



Murilo Guimarães Campolina

**Efeitos do Ozônio no Clareamento Dental Caseiro: Um Estudo Clínico,
Randomizado, Duplo-Cego.**

*Effects of Ozone on At-Home Tooth Bleaching: A Double-Blind,
Randomized Clinical Trial*

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia, como requisito parcial para obtenção do Título de Mestre em Odontologia na Área de Concentração de Clínica Odontológica Integrada.

Uberlândia – 2024

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“A busca pelo conhecimento, a procura pela verdade e a contemplação da beleza são domínios em que nos é consentido ficar crianças toda a vida.”

Albert Einstein

SUMÁRIO

RESUMO/PALAVRAS-CHAVE	7
ABSTRACT/KEYWORDS	9
INTRODUÇÃO E REFERENCIAL TEÓRICO	11
CAPÍTULO - ARTIGO 1	14
CONCLUSÕES	33
REFERÊNCIAS	35

Resumo

RESUMO

O presente estudo avaliou o impacto da aplicação de óleo de girassol ozonizado durante o clareamento dental caseiro na sensibilidade dentária (TS), mudança de cor e percepção do paciente. Um ensaio clínico randomizado e duplo-cego foi conduzido com 40 participantes, distribuídos nos grupos experimental (óleo de girassol ozonizado) e placebo (óleo de girassol). O óleo foi aplicado em moldeiras por 1 minuto após cada aplicação de gel clareador à base de peróxido de hidrogênio a 10% por 30 minutos, em um total de 21 sessões. A TS foi avaliada diariamente com uma escala visual analógica (VAS) e uma escala de classificação numérica (NRS). A cor dos dentes foi medida com um espectrofotômetro (ΔE_{ab} , ΔE_{00} , ΔWID) e uma escala visual de cor ($\Delta SGUs$) nos períodos inicial, 1 semana (T1) e 1 mês (T2) após o tratamento. A percepção dos pacientes foi avaliada com formulários baseados na escala Likert. Os resultados mostraram que 72,5% dos pacientes relataram TS durante o clareamento, independentemente do grupo. Não houve diferenças significativas na intensidade da TS entre os grupos ($p=0,536$) nem no número de dias dolorosos ($p=0,256$). A mudança de cor foi semelhante entre os grupos ($p>0,05$); entretanto, ΔE_{ab} e ΔE_{00} em T2 foram menores que em T1 ($p=0,010$ e $p=0,026$, respectivamente). A percepção dos pacientes em relação ao sabor ($p=0,002$) e odor ($p=0,010$) diferiu significativamente, com o óleo de girassol ozonizado sendo considerado desagradável para uso. Concluiu-se que a aplicação de óleo de girassol ozonizado durante o clareamento dental caseiro não reduziu a TS nem afetou a mudança de cor em comparação ao placebo. A percepção do paciente foi negativa devido, principalmente, ao sabor e odor desagradáveis do óleo de girassol ozonizado. Assim, apesar dos diversos mecanismos de ação, o óleo de girassol ozonizado não mitigou a sensibilidade dentária nem influenciou a mudança de cor durante o clareamento dental caseiro, com seu sabor e odor impactando negativamente o conforto do paciente.

PALAVRAS-CHAVE

Clareamento dental; Sensibilidade dentária; Agentes dessensibilizantes dentinários; Peróxido de hidrogênio; Ozônio.

Abstract

ABSTRACT

This study evaluated the impact of ozonized sunflower oil application during at-home tooth bleaching on tooth sensitivity (TS), color change, and patient perception. A double-blind, randomized clinical trial was conducted with 40 participants, divided into experimental (ozonized sunflower oil) and placebo (sunflower oil) groups. The oil was applied in trays for 1 minute following each application of 10% hydrogen peroxide gel for 30 minutes, over a total of 21 sessions. TS was assessed daily using a visual analog scale (VAS) and a numerical rating scale (NRS). Tooth color was measured with a spectrophotometer (ΔE_{ab} , ΔE_{00} , ΔWID) and a visual shade guide ($\Delta SGUs$) at baseline, 1 week (T1), and 1 month (T2) post-treatment. Patient perception was evaluated using Likert scale-based forms. Results showed that 72.5% of patients reported TS during bleaching, regardless of the group. No significant differences were found in TS intensity between the groups ($p=0.536$) or in the number of painful days ($p=0.256$). Color change was similar between the groups ($p>0.05$); however, ΔE_{ab} and ΔE_{00} at T2 were lower than at T1 ($p=0.010$ and $p=0.026$, respectively). Patient perception regarding taste ($p=0.002$) and odor ($p=0.010$) differed significantly, with ozonized sunflower oil being considered unpleasant for use. It was concluded that the application of ozonized sunflower oil during at-home tooth bleaching did not reduce TS or affect color change compared to the placebo. Patient perception was negative primarily due to the unpleasant taste and odor of ozonized sunflower oil. Thus, despite various mechanisms of action, ozonized sunflower oil did not mitigate tooth sensitivity or influence color change during at-home tooth bleaching, with its taste and odor negatively impacting patient comfort.

KEYWORDS:

Tooth bleaching; Tooth sensitivity; Dentin desensitizing agents; Hydrogen peroxide; Ozone.

Introdução e Referencial Teórico

INTRODUÇÃO E REFERENCIAL TEÓRICO

O clareamento dental é um procedimento odontológico amplamente difundido globalmente. Trata-se de um tratamento conservador e simples, comumente realizado para alcançar um sorriso esteticamente agradável [1] e tem sido objeto de numerosos estudos laboratoriais e clínicos [2-5]. A técnica envolve a aplicação de agentes clareadores à base de peróxido na superfície vestibular dos dentes. Os radicais produzidos pela degradação do peróxido oxidam os componentes orgânicos do tecido dental, resultando em dentes mais brancos [3]. O efeito adverso mais comum relatado por pacientes que realizam clareamento é a sensibilidade dentária [2-4,6,7], especialmente quando se utiliza peróxido de hidrogênio altamente concentrado [3,5,6,8,9]. A sensibilidade dentária resulta do contato do peróxido e seus subprodutos na polpa, levando a uma resposta inflamatória neste tecido [10]. O risco absoluto médio de sensibilidade dentária é de aproximadamente 51% para técnicas de clareamento caseiro [8,9]. A abordagem mais eficaz para reduzi-la, tem sido a aplicação tópica de agentes dessensibilizantes, como aqueles contendo glutaraldeído [11,12], nitrato de potássio [13,14] e agentes à base de cálcio [15,16]. Embora esses agentes dessensibilizantes tenham sido propostos para mitigar este efeito adverso, eles não conseguem erradicar totalmente a dor, apesar de apresentarem efeitos positivos [17-20].

A terapia com ozônio, ganhou destaque na odontologia já na década de 1930 [21]. Administrado na forma de gás ou dissolvido em base aquosa ou oleosa, o ozônio proporciona benefícios terapêuticos, especialmente propriedades anti-inflamatórias, antioxidantes e analgésicas [22-25]. Estudos clínicos demonstraram efeitos de clareamento dental através da rápida e poderosa degradação oxidativa dos componentes descoloridos, bem como redução da dor durante o clareamento dental em consultório [23,26-28]. O gás ozônio tem mostrado eficácia na abordagem da sensibilidade dentinária, reduzindo a dor durante o clareamento dental e modulando vias inflamatórias ao reduzir a atividade das prostaglandinas e da cicloxigenase [23-25,29].

No entanto, sua aplicação em cenários de clareamento dental, com foco na resolução da sensibilidade dentária, permanece relativamente inexplorada. Além disso, a literatura disponível foca no uso do gás ozônio, que apresenta várias limitações. O gás requer equipamentos geradores de ozônio, é potencialmente tóxico para o sistema

respiratório em altas concentrações e necessita de uma equipe treinada para manuseio [22]. Para procedimentos de clareamento, ele só pode ser usado em consultório. Em contraste, o óleo ozonizado é mais simples de utilizar, pode ser adquirido por profissionais e pacientes de indústrias registradas, e não apresenta as limitações de uso relatadas, potencialmente oferecendo mais valor clínico do que o gás e permitindo protocolos dentais caseiros, supervisionados pelo dentista.

Óleos ozonizados contêm um complexo de oxigênio ativo (formado a partir da reação do ozônio com ácidos graxos insaturados, peróxidos de ozônio e trioxolanos) que favorece a cicatrização de feridas, estimula o metabolismo celular e elimina bactérias, vírus e fungos [30,31]. O índice de peróxido no processo de ozonização do óleo deve ser de aproximadamente 600 meq/kg para garantir todos os benefícios terapêuticos do ozônio [30-32]. O óleo de girassol é o mais frequentemente utilizado devido aos seus efeitos terapêuticos naturais [32]. A forma ozonizada dos óleos é fácil de manusear, pois retém os compostos derivados da ozonização por um período mais longo, tornando-o utilizável fora do ambiente clínico e hospitalar e acessível à população em geral [32].

Portanto, explorar a potencial eficácia do óleo ozonizado como um agente dessensibilizante experimental, bem como avaliar as alterações na cor dos dentes e a percepção dos pacientes em relação ao uso deste tratamento, são promissores. A maioria dos ensaios clínicos sobre clareamento dental e a avaliação de materiais de tratamento adjuntos tem se centrado predominantemente na avaliação apenas da ocorrência de sensibilidade ao clareamento e das alterações na tonalidade dos dentes [33]. Reconhecendo a importância da percepção dos pacientes, particularmente no contexto de tratamentos domiciliares, é imperativo conduzir avaliações rigorosas, especialmente no que diz respeito à utilização de novos agentes experimentais, como o ozônio.

Entendendo os mecanismos de ação do ozônio e reconhecendo que, quando sujeito a um veículo oleoso, é mais facilmente aplicável clinicamente do que o gás, realizamos este ensaio clínico. Nossa hipótese é que o óleo ozonizado poderia produzir um efeito dessensibilizante durante o clareamento. Portanto, nosso objetivo foi avaliar o impacto da aplicação tópica do óleo ozonizado no risco absoluto e na intensidade da sensibilidade dentária induzida pelo clareamento e na alteração da cor após o clareamento domiciliar com peróxido de hidrogênio a 10%.

Capítulo

CAPÍTULO 1

ARTIGO 1

Effects of Ozone on At-Home Tooth Bleaching: A Double-Blind, Randomized Clinical Trial

***Artigo em processo de submissão no periódico Clinical Oral Investigations.**

Effects of Ozone on At-Home Tooth Bleaching: A Double-Blind, Randomized Clinical Trial

Abstract

Objectives To evaluate the impact of ozonized sunflower oil (OSO) application during at-home bleaching (AHB) on tooth sensitivity (TS), color change (CC), and patient perception (PP).

Material and methods A double-blind, randomized clinical trial included 40 participants assigned to the experimental (OSO) or placebo (sunflower oil) group. Oil was applied into trays for 1 minute after each AHB session (10% hydrogen peroxide gel, 1x30min, 21 sessions). TS was evaluated daily using a visual analog scale (VAS) and a numerical rating scale (NRS). Tooth color was measured with a spectrophotometer (ΔE_{ab} , ΔE_{00} , ΔWID) and visual shade guide units ($\Delta SGUs$) at baseline, 1 week (T1) and 1 month (T2) after the end of treatment. PP was assessed using Likert scale-based forms

Results Regardless of the group, 72.5% of patients reported TS during AHB. No significant differences were observed in TS intensity between groups ($p=0.536$) or in the number of painful days ($p=0.256$). CC was similar between groups ($p>0.05$). However, ΔE_{ab} and ΔE_{00} at T2 were lower than at T1 ($p=0.010$ and $p=0.026$, respectively). PP regarding taste ($p=0.002$) and odor ($p=0.010$) differed, with OSO being considered unpleasant.

Conclusions Ozonized oil application during AHB did not reduce TS or affect CC compared to placebo. PP was negative due to its unpleasant taste and odor.

Clinical relevance Despite various mechanisms of action, ozonized oil did not mitigate tooth sensitivity or influence color change during at-home bleaching. Its poor taste and odor seems unsuitable for patient comfort.

Clinical trial registration number RBR-6V7M9ZK.

Keywords Tooth bleaching • Dentin sensitivity • Dentin desensitizing agents • Hydrogen peroxide • Ozone

Introduction

Tooth whitening is a globally widespread cosmetic procedure. It's a conservative, simple treatment commonly done to achieve an aesthetically pleasing smile [1] and has been the subject of numerous laboratory and clinical studies [2–5]. The technique involves applying peroxide-based whitening agents to the vestibular surface of discolored teeth. The radicals produced by the breakdown of peroxide oxidize the organic components of dental tissue, resulting in whiter teeth [3]. The most common adverse effect reported by patients undergoing whitening is tooth sensitivity [2–4, 6, 7], especially when highly concentrated hydrogen peroxide is used [3, 5, 6, 8, 9]. Tooth sensitivity results from the peroxide and its byproducts in the pulp, leading to an inflammatory response in this tissue [10]. The absolute average risk of tooth sensitivity is approximately 51% for at-home whitening techniques [8, 9]. The most effective approach for reducing dentin sensitivity has been the topical application of desensitizing agents, such as those containing glutaraldehyde [11, 12], potassium nitrate [13, 14], and calcium-based agents [15, 16]. While these desensitizing agents have been proposed to mitigate this adverse effect, they are unable to entirely eradicate pain, despite yielding positive effects [17–20].

Ozone therapy, recognized within medical science, gained prominence in dentistry as early as the 1930s [21]. Administered in the form of gas or dissolved in a water or oil base, ozone provides therapeutic benefits, especially anti-inflammatory, antioxidant, and analgesic properties [22–25]. Clinical studies have demonstrated teeth-whitening effects through the rapid and powerful oxidative degradation of discolored components, as well as pain reduction during in-office dental whitening [23, 26–28]. Ozone gas has shown efficacy in addressing dentin sensitivity, reducing pain during dental whitening, and modulating inflammatory pathways by reducing prostaglandin and cyclooxygenase activity [23–25, 29]. However, its application in tooth bleaching scenarios, focusing on resolving dental sensitivity, remains relatively unexplored.

Furthermore, the available literature focuses on the use of ozone gas, which has several limitations. The gas requires ozone-generating equipment, is potentially toxic to the respiratory system in high concentrations, and requires a trained team to handle it [22]. For bleaching procedures, it can only be used in-office. In contrast, ozonized oil is simpler to use, could be purchased by professionals and patients from registered industries, and has not been presented with the limitations of use reported, potentially offering more clinical value than gas and allowing for at-home dental protocols.

Ozonized oils contain an active oxygen complex (formed from the reaction of ozone with unsaturated fatty acids, ozone peroxides, and trioxolanes) that encourages wound healing, stimulates cellular metabolism, and eliminates bacteria, viruses, and fungi [30, 31]. The peroxide index in the oil ozonation process should be approximately 600 meq/kg to ensure all therapeutic benefits of ozone [30–32]. Sunflower oil is the most frequently used due to its natural therapeutic effects. The ozonized form of the oils is easy to manage, as it retains the compounds derived from ozonation for a longer duration, making it usable outside the clinical and hospital setting and accessible to the general population [32].

Therefore, exploring the potential efficacy of ozonized oil as an experimental desensitizing agent, as well as evaluating tooth color alterations and patient perception regarding the use of this treatment, are promising. The majority of clinical trials on tooth bleaching and the evaluation of adjunctive treatment materials have predominantly centered on assessing only occurrences of bleaching sensitivity and alterations in tooth shade [33]. Recognizing the significance of patient perception, particularly in the context

of at-home treatments, it is imperative to conduct thorough evaluations, especially concerning the utilization of novel experimental agents such as ozone.

Understanding ozone's mechanisms of action and recognizing that when subjected to an oily vehicle, it is more easily applicable clinically than gas, we performed this clinical trial. We hypothesized that ozonized oil could produce a desensitizing effect during bleaching. Therefore, we aimed to evaluate the impact of the topical application of ozonized oil on the absolute risk and intensity of bleaching-induced TS and color change following at-home bleaching with 10% hydrogen peroxide.

Material and methods

Ethics approval and protocol registration

This trial was approved by the Research Ethics Committee on Human Subjects (CEP) of the Federal University of Uberlândia, Uberlândia, MG, Brazil (CAAE: 68506423.5.0000.5152) and was registered in the Brazilian Clinical Trials Registry under “RBR-6V7M9ZK”. The research started following the analysis, adequacy, and acceptance of the volunteers. Selected volunteers were informed about the research protocol, and those who agreed to participate signed an informed consent form.

Trial Design and location

This study is a randomized, parallel and double-blind controlled trial. Allocation ratio was equal between groups, designed in accordance with the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) [34]. It was conducted at the School of Dentistry of the Federal University of Uberlândia (FOUFU) in Uberlândia, MG, Brazil, from September 2023 to April 2024.

Sample Size estimation, recruitment, eligibility criteria and allocation

Considering that the primary outcome in this study was the TS, with a 90% absolute risk in a clinically relevant parallel design, the sample size calculation was conducted for a superiority test with a binary outcome, considering a power of 80% and a significance level of 5%. It results in an estimated sample size of 40 patients, 20 subjects per group.

Recruitment was conducted through social media. Volunteers were told of the study's aims and signed an informed consent form prior to enrollment. The patient selection was conducted at the Dental Clinic of the School of Dentistry at the Federal University of Uberlândia. Initially, a detailed anamnesis was performed for each case, followed by professional prophylaxis using a rubber cup associated with pumice paste (SS White, Rio de Janeiro, RJ, Brazil) and water, aiming to remove extrinsic stains and facilitate the clinical examination. This examination was carried out by two examiners to verify the inclusion and exclusion criteria.

As demonstrated in **Figure 1**, a total of 83 patients were evaluated. Forty patients aged between 18 and 40 years, with good oral and general health, anterior maxillary teeth devoid of restorations and carious lesions, were included. Canine tooth color was established as A2 or darker, according to the Vita Classic shade guide (Vita Zahnfabrik, Bad Säckingen, Germany), for inclusion in the study.

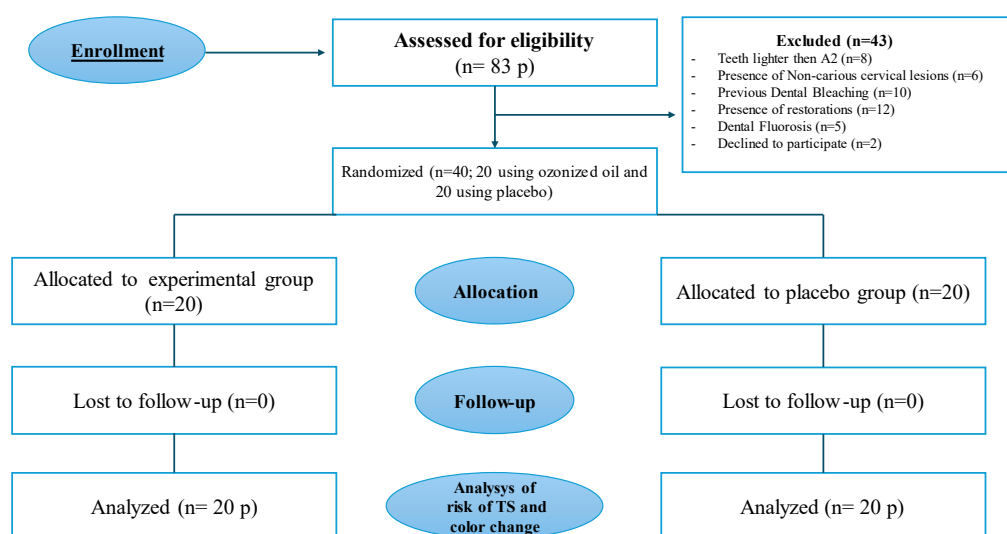


Figure 1 - Schematic depiction delineating the progression of the study, inclusive of the processes of participant recruitment and allocation into respective groups.

Forty-three patients were excluded (**Figure 1**). The exclusion criteria included patients with severe discoloration (e.g., stains caused by tetracycline), enamel hypoplasia, gingival recession, dentin exposure, visible enamel cracks, pulpitis, or endodontic treatment in any of the six upper anterior teeth. Participants who had undergone previous whitening procedures, experienced prior dental sensitivity, were continuously using anti-inflammatory or analgesic drugs, were smokers, engaged in parafunctional habits, undergoing treatment with fixed or removable orthodontic appliances, pregnant, or lactating were also excluded.

The patients were randomly allocated into 2 groups (n=20), according to the oil used. All participants underwent a 21-day regimen of at-home whitening with daily application of the gel for 30 minutes. Following the application of the whitening agent, the oils were applied in the individual trays for 1 minute. The experimental group received a daily application of ozone oil, while the control group received sunflower oil (placebo), as their respective allocations. Hydrogen peroxide 10% (HP) was utilized following the manufacturer's instructions. The products employed in the study, their compositions, and application methods are delineated in **Table 1**.

Table 1 - The manufacturer, composition, and application method of the primary products analyzed in this study.

Manufacturer	Composition	Application Method
White Class 10% (FGM, Joinville, SC, Brazil)	Hydrogen Peroxide 10%, neutralizing, potassium nitrate, sodium fluoride, calcium gluconate, stabilizer, humectant, deionized water	A daily 30-min application of the gel for 21 days, using the individual trays
Ozonized Sunflower Oil (Philozon, Balneário Camboriú, SC, Brazil)	Helianthus annuus (sunflower) seed oil, ozone (629meq/kg peroxide concentration).	Daily 1-minute application after using the bleaching gel
Sunflower Oil (Liza, São Paulo, Brazil)	Helianthus annuus (sunflower) seed oil	Daily 1-minute application after using the bleaching gel

Randomization and blinding

Clinical files, specifically designed for the study, were created with patient personal information, data on the characteristics of the teeth involved, and patient signatures. To protect the anonymity of the volunteer's name, all documents handled during the visit were coded with an Arabic number.

We use a blocked randomization (block size of 2) to ensure equal-sized groups with equal allocation ratios at www.sealedenvelope.com. A random list was computer-generated by a person not involved in the intervention or assessment (LVMU). The allocation sequence was inserted into sealed envelopes numbered from 1 to 40, and opened by the operator (MGC) only at the time of the intervention. Patients were numbered according to the allocation sequence.

This was a double-blind study, where evaluators (JMM and HLC) and patients had no knowledge of what material was applied together with whitening. Since ozone has a characteristic pungent odor, and was already used in other studies by the operators, we could not blind them.

Intervention

During the patient selection process, an initial step involved professional prophylaxis employing a rubber cup in conjunction with pumice paste (SS White, Rio de Janeiro, RJ, Brazil) and water, aimed at eliminating extrinsic stains and facilitating subsequent clinical examinations. Subsequently, patients enrolled in the study underwent the creation of upper and lower dental arch impressions using alginate material (Dentsply Sirona, Milford, DE, United States).

Following disinfection with alcohol 70% spray and water, plaster models were generated (Asfer Indústria Química Ltda., São Caetano do Sul, SP, Brazil). Utilizing these plaster models, customized top and bottom 2 mm acetate trays were crafted for each patient (Whiteness Plates for Molders, FGM, Joinville, SC, Brazil) employing a vacuum plasticizer (Plastivac P7, BioArt, São Carlos, SP, Brazil). Excess material on the labial and lingual surfaces was removed, providing a 1mm distance from the gingival margin. Subsequently, the trays underwent fitting tests in patients and were adjusted accordingly.

Both groups used hydrogen peroxide-based whitening agent at a concentration of 10% (White Class, FGM, Joinville, SC, Brazil) in accordance with the manufacturer's instructions. The volunteer was provided with the tray, the whitening gel tube, and a 5 ml syringe containing the oil, according to the allocation group, and was instructed as follows:

1. Depress the syringe plunger and apply the whitening gel to the tray indentations. Typically, a small drop per tooth is adequate for coverage.
2. Fit the tray onto the teeth and lightly press to ensure the gel surrounds them.
3. Utilize the gel for 21 days, 30 minutes daily.
4. Rinse the tray before storage and before each use. Store the gel in a ventilated place, preferably in a refrigerator. Avoid prolonged exposure of the syringe to light. Dispose the empty syringes.
5. Use the individual tray for daily application of the oil, right after whitening. Place 1 drop of oil on each tooth of the tray and position it over the whitened teeth for 1 minute.

Color Change

Two calibrated evaluators (JMM and HLC) with superior color discrimination competency according to ISO/TR 28642 and an inter-examiner agreement level of agreement of at least 85% (Kappa statistic) assessed color before the bleaching (baseline), one week after bleaching (T1), and one month after bleaching (T2). Immediate color evaluation following the end of the bleaching process was purposely excluded to avoid the potential effects of dehydration and demineralization on color readings. Color evaluation was carried out using the value-centric shade guide Vita Classical (Vita Zahnfabrik) and the Vita Easyshade spectrophotometer (Vita Zahnfabrik). The Vita Classical shade guide's 16 tabs were placed in descending order from highest (B1) to lowest (C4) for subjective rating. For tooth matching, we use the middle portion of the right upper canine. Color changes were tracked from active phase to recall times using Δ SGUs, with a concentration on lighter hues on the value-oriented shade tab list. In circumstances where assessors disagreed, a consensus had to be established before discharging the patient.

When using the Vita Easyshade spectrophotometer (Vita Zahnfabrik), to standardize the color measurement area throughout the entire experiment, a cast of the upper arch was created using condensation silicone (Maquira Dental Group, Maringá, PR, Brazil). A 6 mm diameter perforation was made at the index corresponding to the vestibular surfaces of the canines to allow for the placement of the spectrophotometer tip (Easyshade Compact Advance 4.0, Vita-Zahnfabrik, Bad Säckingen, Germany). The L* (brightness), a* (hue on the red-green axis), and b* (hue on the blue-yellow axis) values in the canines were measured in triplicate, and the mean of the measurements was

recorded [35]. The color change result (difference between baseline-T1 and baseline-T2) was calculated using three methods [36–38]: CIELab: $\Delta E_{ab} = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2].1/2$; CIEDE2000 formula: $\Delta E_{00} = [(\Delta L/k_{LSL})^2 + (\Delta C/k_{CSC})^2 + (\Delta H/k_{HSH})^2 + RT (\Delta C \times \Delta H/SC \times SH)]$ and the whiteness index, $\Delta WID = (0.511L^*) - (2.3424a^*) - (1.100b^*)$. In assessing color change, perceptibility thresholds were established at $\Delta E_{ab}=1.2$ and $\Delta E_{00}=0.8$, while acceptability thresholds were set at $\Delta E_{ab}=2.7$ and $\Delta E_{00}=1.8$ [37, 39].

Tooth sensitivity

Patient-reported tooth sensitivity was recorded daily during the 21 days of bleaching protocol, using the universal pain assessment tool, considering a 0-10 visual analog scale (VAS) and a 5-point numerical rating scale (NRS) [40, 41].

The VAS scale consists of a 10-centimeter line, with endpoints labeled as zero to 10. Zero means no sensitivity and 10 means severe tooth sensitivity. The participant was required to indicate the intensity of TS by drawing a vertical line along the horizontal VAS scale. Subsequently, the distance in millimeters from the zero point was measured using a millimeter ruler to indicate the level of TS recorded.

Tooth sensitivity was also scored according to the 5-point numerical rating scale (NRS: 0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = severe).

For statistical analysis, the highest score (NRS) or numeric value (VAS) recorded during all assessments were considered. The NRS defined the presence (score different from 0) or absence of tooth sensitivity in all assessments. This binary outcome was used to define the risk of tooth sensitivity, representing the proportion of participants who reported TS at least once during the treatment period and also the number of days with pain. Meanwhile, the VAS determined the intensity of tooth sensitivity based on the daily higher recorded numbers from each patient according to its allocation group.

Patient Perception

After completing the 21-day bleaching regimen and applying the oil, participants completed a questionnaire to evaluate their experience. The self-administered questionnaire comprised five statements. Given the characteristic odor and taste of ozone oil, two statements inquired about the subjective sensations experienced by patients using it. Another statement addressed the ease of handling the materials, while the final two statements sought feedback on patient satisfaction with the whitening results and any gum irritation experienced during treatment.

The patients used a Likert scale to score each statement, were: 1 – Completely disagree, 2 – Partially disagree, 3 – No opinion, 4 – Partially agree, and 5 – Completely agree [42].

Data Analysis

The statistician (GJPLO) involved in the study was blinded to the group allocations. Data collected during the study, derived from analyses utilizing both the experimental ozone oil and the placebo, were compiled. Statistical analyses were conducted using the Jamovi software, with all tests being performed at a significance level of 5%. The assumptions

of the normal distribution (Shapiro-Wilk test) and equal variance (Levene's test) of the continuous data were inspected.

Mann-Whitney test was used to compare the TS intensity in the NRS scale, and t-test to compare data from the VAS scale and the number of days feeling pain. Fisher's test was used to compare data from TS risk. Color data (ΔE_{ab} , ΔE_{00} , ΔWID , and ΔSGU) were subjected to analysis for treatment comparison (placebo vs. experimental) and across different time points (T1 and T2) using repeated measures ANOVA (RM ANOVA). Patient perception was assessed utilizing Fisher's exact test.

Results

Characteristics of included participants and adherence to the study

A total of 83 individuals were initially assessed for eligibility according to predefined inclusion and exclusion criteria (**Figure 1**). The baseline tooth color of canines in the Vita Classical Shade Guide units was very similar between groups (experimental ozonized oil: 10.7 ± 1.0 ; placebo: 10.6 ± 1.1). The patients were predominantly female (67.5%). Most of the participants were young adults, with an average age of 22.3 ± 1.7 years. The 40 participants diligently attended the scheduled follow-up visits all over the duration of the study.

Risk and intensity of tooth sensitivity

Irrespective of treatment, 72.5% of participants encountered tooth sensitivity during at-home bleaching, with no reports of severe pain scores (NRS=4) (**Table 2; Figure 2**). Statistical analysis revealed no significant difference between the experimental ozonized oil and the placebo group in terms of pain intensity ($p=0.468$) and the number of days with tooth sensitivity ($p=0.256$) reported by the patients throughout the 21-day bleaching period (**Table 3; Figure 2**).

Table 2. Risk to tooth sensitivity during any assessment time according to group.

Group	# patients with any TS/ # total	Absolute risk (%)	Relative risk* (95% CI)	p-value
Placebo	17/20	85%	1.42	0.155
Experimental	12/20	60%	(0.94 – 2.12)	

* Risk relative calculated using Fisher's exact test. TS – tooth sensitivity. CI – confidence interval.

Table 3 - Intensity of TS and number of days with pain for both groups in means and standard deviations according to VAS scale, along with p-value (Mann-Whitney test)

Pain scales	Groups		p-value
	Placebo	Experimental	
VAS 0-10	1.58±1.25	1.29±1.71	0.536
Number of days having pain	3.70±3.34	2.50±3.24	0.256

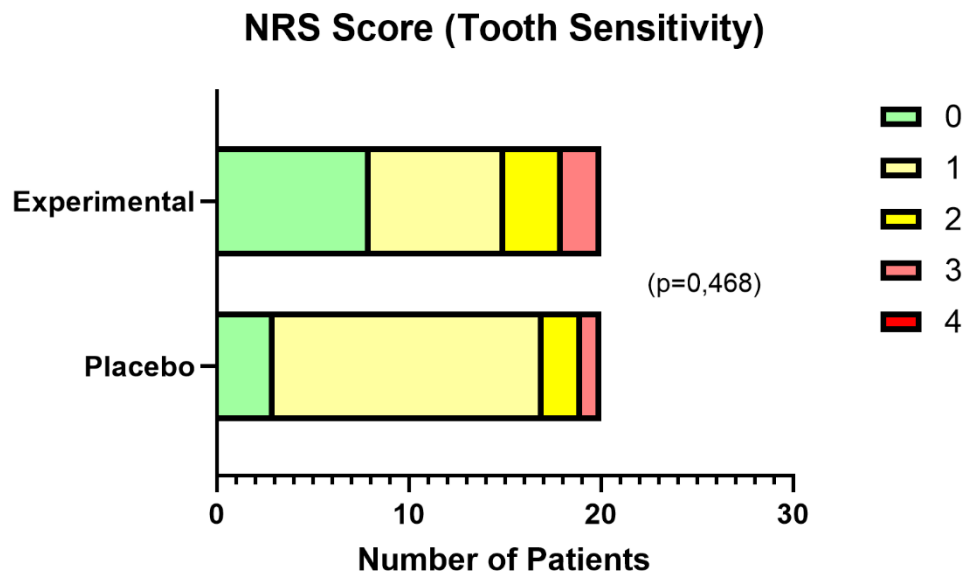


Figure 2 - NRS scores for tooth sensitivity, indicating the presence and intensity of TS as reported by patients, with 0 representing none, 1 for mild, 2 for moderate, 3 for considerable, and 4 for severe sensitivity. The comparison of absolute and relative risk, as well as the intensity of TS, was conducted using Fisher's test. No patient, regardless of treatment, reports severe TS (4).

Color evaluation

A Significant color change was observed in all groups. Four color evaluation tools were utilized to assess color change: ΔE_{ab} , ΔE_{00} , ΔWID , and ΔSGU (**Table 4**). The analysis revealed no significant difference in color change between the groups ($p > 0.05$). However, both ΔE_{ab} and ΔE_{00} values at T2 were lower compared to T1 ($p = 0.010$ and $p = 0.026$, respectively) (**Table 4**). While significant color change was observed between the different evaluation times (T1 and T2) when using the Vita Easyshade spectrophotometer

(ΔE_{ab} , ΔE_{00}), no visual difference was observed by operators using the Vita Classical shade guide (ΔSGU) at T1 and T2 ($p=0.967$)

Table 4 - The means and standard deviations of ΔE_{ab} , ΔE_{00} , ΔWID , and ΔSGU (Classical) were calculated between the baseline and 1 week after the end of bleaching (T1), as well as between the baseline and 1 month (T2) after the end of bleaching. Furthermore, the mean difference and its p-value were determined for each comparison (RM Anova).

* Comparisons between groups at each assessment time

** Comparisons of values between time of evaluation (T1 or T2)

Color evaluation tool	Groups - T1		p-value*	Groups - T2		p-value**
	Placebo	Experimental		Placebo	Experimental	
ΔE_{ab}	8.01 $\pm$ 3.31	9.18 $\pm$ 3.13	p-value* 0.218	7.61 $\pm$ 3.28	8.94 $\pm$ 3.04	0.010
ΔE_{00}	5.43 $\pm$ 2.36	5.41 $\pm$ 1.83		5.16 $\pm$ 2.38	5.32 $\pm$ 1.81	0.026
ΔWID	11.4 $\pm$ 6.39	14.0 $\pm$ 6.20	p-value* 0.923	10.9 $\pm$ 6.22	14.1 $\pm$ 6.17	0.603
			p-value* 0.145			
ΔSGU classical	7.55 $\pm$ 1.79	7.55 $\pm$ 2.01	p-value* 0.967	7.50 $\pm$ 1.76	7.55 $\pm$ 2.01	0.324

Patient perception assessment

Patients utilized a Likert scale to evaluate their perception during treatment, with ratings ranging from 1 (Completely disagree) to 5 (Completely agree) (**Table 5**). In comparison to the placebo, patient perception of the ozonized oil was negative regarding its taste ($p=0.005$), odor ($p=0.013$) and usability ($p=0.048$). Patients expressed overall satisfaction with the whitening results achieved by the protocol. Furthermore, both experimental and placebo groups experienced similar levels of gum irritation during treatment (**Table 5**).

Table 5 - Medians and interquartile ranges of patient perceptions over different topics compared between the placebo and experimental treatment groups. The scoring system employed was as follows: 1 – Completely disagree, 2 – Partially disagree, 3 – No opinion, 4 – Partially agree, and 5 – Completely agree. P-values were calculated using Friedman Repeated Measures Analysis of Variance on Ranks (95% CI).

Questions	Groups		p-value
	Placebo	Experimental	
The flavor of the oil was pleasant.	4 (3.75/5.0)	2 (1/3)	0.002
The smell of the oil is pleasant.	4 (3.0/4.0)	2 (1.75/3.0)	0.010
It was easy for me to apply the oil.	5 (4.75/5.0)	4 (4.0/5.0)	0.048
I was satisfied with the whitening result.	5 (4.0/5.0)	5 (4.0/5.0)	0.575
I had gum irritation during whitening.	4 (2.0/4.0)	2.5 (1.0/4.0)	0.245

Discussion

Contrary to our expectations, the ozonized oil application did not cause any reduction of the risk and intensity of TS induced by bleaching. It appears that the 1-minute application at home following bleaching did not induce an anti-inflammatory response within the pulp chamber, which could have potentially contributed to a desensitizing effect during the 21-day treatment period. It was observed that none of the patients, regardless of the treatment, reported severe tooth sensitivity (Figure 2). Even though eight patients in the ozonized oil group reported no pain compared to three in the placebo group, this difference was not statistically significant overall. Similarly, there were no statistically significant differences observed in the intensity of pain or the number of days experiencing pain during treatment (Table 2). Perhaps extending the application time of the ozonized oil daily could yield effects; however, we opted to test the product with only a 1-minute application due to its unfavorable taste and odor, which were later confirmed to be problematic for patient compliance (Table 5).

Similarly, the ozonized oil does not influence color alteration, neither enhancing nor reducing the bleaching effect. The efficacy of tooth bleaching is attributed to the oxidative action of free radicals, which are generated upon the breakdown of hydrogen peroxide. These free radicals include hydroxyl and perhydroxyl radicals, as well as superoxide anions and hydrogen peroxide anions [33]. Although there is no consensus in the literature, some authors state that the whitening mechanism occurs through the conversion of chromophores within hard dental tissues into simpler structures [43] or by altering the optical properties of the dentin and enamel, thereby increasing light reflection

and resulting in a lighter shade, enhancing the appearance of the tooth [44]. Specific concentrations for using ozone during at-home dental whitening are not well-established. However, to achieve the maximum therapeutic benefits of ozone, the concentration should be at least 600 meq/kg [32]. In this study, the concentration of peroxide present in the oil was 629 meq/kg, but it was not sufficient to produce any effects.

The rebound effect, a well-recognized phenomenon observed subsequent to bleaching procedures, manifests as the regression of tooth whitening [45]. Immediately following treatment, tooth color may appear whiter due to enamel dehydration, emphasizing the importance of evaluating tooth color changes at multiple time points. In this investigation, color change assessment was conducted one week (T1) and one month (T2) after the completion of the bleaching procedure. We observed that while a statistically significant color change was discerned between the different evaluation times (T1 and T2) using the spectrophotometer machine (ΔE_{ab} , ΔE_{00}), operators did not perceive any visual difference using the Vita Classical shade guide (ΔSGU) (Table 4). This suggests that the rebound color change detected was perceptible only under spectrophotometer machine assessment, but not from a human perspective. This is further supported by the fact that the difference in ΔE_{ab} and ΔE_{00} values did not surpass the perceptibility thresholds [35, 36]. Therefore, despite statistical differences, we do not consider the color difference between times in this study as a clinically relevant outcome.

A vital aspect evaluated in this research was patient perceptions of treatment. Often overlooked in randomized controlled trials (RCTs) on tooth bleaching and adjunctive treatments, patient perceptions are typically overshadowed by assessments of bleaching sensitivity and changes in tooth shade [33]. We acknowledge the significance of patient perceptions, particularly in the context of at-home therapies, and consider it imperative to conduct subjective evaluations, especially when employing novel experimental agents. Therefore, after the 21-day treatment period was completed, participants were asked to complete a questionnaire to evaluate their experiences. Patients generally expressed contentment with the results of the tooth whitening procedure, regardless of the method utilized. However, it became evident that ozonized oil had a substantial adverse effect on patient satisfaction due to its pungent taste and odor, making it challenging to use as a desensitizer for self-application (Table 5). Ozone has a distinct odor that was first identified as a distinct chemical compound when, after electrolysis, water emitted an odor at the cathode, defined as "the odor of electrical matter," later termed "ozone," from the Greek word "ozein" (to smell) [31,22]. This issue is practically unreported nowadays in studies using ozone, highlighting its importance as an outcome that could guide future research in ozonotherapy.

There was also a difference in terms of ease of use. As the taste and smell were unpleasant, patients who used ozone tended to report more negative experiences with the oil, even though technically, it was the same process as applying the placebo, so we believe that this influenced this particular outcome. Gum irritation observed by subjects was also assessed in the study. While it was initially hypothesized that ozone's anti-inflammatory and analgesic properties would mitigate gum irritation, the incidence was statistically similar to that observed with the placebo.

In conclusion, the experimental ozonized oil appears to elicit more negative than positive impacts, particularly concerning its application during at-home bleaching procedures. Furthermore, the majority of participants were young adults, potentially limiting the generalizability of the findings to the broader population. Further research is necessary in ozone therapy to address these concerns and offer definitive insights.

Conclusion

The application of ozonized oil during at-home bleaching neither reduces tooth sensitivity nor affects color change compared to the placebo. Moreover, the patient's perception of its use was negative due to its unpleasant taste and odor.

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C onclusão

CONCLUSÃO

Concluimos que a aplicação de óleo ozonizado durante o clareamento dental caseiro não reduz a sensibilidade dentária nem afeta a mudança de cor em comparação ao placebo. Além disso, a percepção dos pacientes em relação ao seu uso foi negativa devido ao sabor e odor desagradáveis.

A continuidade das pesquisas nesta área é fundamental para a descoberta e otimização de produtos eficazes no controle da sensibilidade dentária, especialmente em tratamentos de clareamento dentário.

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