

Aplicação prolongada de gel dessensibilizante antes e após o clareamento dental em consultório para evitar a sensibilidade induzida pelo clareamento: ensaio clínico, randomizado, triplo-cego

Cascavel-PR
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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia – Nível Mestrado, Centro de Ciências Biológicas e da Saúde, Universidade Estadual do Oeste do Paraná, como requisito parcial para a obtenção do grau de Mestre em Odontologia.

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Orientadora: Profª. Drª. Vera Lucia Schmitt
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Aplicação prolongada de gel dessensibilizante antes e após o clareamento dental em consultório para evitar a sensibilidade induzida pelo clareamento: ensaio clínico, randomizado, triplo-cego

RESUMO

Alguns estudos mostraram que o uso de agentes dessensibilizantes como o nitrato de potássio/fluoreto de sódio pode reduzir a intensidade da sensibilidade dentária (SD). Este estudo avaliou o uso prolongado dos agentes dessensibilizantes nitrato de potássio 5%/fluoreto de sódio 0,2% dez dias antes e após o clareamento em consultório para evitar a SD. Um estudo paralelo, controlado por placebo, triplo-cego, randomizado, foi realizado em 115 adultos saudáveis com dentes com cor A2 ou mais escura. Os pacientes usaram nitrato de potássio 5%/fluoreto de sódio 0,2% ou gel placebo, durante 10 dias em uma moldeira por 10 min, antes, durante e dois dias após o clareamento em consultório (peróxido de hidrogênio 35%). O desfecho primário de SD foi registrado nas escalas VAS 0-10 e NRS 0-4, durante o clareamento e em períodos que variaram de 1-6 h, 12-18 h, 18-24 h e 24-48 h pós-clareamento. A cor foi medida antes e um mês após o clareamento dental com duas escalas visuais de cores (Vita Classical e Vita Bleachedguide) e espectrofotômetro Easyshade. A variável de desfecho primário foi o risco absoluto de SD. Uma análise da intenção de tratar foi usada para analisar dados de todos os pacientes que foram designados aleatoriamente para receber o gel dessensibilizante e placebo. Não houve diferença significativa (p = 0,66) no risco absoluto de SD entre o grupo dessensibilizante (80%; IC 95% 69 a 89) e o grupo placebo (88%; IC 95% 77 a 94) com um risco relativo de 1,1; IC 95% 0,9 a 1,3. Não foram observadas diferenças estatisticamente significantes entre os grupos em termos de intensidade de SD e mudança de cor (p> 0,05) para nenhuma das escalas. Nenhum efeito adverso foi observado. O uso dos agentes dessensibilizantes nitrato de potássio 5%/fluoreto de sódio 0,2% 10 dias antes e após o clareamento em consultório não reduziu o risco e a intensidade da SD induzida pelo clareamento.

Palavras-chave: Sensibilidade da dentina, peróxido de hidrogênio, clareamento dental, dessensibilizantes dentinários.

Prolonged application of a desensitizing gel before and after in-office bleaching to avoid bleaching-induced tooth sensitivity: a randomized, triple-blind controlled trial

ABSTRACT

Some studies showed the use of potassium nitrate/sodium fluoride desensitizing agents might reduce the intensity of tooth sensitivity (TS). This trial evaluated the use prolonged of 5% potassium nitrate/0.2% sodium fluoride desensitizing agents ten days before and after in-office bleaching to avoid the TS. A parallel, placebo-controlled, triple-blind, randomized trial, was conducted on 115 healthy adults having teeth shade A2 or darker. The patients used 5% potassium nitrate/0,2% sodium fluoride desensitizing agents or placebo gel, for 10 days in a tray for 10 min, prior, during and two days after to the in-office bleaching (35% hydrogen peroxide). The primary outcome TS was recorded on VAS 0-10 and NRS 0-4 scales, during bleaching and in periods that ranged from 1-6 h, 12-18 h, 18-24 h and 24-48 h post-bleaching. The color was measured before and one month after dental bleaching with two visual shade guides (Vita Classical and Vita Bleachedguide) and Easyshade spectrophotometer. The primary outcome variable was absolute risk of TS. An intent-to-treat analysis was used to analyze data from all patients who were randomly assigned to receive the desensitizing and placebo gel. No significant difference ($p = 0.66$) in the absolute risk of TS between the desensitizing group (80%; 95% CI 69 to 89) and placebo group (88%; 95% CI 77 to 94) with a relative risk of 1.1; 95% CI 0.9 to 1.3. No significant differences between groups were observed in terms of intensity of TS and color change ($p > 0.05$) for any of scales. No adverse effect was observed. The use of 5% potassium nitrate/0,2% sodium fluoride desensitizing agents 10 days before and after in-office bleaching does not reduce the risk and intensity of bleaching-induced TS.

***Keywords*:** Dentin sensitivity, hydrogen peroxide, tooth bleaching, dentin desensitizing agents.

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

LISTA DE ABREVIATURAS

CI – confidence interval

K^+ – potassium ions

NRS – numeric rating scale

TS – tooth sensitivity

VAS – visual analogue scale

ΔSGU – shade guide units

ΔE – color change

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SUMÁRIO

1. Introduction

Tooth bleaching is an acceptable and conservative approach to improve teeth color and produce a pleasant smile [1-5]. In a study conducted in Malaysia, 56.2% of the adult population reported not to be satisfied with their tooth color [6], and this lack of satisfaction is associated with increased desire for treatments that improve dental aesthetics, including dental bleaching [7,8]. This is probably the reason of why tooth bleaching market has grown significantly with several available products and techniques.

Notwithstanding, bleaching-induced tooth sensitivity (TS) is reported to be the most common side effect and many studies have aimed to investigate protocols capable of reducing TS [9-22]. In-office bleaching has a higher risk and intensity of TS than at-home protocol, affecting more than 80% of the patients who undergo such procedure [11,13,23,24].

This sensitivity is usually reported by patients as a sharp and transient pain resulted from an inflammatory response of the pulpal tissue [25] mediated by the release of chemical mediators such as adenosine triphosphate and prostaglandins. Such inflammatory response occurs due to easy passage of the hydrogen peroxide through dental reaching the pulp tissue in periods shorter than 15 min [26]. Considering the inflammatory process involved in bleaching-induced TS, the preemptive administration of anti-inflammatory and/or analgesic drugs has been investigated as alternative to mitigate such adverse effect in many clinical trials [10-14,27,28] but unfruitful results. A more promising approach, which has shown reduction of the risk and intensity of TS was the topical application of desensitizing agents (fluorides, potassium nitrate, glutaraldehyde) before or after dental bleaching [19-22,29].

Topical application might allow for the penetration of the desensitizing agent at the pulp in a high concentration and exert its function or even prevent the easy passage of hydrogen peroxide radicals [20]. Among the available desensitizing agents, potassium nitrate desensitizing products have been reported as an effective product to minimize TS [30]. Potassium ions (K+), which are the active component of potassium nitrate desensitizing agents can reduce the dentinal sensory nerve activity due to the repolarizing activity of the K+ [31]. Although this approach can reduce by half the risk of TS, a great percentage of patients still experience this side effect during bleaching.

Perhaps longer desensitization before and after regimens can be able to eliminate TS and discomfort during and after in-office bleaching. Therefore, the aim of this randomized controlled trial was to evaluate if the prolonged 10-day application of a desensitizing agent

based on 5% potassium nitrate, compared to a placebo, could reduce the risk and intensity of bleaching-induce TS.

2. Material and methods

2.1. Ethics approval and protocol registration

This clinical investigation was approved (protocol number 45733615.6.0000.0109) by the Scientific Review Committee and by the Committee for the Protection of Human Subjects of the University of Paraná – UNIPAR (Cascavel, PR, Brazil). It was registered in clinical trials registry (REBEC) under identification number RBR-9GXBG6. This clinical report follows the protocol established by the Consolidated Standards of Reporting Trials (CONSORT) statement with extension for within-person designs [32] and followed the methodology used by Rezende et al., [11], DE PAULA et al., [23], DE PAULA et al., [12] and COPPLA et al., [14].

2.2. Trial design, settings and locations of data collection

This study was a randomized, placebo-controlled, parallel superiority clinical trial. This study was performed from 01/2016 to 12/2017 in the city of Cascavel (Paraná, Brazil). All bleaching procedures were carried out within the Clinics of the Dental School of the State University of Western of Paraná (Cascavel, Paraná, Brazil).

2.3. Recruitment

Participants were recruited through written advertisements placed on the university walls. All participants signed an informed consent form before being enrolled in the study.

2.4. Eligibility criteria

Patients included in this clinical trial were at least 18 years old and had good general and oral health and did not report any type of TS. The participants were required to be caries-free and to have the six upper anterior teeth without restorations. They should not have periodontal disease and must review and sign the informed consent form. The central incisors should be shade A_2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical, Vita Zahnfabrik, Bad Säckingen, Germany).

Participants with orthodontics apparatus, severe tooth discoloration (tetracycline stains, fluorosis, pulpless teeth) were not included in the study. Additionally, pregnant/lactating women, smokers, bruxists, participants with any other pathology that could cause sensitivity

(such as recession, dentine exposure, presence of visible cracks in teeth), taking anti-inflammatory and/or analgesic drugs, or participants that had already undergone tooth-whitening procedures were also excluded.

2.5. Sample size calculation

The primary outcome of this study was the absolute risk of TS. The absolute risk of TS (that is, the percentage of patients who reported pain at some point during tooth bleaching) was reported to be approximately 86% [12,19] for the bleaching product Whiteness HP Maxx (FGM Dental Products, Joinville, SC, Brazil). Using an alpha of 0.05, 90% power and a two-sided test, the minimum sample size in this superiority trial was 114 patients to detect a 26% difference in the risk of tooth sensitivity between groups.

2.6. Random sequence generation and allocation concealment

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

2.7. Blinding

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

Both the desensitizing and placebo gels were similar in consistency, color and delivered in identical syringes coded as “A” and “B”. Only the research coordinator knew the coding system. The placebo gel had the same composition of the desensitizing gel, except that it did not contain the active ingredients (potassium nitrate and sodium fluoride).

2.8. Study intervention

Two weeks before the bleaching procedures, the operators made an alginate impression of each subject's maxillary and mandibular arch and filled them with dental stone. The operators used a 0.9-millimeter soft vinyl material, provided by the manufacturer, to fabricate the custom-fitted tray for the treatment gel. The operators trimmed the excess of labial and lingual surfaces 1 mm away from the gingival margin.

Ten days prior to in-office bleaching, each patient received the upper and lower bleaching and one syringe (3g) containing the placebo or the desensitizing gel based on 5% potassium nitrate and 0.2% sodium fluoride gel (Desensibilize KF 0.2%, FGM). Participants were instructed to fill in the bleaching tray with the experimental/placebo gel in a way that the whole dental surface could be covered with the product without excess.

The patients were instructed to apply the experimental/placebo gel daily for 10 minutes prior during ten days before the first in-office bleaching session. After 10 minutes, the operator instructed the patients to remove the tray, wash it and brush their teeth regularly using fluoridated toothpaste.

On the 10^{th} day after treatment with desensitizing or placebo gel, the operator placed a lip retractor (Arcflex, FGM) and isolated the gingival tissue of the teeth to be bleached using a light-cured resin dam (Top Dam, FGM), being each tooth was light-cured for 10 s (Radii-cal, SDI, Victoria, Australia). The 35% hydrogen peroxide gel (Whiteness HP Automixx, FGM) was applied in a single 50-minute application for both groups in accordance with the manufacturer's directions. Two bleaching sessions were performed with one-week interval. The patients were instructed to continue using the experimental/placebo gels in the week interval and for two days after the second bleaching session. For details about the composition of the bleaching materials are depicted in Table 1.

2.9. Outcomes

2.9.1. Tooth sensitivity evaluation

Before the implementation, patients were instructed to record the bleaching-induced TS, using the 5-point numeric rating scale (NRS) and 0-10 visual analogue scale (VAS), in six times

assessments: 1) during bleaching and up to 1 h, 2) 1 h up to 6h; 3) 6 h up to 12 h and 4) 12h up to 18h, 5) 18 h up to 24 h, and 6) from 24 h up to 48 h post-bleaching.

For the NRS scale, the patient was asked to record the degree of TS in a zero to 4 scores, where 0 means no sensitivity, 1 mild tooth sensitivity, 2 moderate tooth sensitivity, 3 considerable tooth sensitivity, and 4 severe tooth sensitivity [12,19,23,33-35]. For the VAS scale the patient should mark with a vertical line across a 10-cm horizontal line the intensity of the TS [20,36,37]. In the extremes of this horizontal line, the numbers 0 and 10 were written, with 0 meaning no sensitivity and 10 meaning severe sensitivity. Then, the distance in mm from the zero ends was measured with the aid of a millimeter ruler.

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

The data from both bleaching sessions were merged for statistical purposes, as they did not show any different patterns (data not shown). For this purpose, the worst score (NRS scale) and the highest numerical value (VAS) from the two bleaching sessions in every assessment period was used to analyze the bleaching-induced TS. If the patient scored zero (no sensitivity) in all time assessments from both bleaching sessions, this patient was considered to be insensitive to the bleaching protocol. In all other circumstances, the patients were considered to have sensitivity to the bleaching procedure.

2.9.2. Color evaluation

Two experienced and calibrated dentists (kappa statistics higher than 80% after previous calibration), who were not involved in the randomization procedures, performed clinical assessments at baseline, 1 week after the first bleaching session and 1 month after the end of the bleaching treatment. Color was not evaluated immediately after each bleaching session to avoid the effects of dehydration and demineralization on the color measures. We evaluated color using the VITA Classical and VITA Bleachedguide 3D-MASTER shade guides. In addition, we performed an objective color evaluation with a VITA Easyshade spectrophotometer (VITA Zahnfabrik, Bad Säckingen, Germany).

The Vita Classical scale is arranged in 16 tabs from the highest value (B1) to the lowest (C4): B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4, C4. The VITA Bleachedguide 3D-MASTER contains lighter shade tabs and it is already organized from the highest value (0M1) to the lowest value (5M3).

The middle third of the buccal surfaces of the upper anterior central incisor was used as the tooth-matching area. Color changes were calculated from the beginning of the active phase up to the individual recall times by calculating the change in the number of shade guide units (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs. In case of disagreement between the operators, they reached a consensus.

To measure color with the spectrophotometer, the examiner took an impression of the maxillary arch with dense silicone paste (Zetaplus and Oranwash® Kit, Zhermack, Italy). The impression was extended to the maxillary canines and served as a standard color measurement guide for the spectrophotometer. To evaluate each central incisor, we created a window on the buccal surface of the silicone guide using a metal device with a radius of 3 millimeters, which is exactly the diameter of the tip of the spectrophotometer [38]. We then inserted the tip of the device into the silicone guide and obtained the L*, a*, and b* parameters of color from the spectrophotometer. The L* value represents the luminosity (value from 0 [black] to 100 [white]), the a* value represents the measurement along the red-green axis, and the b* value represents the measurement along the yellow-blue axis. The color change (ΔE) was given by the differences between the baseline and the color at each assessment, calculated using the following formula: $\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.

2.10. Statistical analysis

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

The TS intensity data set for both the VAS and NRS scales were plotted in histograms and inspected for normal distributions. As data did not have normal distribution, the groups

were compared using Mann-Whitney test. Comparisons between assessment times within each group were performed with the Friedman test ($\alpha = 0.05$). The means and standard deviations of color change in ΔSGU and ΔE between baseline and 30 days after bleaching were calculated. In order to assess whether the bleaching therapies were effective, data from both groups were compared using Student t-test. The level of significance of all tests was set at 5%.

3. Results

3.1. Characteristics of included participants

A total of 184 participants were examined according to the inclusion and exclusion criteria (Figure 1), but only 115 participants remained for the clinical trial. Table 2 describes the baseline color of the participants and their gender distribution. No hypothesis testing was performed for the baseline features, as any differences between these features were attributed to chance alone.

3.2. Adherence to the protocol

One patient from the desensitizing group and two from the placebo group discontinued intervention in this clinical trial due to intense pain. One patient of desensitizing group moved so that we lost contact. These patients performed only the first bleaching session. Four participants did not attend the recall visits one-month post-bleaching, including the participant from the placebo group that discontinued treatment. For these participants, the last observation was carried forward for statistical purposes to keep the intention-to-treat analysis. Figure 1 depicts the participant flow diagram in the different phases of the study design.

3.3. Risk of tooth sensitivity

A total of 51 patients presented pain in the placebo group (88%; 95% CI 77 to 94) and 46 patients reported pain in the desensitizing group (80%; 95% CI 69 to 89). In comparative terms, the risk ratio for pain was 1.1 (95% CI 0.9 to 1.3; Table 3). As the 95% CI does not exclude benefit or harm (it crosses the null value of 1), no significant differences between groups were detected (Table 2; chi-square test; $p = 0.66$).

3.4. Intensity of tooth sensitivity

The NRS and VAS scale was unable to detect significant differences between groups at the different time assessments (Table 4 and 5; $p > 0.05$). None of the patients had TS after 48 hours.

3.5. Painful teeth

A total of 115 patients were bleached in this trial in both groups and 95 patients presented sensitivity symptoms during and immediately after the bleaching sessions. 24 patients from the control group and 21 patients from the experimental group presented sensitivity in the central incisors, 25 patients from the control group and 25 patients from the experimental group presented sensitivity in the lateral incisors, 36 patients from the control group and 28 patients from the experimental group presented sensitivity in the canines and 19 patients from the control group and 15 patients from the experimental group presented sensitivity in the premolars (Table 6).

3.6. Color evaluation

Significant whitening was detected by three different tools. A bleaching of approximately 4 units of color in the Vita Classical scale, 6 units in the Vita Bleachedguide, and 8 units in the ΔE was observed. No significant difference of color change was observed between groups (Table 7; $p > 0.05$).

3.7. Adverse effects

Six patients from the placebo group and one patient from the desensitizing group showed intense pain and took an analgesic (rescue medication) to alleviate the bleaching-induced TS (six patients took Paracetamol 750 mg, Brainfarma Indústria Química e Farmacêutica S.A., Anápolis, Goiás, Brazil and one patient took Toragesic 10 mg, São Bernardo do Campo, São Paulo, Brazil).

4. Discussion

It is generally believed that high concentrate hydrogen peroxide produces more TS than do lower-concentrate solutions [11,39,40]. Indeed, this clinical trial demonstrated that approximately 84% of patients from both groups reported TS at some stage of the in-office bleaching, confirming the high prevalence of TS shown by previous studies [12,20,24].

The pulp tissue damage caused by tooth bleaching likely causes the release of cell-derived factors, such as ATP and prostaglandins, that excite or sensitize pulpal nociceptors [41,42], besides that, the increase in the expression of substance-P (a nerve-released vasoactive peptide) indicates that neurogenic inflammation plays a role in bleaching-induced TS [43].

Theoretically, the potassium nitrate treats the bleaching-induced TS preventing the nerve repolarization. Because of the persisting high levels of extracellular potassium a sustained depolarized state occurs that results in an inactivation of the action potential, reducing nerve excitability and the ability of the nerve to transmit pain [44]. On the other hand, fluoride treats tooth sensitivity probable by blocking exposed dentinal tubules or reducing the fluid flow into the pulp and blocking transmission of stimuli [31,45]. This is explanation given by authors who detected that the application of a 5% potassium nitrate and 2% sodium fluoride desensitizing agent prior to the in-office bleaching protocol was efficient to reduce the prevalence and intensity of TS in previous studies [19,20,46-48].

To inhibit nerve excitability, the inward diffusion of potassium has to increase the concentration of K^+ in the vicinity of the intradental nerve endings by 10 mM. This is the concentration of K^+ that inhibits impulses in isolated non-dental nerve bundles [49]. The ability of potassium ions to diffuse through dentin may be limited by the normally present outward flow that opposes inward diffusion [50]. Another factor influencing the magnitude of potassium influx to the intradental nerve endings is the permeability of the odontoblast layer, which to hinder the movement of large molecules [51,52], and the effect on K^+ diffusion is unknown.

In view of the problematic nature of potassium diffusion through dentin and its apparent poor ability to inhibit intradental nerve activity induced by natural (hydrodynamic) stimuli, the desensitizing gel with prolonged application for 10 days before in-office bleaching could ensure the increase the inward diffusion of potassium, the concentration of K^+ in the vicinity of the intradental nerve and to inhibit nerve excitability [53]. However, the desensitizing gel neither

avoided and nor decreased the intensity of tooth sensitivity. This same results were already demonstrated in other trials, as occurred in Loguercio, 2015 [54], where the percentage and level of TS was similar in both desensitizing agents and placebo gel.

The potassium nitrate concentration of 5% used in this study is the maximum concentration allowed by the U.S. Food and Drug Administration to be used for treating tooth sensitivity but there are also other factors to consider when evaluating potassium nitrate penetration levels, one of which is the viscosity of the material [8]. According to Paris et al 2014 [55], the deeper penetration into the tooth structure is with the material of lower viscosity [8].

Other reason for this results could be due the properties of membrane gates where the period of inactivation does not last long, and the action potentials begin to occur again [3]. In the laboratory, suppression of nerve activity occurred rapidly and did not last much more than 10 minutes [56] following removal of the potassium solution from the deep dentinal cavity. This fast desensitizing effect seem to explain why the 5% potassium nitrate used in tray for prolonged time, was ineffective in reducing the tooth sensitivity. Based on a detailed review of the literature Orchardson and Gillam [57], expressed skepticism concerning the ability of K^+ ions to depress nerve activity when administered in dental products to the dentin surface.

About the action of fluoride, Ubaldini et al. 2013 [58] reported that the amount of hydrogen peroxide in enamel after application of the bleaching gel is minimal compared to dentin, suggesting that enamel does not pose any barrier to penetration of the hydrogen peroxide. For Loguercio et al. 2015 [54] this explains why the obliterating products (fluoride and calcium phosphates) did not reduce the tooth sensitivity.

It’s worth to emphasize, this research showed bigger sample size than other clinical trials that investigated the desensitizing agent which the components of the desensitizing gel varied slightly among studies, but all of them contained 5% potassium nitrate [19,29,46-48]. In addition, different of them, this research had a power of the 90%, where the number of patients is higher to avoid a type II error. As Martini (in press), this study was very efficient at detecting significant differences. Proper control of randomization, allocation concealment and blinding put the study at a low risk of bias; factors not observed in some of the earlier studies that investigated this issue. Altogether, these factors increase the reliability of the current study findings; but they do not exclude the need for further well-designed randomized clinical trial

on this issue. Commercially, the 5% potassium nitrate gel may be associated with 2% or 0.2% sodium fluoride [59]. This lower concentration 0.2% was used in this research because is the protocol was for daily use in tray.

In relation the descriptive analysis of the teeth that presented sensitivity, Haywood [22] and Bonafe [46] reported that TS from bleaching usually affects the smaller teeth, such as the maxillary lateral incisors and the mandibular incisors. The present clinical study found all teeth presented tooth sensitivity symptoms post bleaching by the risk of TS varied from tooth to tooth. Costa et al., [25] and others in a histological pulp evaluation after bleaching, showed notable damage to the pulp tissue of mandibular incisors but not premolars. In this research, the premolars were the tooth less cited by patients. The less sensitivity in the premolars can be explained because about 87% of all axons that enter human premolars are non myelinated C fibers, with lower intensity pain [60].

The pain scale used in this study was VAS and NRS, although both pain scales measure the same objective, Charakorn et al., [10] stated that the pain ratings of the pain scales were not associated, on the other hand, Bijur et al., [61] states that they are strongly correlated. Nevertheless, this methods have been used in numerous studies [20,46,62-65].

In spite of the dental sensitivity, the use of desensitizing agent prior to bleaching treatment, the potassium nitrate and sodium fluoride did not interfere with the bleaching efficacy, regardless of the method of color change used, Vita Classical and Vita 3D Master, considered subjective assessment methods, or spectrophotometer, provides an objective color assessment, all had had efficacy in the bleaching treatment in booth groups.According to the Vita Classical shade guide, the degree of whitening observed in this study, for both groups, was approximately 5 SGU, as cited in another studies [48,66,67].

Finally, the limitations of this investigation should be reported. A lower concentration of sodium fluoride was evaluated, therefore futher studies with increased of sodium fluoride concentration, as well as the split-mouth design to remove interindividual variability from the estimates of the effect of the treatment, are indicated.

5. Conclusion

The prolonged use of 5% potassium nitrate/0,2% sodium fluoride desensitizing agents 10 days before and after in-office bleaching did not avoid nor reduce the bleaching-induced TS.

6. Acknowledgements

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7. 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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9. Figures

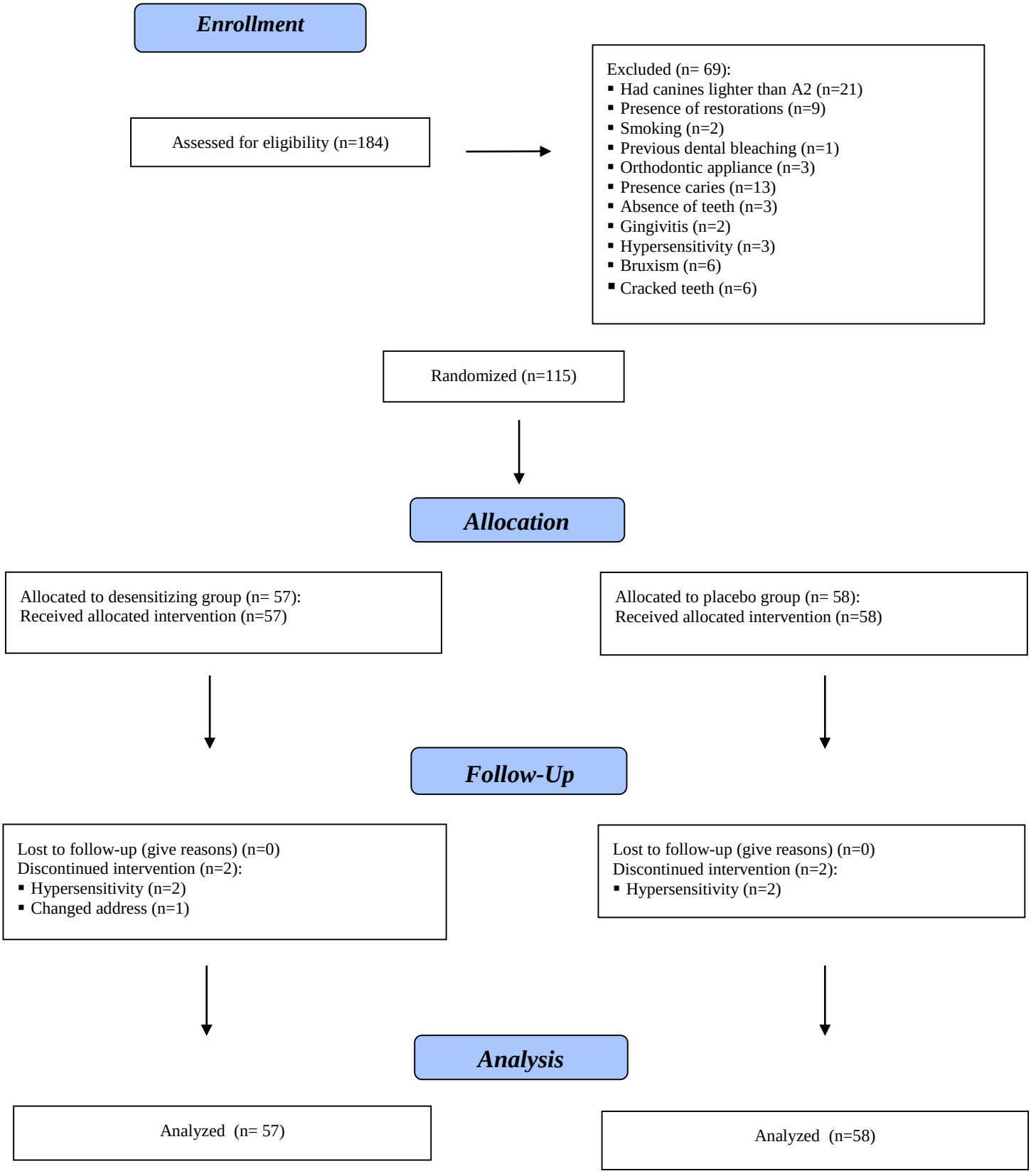

Figure 1. Flow diagram of study design phases including enrollment and allocation criteria.

10. Tables

Table 1 - Bleaching Gel (Manufacturer, Composition, Groups and Application Method).

Manufacturer	Composition	Groups	Application Method
Hydrogen peroxide 35% (Whiteness HP AutoMixx, FGM, Joinville, SC Brazil)	Hydrogen peroxide 35%, thickening, neutralizing, consisting of calcium, glycol, dye, inorganic filler and deionized water	Desensitizing: 5% potassium nitrate/0,2% sodium fluoride (lot: 171116) Placebo: The gel did not desensitizing agent (lot: 060916)	A single 50-minute application

Table 2 - Baseline characteristics of the participants.

Characteristic		Groups	
		Desensitizing agent (n=57)	**Placebo (n=58)**
Baseline color (SGU*; mean ± SD)		6.5 ± 2.4	6.3 ± 2.0
Age (years; mean ± SD)		21.4 ± 2.5	22.2 ± 3.2
Gender (female; %)		65.0	69.0
Race	White (%)	93.1	84.4
	Black (%)	1.7	5.2
	Mulatto (%)	1.7	5.2
	Yellow (%)	3.5	5.2
Patients that used whitening toothpaste		0	0

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

Table 3 – Comparison of absolute risk of tooth sensitivity (percentage, 95% confidence interval) along with the risk ratio (*).

Treatment	**Absolute risk (95% CI)**	**Risk ratio (95% CI)**
Desensitizing agent (n=57)	80 (69 - 89)	1.1 (0.9 to 1.3)
Placebo (n = 58)	88 (77 - 94)	

(*) chi-square test (p-value = 0.66).

Table 4 – Medians and interquartile ranges of the tooth sensitivity intensity at different assessment points using the NRS and VAS scale (*).

Time assessment periods	NRS scale			VAS scale		
	Desensitizing	**Placebo**	**p-value****	**Desensitizing**	**Placebo**	**p-value****
During bleaching	1 (1-2) aBD	2 (1-3) aC	0.19	3 (1-6) aE	3 (2-7) aE	0.27
Up to 1 h	2 (1-3) aD	2 (1-3) aD	0.33	3 (1-6) aC	4 (2-7) aD	0.55
1 h to 6 h	2 (0-3) aC	2 (1-3) aD	0.84	3 (0-7) aD	3 (1-7) aD	0.80
6 h to 12 h	1 (0-1) aB	1 (0-2) aBC	0.40	1 (0-4) aC	1 (0-4) aCE	0.98
12 h to 24 h	0 (0-1) aAB	0 (0-1) aAB	0.60	0 (0-2) aBC	0 (0-2) aBC	0.44
24 h to 48 h	0 (0-0) aA	0 (0-0) aA	0.82	0.0 (0-0) aAB	0 (0-0) aAB	0.30

(*) Comparisons are valid only within the same pain scale. At each period, the two treatments were compared with the Mann-Whitney U-test and differences are represented by differences are represented by different lowercase letters. For each treatment, the three periods were compared with the Friedman test (α=0.05), and differences are represented by different uppercase letters.

Table 5 – Means and standard deviations of the TS intensity at the different time assessment periods along with the effect size and the 95% confidence interval with VAS scale (*).

Time assessement periods	Groups		Mean difference (95% CI)
	Desensitizing	Placebo	
During bleaching	3.3 ± 3.0a	3.9 ± 3.0a	-0.6 (-1.6 to 0.5)
Up to 1 h	3.8 ± 3.2a	4.1 ± 2.9 a	-0.3 (-1.4 to 0.8)
1 h to 6 h	3.9 ± 3.4a	3.7 ± 3.1a	0.1 (-1.0 to 1.3)
6 h to 12 h	2.4 ± 3.0a	2.4 ± 3.0a	0.0 (-1.1 to 1.1)
12 h to 24 h	1.2 ± 2.0a	1.2 ± 2.3a	0.0 (-0.7 to 0.8)
24 h to 48 h	0.4 ± 1.2a	0.6 ± 1.7a	-0.2 (-0.7 to 0.3)

(*) Comparisons are only valid within rows. Means indicated by the same lowercase letters indicate statistically similar means (Student t-test, $\alpha=0.05$).

Table 6 - Number of patients who reported tooth sensitivity at least once in the different tooth types.

Kind of Teeth	Number of patients of each group (*)			Overall proportion (95% CI)
	Control	Experimental	Overall	
Central incisor	24	21	45	39 (30 to 48) AB
Lateral incisor	25	25	50	43 (34 to 52) A
Canines	36	28	64	55 (46 to 64) A
Premolars	19	15	34	29 (28 to 38) B

(*)Proportions indicated by the same uppercase letters are statistically similar (chi-square test, $\alpha=0.05$).

Table 7 – Means and standard deviations of ΔSGU obtained with the Vita Classical and Vita Bleachedguide and ΔE obtained by spectrophotometer between baseline vs. 1-month post bleaching. P-values of the pairwise comparison as well as the effect size (95% confidence interval) are described.

Color evaluation tool	Groups		p- value*	Mean difference (95% CI)
	Desensitizing	Placebo		
Vita Classical	4.5 ± 2.3 a	4.5 ± 2.2 a	1.0	0.0 (-0.8 to 0.8)
Vita Bleached	6.0 ± 3.3 b	6.2 ± 3.6 b	0.74	-0.2 (-1.1 to 1.5)
ΔE	8.4 ± 4.9 c	7.7 ± 3.7 c	0.34	-0.6 (-0.7 to 2.0)

**Comparisons are only valid within rows. Means indicated by the same lowercase letters indicate statistically similar means (Student t-test, α=0.05).*

11. Annexes

11.1. Annex 1

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Pesquisa: "O efeito de diferentes medicamentos na prevenção da sensibilidade causada pelo clareamento dental". Pesquisador para contato, se necessário: Wilson da Silva Junior.
Por esse instrumento particular, declaro, para os devidos fins éticos e legais, que eu (nome) _____,
(nacionalidade)_____, (profissão) _____, portador do R.G_____, C.P.F._____,residente à Rua / Av. _____, na cidade de _____, Estado _____, concordo em participar da pesquisa intitulada "O efeito de diferentes medicamentos na prevenção da sensibilidade causada pelo clareamento dental".

Fui informado que os objetivos desta pesquisa são o avaliar o efeito de diferentes medicamentos na redução da sensibilidade dental causada pelo clareamento dental de consultório, associado ou não ao clareamento caseiro.

Fui esclarecido que, para tanto, serei submetido ao clareamento dental, fazendo uso de medicamentos (tópicos ou sistêmicos) e deverei responder questionários de sensibilidade dental. Fui informado também que, como parte do estudo, receberei tratamento profilático básico e, caso sejam relatadas alterações de qualquer natureza, serei encaminhado para avaliação médica e somente poderei participar do estudo quando houver autorização do profissional.

Torno ciente que recebi todas as informações sobre a minha participação nesta pesquisa e receberei novos esclarecimentos que julgar necessários durante o decorrer da mesma.

Fui esclarecido que as medicações quando necessárias serão fornecidas pela equipe do Projeto, e que meu consentimento não remove a responsabilidade dos profissionais que estão realizando esta pesquisa. Além disso, tenho plena liberdade para desistir da referida pesquisa, retirando o meu consentimento a qualquer momento, sem sofrer nenhum tipo de pena.
Por fim, fica esclarecido que eu não receberei pagamento nem terei que pagar para participar da pesquisa. Após ler e receber explicações sobre a pesquisa, e ter meus direitos de:
1. Receber resposta a qualquer pergunta e esclarecimento sobre os procedimentos, riscos, benefícios e outros relacionados à pesquisa;
2. retirar o consentimento a qualquer momento e deixar de participar do estudo;
3. não ser identificado e ser mantido o caráter confidencial das informações relacionadas à privacidade;
4. procurar esclarecimentos com o Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Paranaense/UNIPAR através do telefone (44) 4436-2128 ou com o Comitê de Ética em Pesquisa da Unioeste-CEP/Unioeste, através do telefone (45) 3220-3272, em caso de dúvidas ou notificação de acontecimentos não previstos.
Declaro estar ciente do exposto e desejar participar da projeto de pesquisa.

Cascavel, _____de_____ de 20____ .
Assinatura:_____

Nome do voluntário:_____

Eu, Wilson da Silva Junior, declaramos que fornecemos todas as informações referentes ao projeto ao participante e/ou responsável. Além disso, declaramos que este Termo será feito em duas vias, sendo uma entregue ao participante e outra sob responsabilidade do pesquisador
Assinatura:_____
Telefone: (45) 9 9910-1067

11.2. Annex 2

DEVERES DOS VOLUNTÁRIOS DA PESQUISA DE CLAREAMENTO

Nome do paciente:_____

Leia as seguintes orientações:

Gostaríamos de saber como você reage ao tratamento de clareamento (se terá ou não sensibilidade dental); suas informações serão obtidas através de um DIÁRIO composto de duas escalas de sensibilidade, o qual inicia na página 2. No cabeçalho de cada escala constam as instruções de como devem ser preenchidas.

(OBS: não estamos testando nenhum produto novo, o produto clareador (Whiteness HP Automixx – FGM) utilizado nesta pesquisa é utilizado rotineiramente em consultórios odontológicos e tem seus resultados comprovados).

Agradecemos sua colaboração nesta pesquisa. Você está contribuindo com a ciência e com o desenvolvimento de alternativas para evitar a sensibilidade que pode ocorrer durante e após o tratamento de clareamento dental.

Primeira orientação ao voluntário participante da pesquisa

Nós pesquisadores o ajudaremos a lembrá-lo das próximas instruções. Como você prefere que isso seja realizado? Através de:

( ) ligações por telefone/celular ( ) mensagens de texto

Deveres e comprometimento do voluntário participante da pesquisa

1 – Se sentiu e mesmo que não tenha sentido sensibilidade, fazer anotações sobre as suas reações ao decorrer e cada período indicado no DIÁRIO.

2 – Se sentiu ou não sensibilidade além dos períodos pré-determinados, utilize a folha extra que consta na página 4.

3 - Realizar a higiene bucal antes de usar o gel;

4 - Usar somente uma vez ao dia por 10 minutos;

5 – Aplicar o gel por 10 minutos, durante 10 dias. Se esquecer aplicar imediatamente ao lembrar.

6 – Trazer o diário na próxima consulta.

Assinatura do voluntário:_____

QUADRO DE HORÁRIO

Confirmar com um X o horário que a placa foi usada.

1ª Dia	hora: ____ : _____ ( )
2ª Dia	hora: ____ : _____ ( )
3ª Dia	hora: ____ : _____ ( )
4ª Dia	hora: ____ : _____ ( )
5ª Dia	hora: ____ : _____ ( )
6ª Dia	hora: ____ : _____ ( )
7ª Dia	hora: ____ : _____ ( )
8ª Dia	hora: ____ : _____ ( )
9ª Dia	hora: ____ : _____ ( )
10ª Dia	hora: ____ : _____ ( )

DIÁRIO __ª Sessão Data:____/____/____ Horário da 1° aplicação: _____:_____ Horário do clareamento: ____:____

HORA:*	ESCALA 1 - Escala verbal de 5 pontos O voluntário deve marcar com um (X) o número (escore) que melhor corresponde as sensações que apresentou durante o decorrer de cada período.					ESCALA 2 - Escala Visual Analógica (EVA) É uma linha de 10 cm e em cada extremo apresenta a indicação "Sem Dor" e no outro "Dor Insuportável". O voluntário deve marcar, com um único traço vertical cortando a linha, o ponto que melhor corresponde as sensações que apresentou durante o decorrer de cada período.
	0 NENHUMA	**1 LEVE**	**2 MODERADA**	**3 CONSIDERÁVEL**	**4 SEVERA**	
						Sem Dor İ_____Ị Dor Insuportável
						Sem Dor İ_____Ị Dor Insuportável
						Sem Dor İ_____Ị Dor Insuportável
						Sem Dor İ_____Ị Dor Insuportável
						Sem Dor İ_____Ị Dor Insuportável

11.3. Annex 3

APROVAÇÃO NO COMITÊ DE ÉTICA

UNIVERSIDADE PARANAENSE - UNIPAR

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: O efeito de diferentes medicamentos na prevenção da sensibilidade causada pelo clareamento dental.

Pesquisador: Eloisa Andrade de Paula

Área Temática:

Versão: 5

CAAE: 45733615.6.0000.0109

Instituição Proponente: ASSOCIACAO PARANAENSE DE ENSINO E CULTURA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.596.016

Apresentação do Projeto:

O presente estudo objetiva determinar o efeito de diferentes medicamentos (tópicos e sistêmicos) na redução da sensibilidade dental causada pelo clareamento de consultório de dentes vitais utilizando peróxido de hidrogênio 35%, bem como verificar a efetividade da alteração de cor. O projeto de pesquisa é apresentado no modelo 'guarda-chuva ou universal', contend 5 projetos; para cada projeto serão selecionados no mínimo 60 pacientes para cada grupo experimental e 60 pacientes para o grupo placebo, totalizando 600 pacientes no projeto universal. As mudanças de cor serão avaliadas utilizando espectrofotômetro (Easy Shade) e escala Vita organizada por ordem de valor. Duas escalas destinadas a avaliar a intensidade de dor (escala verbal de 5 pontos e EVA escala visual analógica) serão utilizadas para avaliar o nível de sensibilidade imediatamente, 1 hora, 24 e 48 horas após o tratamento de clareamento de consultório.

Objetivo da Pesquisa:

Objetivo Primário:

Determinar o efeito de diferentes medicamentos (Tópicos e Sistêmicos) na redução da sensibilidade dental causada pelo clareamento de consultório de dentes vitais, utilizando peróxido de hidrogênio 35%.

Objetivo Secundário:

Endereço: Praça Mascarenhas de Moraes, 8462
Bairro: Umuarama **CEP:** 87.502-210
UF: PR **Município:** UMUARAMA
Telefone: (44)3621-2849 **Fax:** (44)9127-7860 **E-mail:** cepeh@unipar.br

• Avaliar o efeito do medicamento tópico gel de nitrato de potássio 5% + fluoreto de sódio 0.2% (Dessesibilize KF 0.2% - FGM) aplicado sobre os dentes 10 dias antes, durante e 48 horas após o tratamento, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do dentifrício tópico Colgate Sensitive Pró-Alívio (Colgate) com ação dessensibilizante aplicado sobre os dentes 10 dias antes, durante e 48 horas após o tratamento, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do anti-inflamatório não seletivo para as isoformas COX (Toragesic SL 10 mg), administrado de 8 em 8 horas, durante 48 horas, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do anti-inflamatório não seletivo para as isoformas COX (Toragesic SL 10 mg) combinado ao medicamento analgésico (paracetamol 750 mg), administrado de 8 em 8 horas, durante 48 horas, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório;
• Avaliar o efeito do antioxidante (vitamina E ephynal 400 mg), administrado de 8 em 8 horas, durante 48 horas, no risco absoluto de sensibilidade decorrente da realização da técnica de clareamento dental em consultório.
• Em cada projeto será avaliado a alteração de cor causada pelo agente clareador.

Avaliação dos Riscos e Benefícios:

Riscos:

A utilização do peróxido de hidrogênio pode ocasionar efeitos adversos como sensibilidade dentinária. Devido o poder de penetração dos agentes
clareadores no interior do dente,pode causar inflamação da polpa dentária.Efeito adverso com o uso do medicamento (alteração gástrica ou
cardíaca).O contato direto do agente clareador com o tecido gengival pode ocasionar ardência, descamação e ulceração, portanto, para evitar tal
ocorrência, será utilizada uma barreira de proteção fotopolimerizável (Top Dam – FGM).

Avaliação dos Riscos e Benefícios:

Riscos:

A utilização do peróxido de hidrogênio pode ocasionar efeitos adversos como sensibilidade dentinária. Devido o poder de penetração dos agentes
clareadores no interior do dente,pode causar inflamação da polpa dentária.Efeito adverso com o uso do medicamento (alteração gástrica ou
cardíaca).O contato direto do agente clareador com o tecido gengival pode ocasionar ardência, descamação e ulceração, portanto, para evitar tal
ocorrência, será utilizada uma barreira de proteção fotopolimerizável (Top Dam – FGM).

Benefícios:

Os pacientes voluntários receberão de maneira gratuita todo o tratamento de clareamento dental, proporcionando uma melhor estética para os seus dentes.

UNIVERSIDADE PARANAENSE - UNIPAR

Continuação do Parecer: 1.596.016

Comentários e Considerações sobre a Pesquisa:

Prezada Pesquisadora,

Agradecemos as alterações realizadas.

A pesquisa se apresenta de forma conclusiva e pode ser executada, uma vez que os pesquisadores contemplaram todos os requisitos éticos para a sua realização.

Considerações sobre os Termos de apresentação obrigatória:

TCLE - Este documento contém as informações para o bom entendimento e anuência dos participantes da pesquisa, devendo ser elaborado em duas vias, sendo uma retida pelo sujeito da pesquisa e a outra arquivada pelo pesquisador.

DECLARAÇÃO DE PERMISSÃO DE UTILIZAÇÃO DE DADOS ¿ Este documento se apresenta de forma satisfatória com a autorização pelo responsável do local (Instituição) onde a pesquisa será realizada.

Recomendações:

Salientamos que os procedimentos devem assegurar a confidencialidade, a privacidade, a proteção da imagem e a não estigmatização, garantindo a não utilização das informações em prejuízo das pessoas e/ou comunidade, inclusive em termos de autoestima, de prestígio econômico e/ou financeiro.

Conclusões ou Pendências e Lista de Inadequações:

Prezado pesquisador, vosso projeto foi aprovado sem restrições.

De acordo com o Conselho Nacional de Saúde, Resolução 466/2012:

O termo de consentimento livre esclarecido deve ser elaborado em duas vias, sendo uma retida pelo sujeito da pesquisa, ou por seu representante legal, e uma arquivada pelo pesquisador.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_512724.pdf	08/06/2016 15:23:23		Aceito
Folha de Rosto	folhaderosto.pdf	08/06/2016 15:23:02	Gabriela Ulian de Oliveira Somensi	Aceito

Endereço: Praça Mascarenhas de Moraes, 8482
Bairro: Umuarama **CEP:** 87.502-210
UF: PR **Município:** UMUARAMA
Telefone: (44)3621-2849 **Fax:** (44)9127-7860 **E-mail:** cepeh@unipar.br

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Continuação do Parecer: 1.596.016

Projeto Detalhado / Brochura Investigador	projeto.doc	08/06/2016 12:40:15	Eloisa Andrade de Paula	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEviavoluntario.docx	08/06/2016 12:39:44	Eloisa Andrade de Paula	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEviapesquisador.docx	08/06/2016 12:37:59	Eloisa Andrade de Paula	Aceito
Cronograma	Cronograma.docx	15/04/2016 16:40:21	Eloisa Andrade de Paula	Aceito
Outros	FormColetaDadosEVA.pdf	23/02/2016 17:33:42	Fabiana Scarparo Naufel	Aceito
Declaração de Instituição e Infraestrutura	UnioesteCampoEstudo.pdf	23/02/2016 17:31:59	Fabiana Scarparo Naufel	Aceito
Declaração de Instituição e Infraestrutura	UniparCampoEstudo.pdf	23/02/2016 17:31:46	Fabiana Scarparo Naufel	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UMUARAMA, 16 de Junho de 2016

Assinado por:
Nelton Anderson Bespalez Corrêa
(Coordenador)

Endereço: Praça Mascarenhas de Moraes, 8462
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11.4. Annex 4

SUBMISSÃO DO ARTIGO NA REVISTA JOURNAL OF DENTISTRY

Elsevier Editorial System(tm) for Journal of Dentistry or its open access mirror

Manuscript Draft

Manuscript Number:

Title: Prolonged application of a desensitizing gel before and after inoffice bleaching to avoid bleaching-induced tooth sensitivity: a randomized, triple-blind controlled trial

Article Type: Full Length Article

Keywords: Dentin Sensitivity; Hydrogen Peroxide; Tooth Bleaching; Dentin Desensitizing Agent.

Corresponding Author: Ms. Wilson Júnior,

Corresponding Author's Institution:

First Author: Eloisa de Paula, PhD

Order of Authors: Eloisa de Paula, PhD; Bianca Maran, PhD; Wilson Júnior; Vera Schmitt, PhD; Alessandra Reis, PhD; Fabiana Naufel, PhD

Abstract: Objectives: Some studies showed the use of potassium nitrate/sodium fluoride desensitizing agents might reduce the intensity of tooth sensitivity (TS). This trial evaluated the use prolonged of 5% potassium nitrate/0.2% sodium fluoride desensitizing agents ten days before and after in-office bleaching to avoid the TS. Methods: A parallel, placebo-controlled, triple-blind, randomized trial, was conducted on 115 healthy adults having teeth shade A2 or darker. The patients used 5% potassium nitrate/0,2% sodium fluoride desensitizing agents or placebo gel for 10 days in a tray for 10 min, prior, during and two days after to the in-office bleaching. The primary outcome TS was recorded on VAS 0-10 and NRS 0-4 scales, during bleaching and in periods that ranged from 1-6 h, 12-18 h, 18-24 h and 24-48 h post-bleaching. The color was measured before and one month after dental bleaching with two visual shade guides (Vita Classical and Vita Bleachedguide) and Easyshade spectrophotometer. The primary outcome variable was absolute risk of TS. Results: No significant difference ($p = 0.66$) in the absolute risk of TS between the desensitizing group and placebo group. No significant differences between groups were observed in terms of intensity of TS and color change ($p > 0.05$) for any of scales. Conclusion: The use of 5% potassium nitrate/0,2% sodium fluoride desensitizing agents 10 days before and after in-office bleaching does not reduce the risk and intensity of bleaching-induced TS. Clinical Relevance: The use of 5% potassium nitrate/0,2% sodium fluoride desensitizing agents was not capable to prevent TS arising from in-office dental bleaching.