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DIEGO RAFAEL DE ANDRADE HORTKOFF

**EFEITO DE FÁRMACOS COMO AGENTES DESSENSIBILIZANTES NA
SENSIBILIDADE E LONGEVIDADE DO CLAREAMENTO DENTAL**

**PONTA GROSSA
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Tese apresentada como requisito para obtenção do título de
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Orientadora: Profa. Dra. Giovana Mongruel Gomes
Coorientador: Prof. Dr. João Carlos Gomes

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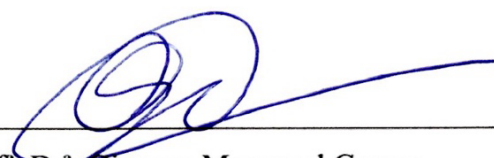
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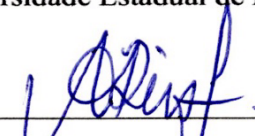
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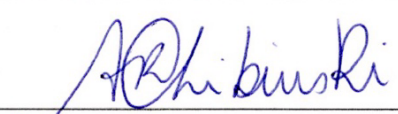
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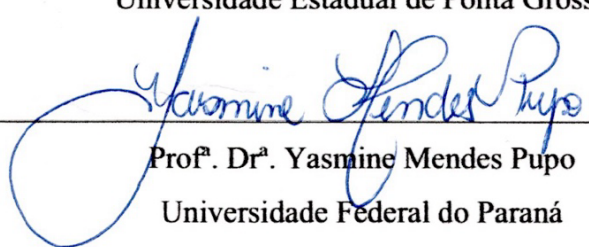
Profª. Drª. Alessandra Reis

Universidade Estadual de Ponta Grossa



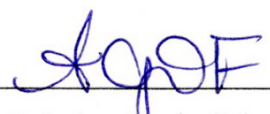
Profª. Drª. Ana Cláudia Rodrigues Chibinski

Universidade Estadual de Ponta Grossa



Profª. Drª. Yasmine Mendes Pupo

Universidade Federal do Paraná



Profª. Drª. Ana Paula Gebert de Oliveira Franco

Universidade Federal do Paraná

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“The absence of evidence does not mean evidence of absence.”

- Carl Sagan

“In politics and in life, ignorance is not a virtue.”

- Barack Obama

DADOS CURRICULARES

DIEGO RAFAEL DE ANDRADE HORTKOFF

NASCIMENTO 22.07.1994

Ponta Grossa, Paraná – Brasil

2013-2017

Curso de Graduação em Odontologia, Centro de Ensino Superior dos Campos Gerais – (CESCAGE). Ponta Grossa -PR, Brasil.

2018- 2020

Curso de Pós-Graduação em Odontologia. Área de concentração Dentística Restauradora. Nível Mestrado. Universidade Estadual de Ponta Grossa (UEPG). Ponta Grossa – PR, Brasil.

2023- 2024

Curso de Especialização em Harmonização Orofacial, Centro Universitário Ingá (UNINGÁ). Ponta Grossa – PR, Brasil.

2020- 2024

Curso de Pós-Graduação em Odontologia. Área de Concentração em Dentística Restauradora. Nível Doutorado. Universidade Estadual de Ponta Grossa (UEPG). Ponta Grossa – PR, Brasil

RESUMO

Hortkoff DR. **Efeito de fármacos como agentes dessensibilizantes na sensibilidade e longevidade do clareamento dental.** [tese]. Ponta Grossa: Universidade Estadual de Ponta Grossa; 2024. 78 p.

Objetivo: Avaliar a eficácia de um gel dessensibilizante contendo ibuprofeno e arginina na redução da sensibilidade dentária (TS) induzida por clareamento, e a longevidade dos efeitos do clareamento dental após 4,5 anos. **Material e Métodos:** Em um conjunto de ensaios clínicos randomizados controlados realizados na Universidade Estadual de Ponta Grossa entre março e setembro de 2019, 62 participantes com caninos com tonalidade A2 ou mais escuros foram divididos em grupos de tratamento com gel dessensibilizante e placebo. O gel foi aplicado 15 minutos antes do clareamento em consultório com gel de peróxido de hidrogênio a 35% por 50 minutos em duas sessões. Avaliou-se a TS usando escalas visuais e numéricas, e a mudança de cor foi medida com Vita Classical, Vita Bleachedguide e Vita EasyShade antes, um mês depois e 55 meses após o procedimento. **Resultados:** Observou-se uma redução significativa na TS no grupo tratado com o gel dessensibilizante em comparação ao placebo, sem comprometer a eficácia do clareamento. Após 4,5 anos, a eficácia do clareamento se manteve, sem diferenças significativas entre os grupos. **Conclusão:** O uso de um gel dessensibilizante contendo ibuprofeno e arginina antes do clareamento dental reduz efetivamente a sensibilidade dentária e não afeta a eficácia do clareamento. Os resultados do clareamento são duradouros até 4,5 anos após o tratamento.

Palavras-chave: Clareamento Dental. Sensibilidade da Dentina. Agentes anti-inflamatórios. Arginina. Ibuprofeno.

ABSTRACT

Hortkoff DR. **Effect of drugs as desensitizing agents on the sensitivity and longevity of dental whitening.** [thesis]. Ponta Grossa: State University of Ponta Grossa; 2024. 78 p.

Objective: To evaluate the effectiveness of a desensitizing gel containing ibuprofen and arginine in reducing tooth sensitivity (TS) induced by in-office bleaching, as well as the longevity of bleaching outcomes after 4.5 years. **Materials and Methods:** In a series of randomized controlled clinical trials conducted at the State University of Ponta Grossa between March and September 2019, 62 participants with canines of shade A2 or darker were assigned to treatment groups receiving either the desensitizing gel or a placebo. The gel was applied 15 minutes before in-office bleaching with 35% hydrogen peroxide for 50 minutes across two sessions. TS was assessed using visual and numeric scales, and color change was evaluated using Vita Classical, Vita Bleachedguide, and Vita EasyShade at baseline, one month, and 55 months after treatment. **Results:** A significant reduction in TS was observed in the group treated with the desensitizing gel compared with the placebo group, without compromising bleaching efficacy. After 4.5 years, bleaching effectiveness was maintained, with no significant differences between groups. **Conclusion:** The application of a desensitizing gel containing ibuprofen and arginine prior to dental bleaching effectively reduces tooth sensitivity without affecting bleaching performance. Bleaching results remain stable up to 4.5 years after treatment.

Keywords: Tooth bleaching; dentin sensitivity; anti-inflammatory agents; Arginine; Ibuprofen.

LISTA DE ABREVIATURAS E SIGLAS

ECR	Ensaio Clínico Randomizado
SD	Sensibilidade dentária
VAS	Visual Analog Scale
NRS	Numerical Rating Scale
REBEC	Registro Brasileiro de Ensaios Clínicos
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CIE	Commission Internationale de l'Eclairage
UEPG	Universidade Estadual de Ponta Grossa
TCLE	Termo de Consentimento Livre e Esclarecido
CONSORT	Consolidated Standards of Reporting Trials
CAAE	Certificado de Apresentação para Apreciação Ética
CEP	Comitê de Ética em Pesquisa
ANOVA	Análise de variância
IC	Intervalo de confiança
CI	Confidence Interval
MD	Mean Difference
HP	Peróxido de hidrogênio
WID	Whiteness Index for Dentistry
SGU	Shade Guide Units
vs.	Versus

LISTA DE SÍMBOLOS

$CIEL^*a^*b^*$	Espaço de cores CIELAB
L^*	Luminosidade
a^*	Coordenada no eixo vermelho/magenta-verde
b^*	Coordenada no eixo amarelo-azul
H	Hue; matiz
C	Croma
ΔL^*	Diferença na coordenada L^*
Δa^*	Diferença na coordenada a^*
Δb^*	Diferença na coordenada b^*
ΔE_{ab}	Diferença total de cor no espaço CIELAB
ΔE_{00}	Diferença de cor calculada segundo a fórmula CIEDE2000
ΔH	Variação do matiz
KhSH	Fator de ponderação para variação de matiz
ΔC	Variação da cromaticidade
kCSC	Fator de ponderação para variação de cromaticidade
%	Porcentagem
$\pm$	Mais ou menos; desvio padrão
$>$	Maior que
$<$	Menor que
$\geq$	Maior ou igual a
$\leq$	Menor ou igual a
p	Valor de significância estatística
α	Alfa; nível de significância
Δ	Delta; variação ou diferença
$\sqrt{}$	Raiz quadrada
mm	Milímetros
cm	Centímetros
mg	Miligramas
min	Minutos
h	Horas

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1 INTRODUÇÃO

A popularização das redes e mídias sociais tem exercido uma influência significativa na percepção e busca de padrões estéticos contemporâneos, intensificando as expectativas dos pacientes quanto à estética odontológica, especialmente no que diz respeito à aparência e descoloração dental [1]. O interesse por intervenções odontológicas destinadas ao clareamento dental é crescente desde a introdução da técnica caseira de clareamento em 1989 [2], a qual destacou-se pela sua abordagem direta, eficaz, acessível e conservadora [3, 4].

Entretanto alguns pacientes não aderem o uso das moldeiras de clareamento, e por este motivo outra modalidade de clareamento dental, começou a ser empregada, o clareamento dental em consultório, o qual emprega concentrações mais altas de peróxido de hidrogênio e deve ser aplicado sob supervisão do profissional [3].

Contudo o procedimento clareador pode gerar alguns efeitos adversos. Isso acontece porque os géis clareadores contêm peróxido de hidrogênio, o qual é altamente reativo e possui um peso molecular baixo, o qual permite uma rápida difusão na estrutura dental, de modo que acaba atingindo a polpa dental em 15 minutos [5, 6], assim podendo desencadear processos inflamatórios no tecido pulpar [7], e então ocorre a ativação de receptores específicos para a dor [8], gerando assim o principal efeito adverso do procedimento, a sensibilidade dental [9].

A sensibilidade dental gerada pelo procedimento clareador é relatada em alguns estudos com uma ocorrência em algum momento do tratamento por 67% a 100% dos pacientes [10-14], sendo principalmente nas primeiras horas após o procedimento [9]. Essa experiência pode ser considerada desagradável pelos pacientes, assim encorajando à interrupção do tratamento clareador [15, 16].

Então, com o intuito de diminuir esse e outros efeitos adversos, vários estudos testaram e propuseram diferentes abordagens, sendo que algumas alternativas propostas foram a redução da frequência e do tempo de aplicação do peróxido de hidrogênio [17], variação da concentração do peróxido de hidrogênio nos géis clareadores [18, 19], alteração do pH dos produtos [20], utilização tópica ou incorporada aos géis de agentes dessensibilizantes, remineralizantes, antioxidantes [21-24], e também a administração pré-operatória e/ou pós-operatória de analgésicos e anti-inflamatórios [25-27].

Um destes anti-inflamatórios testados com o uso pré-operatório foi o ibuprofeno [16], e os resultados encontrados demonstraram que o seu uso pode diminuir a intensidade da sensibilidade dental uma hora após o procedimento [16, 28], porém o medicamento não foi

capaz de evitar a sensibilidade dental durante o clareamento dental. O ibuprofeno é um anti-inflamatório não esteroide capaz de bloquear a via da ciclooxygenase, e apresenta um mecanismo de ação em que é capaz de inibir a síntese periférica de prostaglandina [29, 30].

Contudo o ibuprofeno tem uma absorção lenta que atinge concentrações plasmáticas 1 a 2 horas após a administração [31]. A associação de arginina ao ibuprofeno, que é um aminoácido essencial, altera as propriedades farmacocinéticas do ibuprofeno, acelerando sua absorção e o deixando biodisponível mais rapidamente. Esta associação Ibuprofeno Arginina, é amplamente utilizada na odontologia há algum tempo, para controle da dor pós-operatória em diversos procedimentos e com ótimos resultados que demonstram sua rápida ação [31-33].

Outra forma alternativa de acelerar a absorção destes agentes, permitindo seu mecanismo rápido, é a sua aplicação tópica nas superfícies dentárias, conforme demonstrado em estudos anteriores [15, 34, 35].

Em contrapartida à avaliação da redução dos efeitos adversos imediatamente após ao clareamento dental, é fundamental destacar a importância da avaliação clínica da longevidade dos resultados obtidos com esses tratamentos. A eficácia de qualquer técnica de clareamento dental não se limita apenas a sua capacidade de diminuir a sensibilidade e clarear os dentes de forma imediata, mas também a sua continuidade ao longo do tempo. Esta análise de longevidade é especialmente relevante considerando o impacto potencial que qualquer tratamento pode ter na estabilidade da cor. Estudos focados nos efeitos do clareamento dental são essenciais para desenvolver protocolos efetivos não apenas na sensibilidade dental e efeito estético imediato, mas também se assegurar que os benefícios desse tratamento se perdurem, minimizando talvez a necessidade de retratamentos frequentes e contribuindo para a satisfação geral do paciente.

Entretanto, o uso da associação medicamentosa de ibuprofeno e arginina ainda não foram foco de estudos clínicos. Portanto, a presente tese, terá como objetivo principal responder as seguintes perguntas de pesquisa no formato PICO (P = paciente; I = intervenção; C = controle; O = outcome):

O uso tópico da associação Ibuprofeno arginina é capaz de reduzir o risco e a intensidade de sensibilidade dental em pacientes submetidos ao clareamento de consultório em comparação com o uso de um controle?

Pacientes que foram submetidos ao clareamento dental com peróxido de hidrogênio a 35%, mantiveram a estabilidade de cor após 4.5 anos do tratamento, em comparação ao resultado imediato do clareamento?

2 PROPOSIÇÃO

2.1 EXPERIMENTO 1

2.1.1 Proposição geral

Realizar um ensaio clínico randomizado (ECR) com o objetivo de avaliar o efeito da aplicação tópica de ibuprofeno e arginina em comparação a um grupo controle antes do clareamento em consultório, no risco e intensidade da sensibilidade dental.

2.1.2 Proposição específica

Avaliar o risco e a intensidade da sensibilidade dental após clareamento em consultório com a escala VAS e NRS;

Avaliar a efetividade do clareamento em consultório após 1 mês do clareamento utilizando espectrofotômetro Vita Easyshade usando o sistema CIEL*a*b*, através dos ΔE 76 e $\Delta 00$ e WID e ΔWID ;

Avaliar a efetividade do clareamento após um mês utilizando a escala VITA Classical e VITA Bleachguide através do ΔUGC .

2.2 EXPERIMENTO 2

2.2.1 Proposição geral

Realizar a avaliação clínica da longevidade da cor dental de pacientes que realizaram clareamento em consultório, após 55 meses do procedimento com peróxido de hidrogênio a 35%.

2.2.2 Proposição específica

Avaliar a longevidade da cor dental após 55 meses do clareamento dental com peróxido de hidrogênio a 35% utilizando espectrofotômetro Vita Easyshade usando o sistema CIEL*a*b*, através dos ΔE 76 e $\Delta 00$ e WID e YI;

Avaliar a longevidade da cor dental após 55 meses do clareamento dental com peróxido de hidrogênio a 35% utilizando a escala VITA Classical e VITA Bleachguide através do ΔUGC .

3 MATERIAL E MÉTODOS

Nesta sessão será descrita a metodologia de forma resumida de cada experimento. As informações detalhadas deste item podem ser encontradas nos artigos referentes a cada experimento.

3.1 EXPERIMENTO 1 E 2

Foi aprovado pelo Comissão de Ética em Pesquisa com Seres Humanos da Universidade Estadual de Ponta Grossa (Nº 3.067.235) e registrada no Registro Brasileiro de Ensaios Clínicos – REBEC (Nº RBR-9V2XZ6) A metodologia detalhada deste experimento está descrita no Artigo 1 e 2.

3.1.1 Seleção dos pacientes

Foram recrutados 62 pacientes que procuraram o tratamento no departamento de Odontologia da Universidade Estadual de Ponta Grossa (UEPG), e que se enquadraram nos critérios de inclusão e exclusão do estudo. Os pacientes tinham os caninos superiores como cor A2 ou mais escuros na avaliação subjetiva com a escala Vita Classical (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Alemanha) e que concordaram com os termos da pesquisa presentes no Termo de Consentimento Livre e Esclarecido (TCLE).

3.1.2 Randomização

Um processo de randomização simples foi realizado no site www.sealedenvelope.com. A distribuição dos grupos foi através de cartões numerados sequencialmente e colocados em envelopes opacos e selados. A informação contida no envelope determinou o tratamento a ser atribuído.

3.1.3 Cegamento

Foi um estudo triplo-cego, onde o operador, avaliador e examinador não sabiam a atribuição dos grupos. Ambos os dessensibilizantes foram entregues em seringas idênticas e

com aparência semelhante e codificados. Uma pessoa fora do estudo foi responsável pela codificação.

3.1.4 Procedimento Clareador

A técnica utilizada foi o clareamento dental em consultório com o gel clareador Whiteness HP Automixx (FGM, Joinville, SC, Brasil), antes da aplicação do clareador, foi aplicado o gel de ibuprofeno e arginina de forma vigorosa por 30 segundos em cada dente, e deixado em contato por 15 minutos, após esse tempo foi removido o excesso com gaze e então foi aplicada o gel clareador por 50 minutos, foi realizada duas sessões com o intervalo de 7 dias entre.

3.1.5 Avaliação da sensibilidade dental

Foi avaliado o risco e a intensidade da sensibilidade dental por meio da Escala Visual Analógica (VAS) e a escala de Numeral de cinco pontos (NRS) durante 48 horas após cada sessão de clareamento dental em consultório.

3.1.6 Avaliação de cor

A cor foi avaliada antes do início do estudo, e uma semana após as sessões de clareamento e um mês após o término do tratamento clareador, utilizando o método subjetivo com o auxílio das escalas Vita Classical e Vita Bleachedguide (VITA Zahnfabrik, Bad Säckingen, Alemanha). Para o método objetivo foi com o auxílio do espectrofotômetro Vita Easyshade (VITA Zahnfabrik, Bad Säckingen, Alemanha), para obtenção do sistema CIEL*a*b.

3.1.7 Recall dos Pacientes

Com 4.5 anos depois do fim do tratamento clareador, os pacientes foram chamados para uma avaliação de cor, onde eles responderam umas breves perguntas e posterior avaliação de cor por meio do método subjetivo e objetivo. Como reforço positivo os pacientes foram informados que caso quisessem uma nova sessão de clareamento receberiam na mesma sessão de avaliação. Todos os pacientes disponíveis foram aceitos, até mesmo os que realizaram algum tratamento clareador posteriormente.

3.1.8 Análise estatística

Os dados de cor foram avaliados pelo teste t pareado, os dados de sensibilidade foram avaliados pelo odds ratio, e testes de McNemmar's, Wilcoxon e ANOVA de medidas repetidas, em todos os testes estatísticos foi mantido o nível de significância em 5%.

4 ARTIGOS

4.1 EFFECT OF TOPICAL APPLICATION OF IBUPROFEN/ARGININE IN THE IN-OFFICE BLEACHING-INDUCED TOOTH SENSITIVITY: A RANDOMIZED, TRIPLE-BLIND CONTROLLED TRIAL

Diego Hortkoff ^a DDS, MSc, PhD Student, e-mail: drdiegohk@outlook.com, Karine Letícia da Silva ^a DDS, MSc, PhD Student, e-mail: karinelets@gmail.com, Paulo Vitor Farago ^b BS Pharm, PhD, e-mail: pvfarago@gmail.com, João Carlos Gomes ^a DDS, MSc, PhD, e-mail: gomesjoaocarlos@uol.com.br, Alessandra Reis ^a DDS, PhD, e-mail: reis_ale@hotmail.com, Giovana Mongrueel Gomes ^a DDS, MSc, PhD, e-mail: giomongrueel@gmail.com.

^a Department of Dentistry, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil.

^b Department of Pharmacy, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil.

Corresponding author:

Giovana Mongrueel Gomes. State University of Ponta Grossa, Department of Dentistry. Av. General Carlos Cavalcanti, 4748, Uvaranas - Ponta Grossa, PR, Brazil. Zip code: 84030-900; Telephone: +55 42 3220-3740; E-mail: giomongrueel@gmail.com.

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ABSTRACT

Objective: The application of anti-inflammatories as topical desensitizers before dental bleaching is an approach to reduce bleaching-induced tooth sensitivity (TS). This randomized controlled trial compared the risk and intensity of TS and the color change resulting from in-office dental bleaching after using an experimental desensitizing gel containing ibuprofen and arginine.

Methods: Sixty-two participants with upper canine shades A2 or darker were randomly assigned to either the ibuprofen-arginine desensitizing group or the placebo group. The desensitizing gel was applied for 15 min before in-office bleaching with 35% hydrogen peroxide gel for 50 min (2 sessions). To assess the absolute risk and intensity of TS, visual (0-10) and numeric rating (0-5) scales were used, and group comparisons were made using the McNemar test, Wilcoxon test, and paired Student t-test ($\alpha = 0.05$). Color change was evaluated using Vita Classical, Vita Bleachedguide (Δ SGU), and Vita EasyShade (Δ Eab, Δ E00, and Δ WID) before and one month after the bleaching procedure. Group comparisons for color change were done using a paired t-test ($\alpha = 0.05$).

Results: The odds ratio for TS was 0.14 [95% CI 0.02 to 0.6], meaning lower odds of TS for the desensitizing gel. A lower intensity of TS was also observed for the experimental group ($p < 0.005$) up to 48 hours after bleaching. All color evaluation tools demonstrated effective and similar whitening for both groups ($p > 0.05$).

Conclusions: Using the experimental desensitizing gel containing ibuprofen and arginine effectively reduced the risk and intensity of TS without compromising the bleaching efficacy.

Clinical relevance: The topical application of ibuprofen/arginine on the in-office bleaching reduced risk and intensity of bleaching-induced tooth sensitivity.

Keywords: Tooth bleaching; dentin sensitivity; anti-inflammatory agents; Arginine; Ibuprofen.

INTRODUCTION

Tooth bleaching is one of the most common cosmetic procedures patients seek due to dissatisfaction with color and teeth appearance [1]. Since the introduction of at-home bleaching by Haywood and Heymann in 1989, this technique has quickly gained popularity as an easy, practical, affordable, and conservative way to treat teeth that are discolored or intensely achromatized [2, 3]. Additionally, the in-office bleaching protocol, which employs a high-

concentration hydrogen peroxide, is also requested by patients who prefer not to use at-home bleaching trays and desire quicker results [4, 5].

Despite the success of dental bleaching procedures, adverse effects such as gingival irritation and bleaching-induced tooth sensitivity (TS) are commonly observed. Among these, bleaching-induced TS is the most prevalent [6, 7]. Studies have consistently shown that 67% to 100% of patients undergoing in-office dental bleaching report experiencing TS at some point during treatment [8-12], mainly in the first hours following the procedure [6]. This sensitivity occurs because hydrogen peroxide, which has low molecular weight, penetrates dental tissues and reaches the pulp chamber approximately 15 min after application [13, 14]. Its presence in pulp tissues can trigger inflammatory processes [15] and active pain-specific receptors [16], leading to an uncomfortable experience for patients and causing some to discontinue their bleaching treatment [7, 17].

In order to minimize this adverse effect, several alternatives have been proposed, including reducing the frequency and duration of hydrogen peroxide application [18], varying the bleaching gel concentration [19, 20], and using bleaching agents with neutral or alkaline pH values [21]. Other protocols, such as desensitization and remineralization with different active agents (potassium nitrate, calcium phosphate, fluoride sodium) applied topically or incorporated into the bleaching agent were the focus of other clinical studies [22-25]. The prescription of anti-inflammatories, opioids, and corticosteroid drugs [26-29] were also investigated.

Studies evaluating these medications to minimize TS in dental bleaching have shown to be ineffective or to provide only marginal benefits when administered orally [27, 30]. Numerous factors, including administration method, absorption rate, time for action, and the mechanisms of inflammation and pain, may explain their inefficiency.

Among all the medications evaluated, ibuprofen emerged as the only promising option for reducing TS [7]. Ibuprofen is a non-steroidal anti-inflammatory drug that inhibits the peripheral prostaglandin synthesis [31, 32] by blocking the cyclooxygenase (COX) pathway, thereby reducing inflammation and pain. Previous studies have explored the preoperative oral administration of preoperative ibuprofen in dental bleaching and have demonstrated its efficacy [7, 30]. Combining ibuprofen with other analgesics or anti-inflammatory drugs increased pain relief for extended periods in other dental procedures [33-36].

However, ibuprofen has a slow absorption, with plasma concentrations reaching their peak only 1 to 2 h after administration [37]. This may explain why ibuprofen reduced the

intensity of bleaching-induced TS only during the first following the procedure [7]. To address this issue, the combination of arginine, an essential amino acid, with ibuprofen, has been explored, as it alters the pharmacokinetic properties of ibuprofen, facilitating its rapid absorption and making it bioavailable more quickly. This combination has proven effective and fast in controlling postoperative pain in various dental procedures [37-39].

Another alternative way to accelerate the absorption of desensitizing agents, allowing their fast mechanism, is their topical application to the dental surfaces, as demonstrated in previous studies [17, 40, 41]. We hypothesize that topical application of ibuprofen and arginine may reduce TS. Therefore, the primary objective of the present study is to answer the following research question in *PICO* format (P = patient; I = intervention; C = control; O = outcome): “Is the topical application of Ibuprofen/arginine, compared to a placebo, capable of reducing the risk and intensity of TS in patients undergoing in-office bleaching?”

MATERIAL AND METHODS

Ethics approval and study protocol registration

This randomized controlled trial (RCT) was approved by the Scientific Review Committee for the Protection of Human Participants at the local university and registered in Clinical Trials Registry. The preparation of this study followed the guidelines of the Consolidated Standards of Reporting Trials statement with an extension for within-person designs [42].

Trial design, settings, and locations of data collection

This was a triple-blind, randomized, split-mouth, placebo-controlled RCT in which the patient, operator, and evaluator were blinded to the product being applied. The randomization process was carried out by one of the researchers who was not involved in the clinical stages of the bleaching protocol. The study took place between July 2019 and September 2019 at the clinics of the School of Dentistry within the local university.

Recruitment and eligibility criteria

Recruitment was carried out by posting written advertisements on University notice boards and utilizing social media to obtain a convenient sample. Participants chosen for the study needed to be at least 18 years old and maintain both good oral health and general health. Good oral health was defined as having proper oral hygiene, teeth without cavities, gums without swelling or bleeding, and the absence of chronic bad breath or other dental discomfort. General good health meant that participants were not undergoing any significant medical

treatment. They were also required to have no restorations or cavities in their six maxillary anterior teeth and should have upper canines with a shade of A2 or darker according to the value-oriented classical shade guide (Vita Classical, Vita Zahnfabrik, Bad Säckingen, Germany).

Exclusion criteria involved volunteers with self-reported dental hypersensitivity, any dental pathology that could lead to sensitivity, such as tooth cracks, gingival recession, or dentin exposure, as well as those with anterior restorations, dental prostheses, orthodontic appliances, severe dental discoloration (e.g., fluorosis, pulpless teeth, tetracycline stains). Additionally, pregnant or lactating women, smokers, individuals with bruxism, and those who had previously undergone dental bleaching were excluded from the study.

Before starting the bleaching procedure, all volunteers provided informed consent and received dental prophylaxis using pumice and water applied with rubber cups.

Sample size calculation

The primary outcome of this study was the absolute risk of tooth sensitivity (TS). A previous study reported an absolute risk of approximately 93% for the bleaching product Whiteness HP 35% Automixx (FGM, Joinville, SC, Brazil) [23]. To detect a significant absolute risk difference of 25% between the control and experimental groups, a minimum sample size of 48 patients was required, with a statistical power of 80% and a significance level (alpha) of 5%. To account for possible patient attrition, 15% was added to the sample size, resulting in a final calculation of 55 participants. To err on the side of caution, we assumed a zero coefficient of correlation between hemi-arches, allowing the inclusion of more patients in the sample.

Random sequence generation and allocation concealment

The randomization was performed in blocks (block sizes of 2 and 4) with an equal allocation ratio to form the allocation list for the two comparison groups. The randomization list was prepared on the website www.sealedenvelope.com. A third researcher not involved in the study intervention prepared the randomized list and placed them in individual, opaque, and sealed envelopes containing the group identification. The envelopes could only be opened immediately before treatment implementation. The envelope contained the group to be applied on the right hemi-arcade, and the other hemi-arcade automatically received the other treatment.

Blinding

This was a triple blind RCT in which the patient, operator, and evaluator were blinded to the dental arch the ibuprofen/arginine or placebo was applied. The ibuprofen/arginine and

the placebo gels were delivered to operators in identical white syringes coded with random numbers that could only be identified later by the researcher that performed the randomization list. All procedures were done in the pharmaceutical laboratory of the local university.

Study intervention

Prior to the bleaching procedures, we prepared an experimental desensitizing gel containing 5% ibuprofen and 10% arginine. This gel was formulated with propylene glycol and hydroxyethyl cellulose as thickening agents, with methylparaben as a preservative. Simultaneously, we created a placebo gel using the same thickening agents and preservatives but without the active components (ibuprofen/arginine), maintaining identical viscosity and appearance between gels.

The experimental gel was applied to one hemi-arch (encompassing central incisors to the first premolar), while the placebo gel was applied to the other hemi-arch. Both gels were applied in both the upper and lower arches. The preparation of both gels was carried out at the Nanotechnology Laboratory of the university.

After randomization, the ibuprofen/arginine or placebo gel was gently applied to the enamel surfaces of the teeth designated for bleaching. This application was done for 20 s using disposable micro brushes (Cavibrush, FGM). Subsequently, the gel was left on the surface for a period of 10 min and then carefully removed using clean gauze.

To facilitate the bleaching process, a lip retractor (ArcFlex, FGM, Joinville, SC, Brazil) was positioned in the patient's mouth. We also protected the gingival tissue by applying a light-cured resin dam (Top Dam, FGM). This protective barrier was light-cured for 10 s on each tooth with a LED light curing unit (Radii Cal, SDI, Victoria, Australia).

The 35% hydrogen peroxide gel (Whiteness HP 35% AutoMixx, FGM) was applied for 50 min following the manufacturer's instructions. After bleaching, the hydrogen peroxide gel was removed with a disposable saliva ejector, and dental surfaces were washed with abundant water. Patients were submitted to two bleaching sessions with a one-week interval. All participants were instructed to brush their teeth regularly using fluoridated toothpaste.

Tooth sensitivity (TS) evaluation

Participants were required to assess the intensity of the TS separately for each hemi-arcade within specific time intervals: (1) during the bleaching procedure; (2) within 1 h after each bleaching session; (3) up to 24 h after each bleaching session; and (4) 48 h after each bleaching session. The assessment was conducted using two pain scales.

For the five-point Numeric Rating Scale (NRS), participants were asked to rate the level of TS during each of these assessment periods using a scale ranging from 0 to 4, where 0 represented no sensitivity, 1 indicated mild sensitivity, 2 denoted moderate sensitivity, 3 signified considerable sensitivity, and 4 represented severe sensitivity [18, 23, 27, 28, 43-45]. Likewise, participants were instructed to record their TS intensity using a 0-10 visual analog scale (VAS), where 0 indicated no pain, and 10 indicated severe pain [23, 28, 43, 44, 46, 47].

For statistical purposes and to assess the intensity of tooth sensitivity (TS), we utilized the worst score from both bleaching sessions, whether it was the Numerical Rating Scale (NRS) or the Visual Analog Scale (VAS). If a patient consistently scored zero (indicating no sensitivity) in all assessments during both bleaching sessions, they were classified as having no tooth sensitivity in the bleaching protocol. This categorization allowed the calculation of the absolute risk of TS, representing the percentage of participants who reported TS at least once during the treatment.

Color evaluation

Two trained operators conducted color evaluations at several time points: prior to the beginning of bleaching (baseline), one week after the first bleaching session, one week after the second bleaching session, and one month after the completion of the bleaching treatment. Notably, color assessments were intentionally not carried out immediately after each bleaching session to prevent any potential influence of dehydration and demineralization on the color measurements. To ensure consistency, the middle third of both the right and left upper canines served as the designated tooth-matching area.

The color evaluation was performed with the value-oriented shade guide Vita Classical (Vita Zahnfabrik, Bad Säckingen, Germany) arranged from highest (B1) to lowest (C4) values [23, 27, 43], and the Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik, Bad Säckingen, Germany) already organized from highest (0M1) to lowest (5M3) value [48, 49]. An objective color evaluation was performed with the spectrophotometer Vita Easyshade (Vita Zahnfabrik, Bad Säckingen, Germany) [23, 43, 44, 50].

For the color evaluation, an impression of the maxillary arch was taken with dense silicone paste (Speedex, Vigodent, Rio de Janeiro, RJ, Brazil) to standardize the local color measurement during the intervention. The impression was extended to the maxillary canines and had a 6-mm window created on the labial surface of the silicone in the canines. The color was measured using the Easyshade parameters: L^* , (a^*) , and (b^*) , in which L^* represents the

value from 0 (black) to 100 (white), and a^* and b^* represent the shade, where a^* is the measurement along the red-green axis and b^* is the measurement along the yellow-blue axis.

The color comparison before and after bleaching treatment was evaluated by calculating the ΔE_{ab} (CIELab 1976) [51], ΔE_{00} (CIEDE 2000) [52], and WI_D (Whiteness Index). The color differences between the two colors from baseline and after treatment were calculated using the following formulas:

$$\Delta E_{ab} (CIELab) = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}.$$

$$\Delta E_{00} (CIEDE2000) = [(\Delta L'/k_L S_L)^2 + (\Delta C'/k_C S_C)^2 + (\Delta H'/k_H S_H)^2 + R_T (\Delta C'/k_C S_C \Delta H'/k_H S_H)]^{1/2}.$$

$$WI_D = (0.511 \times L^*) - (2.324 \times a^*) - (1,100 \times b^*). [53, 54]$$

Higher WI_D values indicate whiter teeth (whiteness), while lower WI_D values (including negative values) indicate darker teeth (darkness). The WI_D data were represented by ΔWI_D and calculated as the following equation:

$$\Delta WI_D = WI_{D \text{ (after bleaching)}} - WI_{D \text{ (baseline)}}. [53, 54]$$

Statistical analysis

The statistical analysis followed the intention-to-treat protocol, which involved all randomized participants [55]. For missing data, the last assessment was carried forward. The data were analysed using a statistical software (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY, USA). The statistician was blinded to the study groups. McNemmar's test ($\alpha = 0.05$) compared both group's absolute sensitivity risk. The odds ratio of TS and the confidence interval for the effect size were calculated.

For the NRS scale, we compared the intensity of TS of both groups at each evaluation points using the Wilcoxon Signed-Rank test. Variations over different time within each group were compared with the Friedman test. For the Visual Analog Scale (VAS), we employed a paired t-test to compare groups at each assessment point and one-way repeated measures ANOVA compared changes across different assessment periods within each group.

To compare color changes between groups (ΔSGU , $\Delta\text{E}_{\text{ab}}$, ΔE_{00} , and $\Delta\text{W}_{\text{ID}}$ baseline vs. one-month post bleaching) we employed a paired t-test. In all these statistical tests, the significance level was established at 5%.

RESULTS

Characteristics of the Participants

Ninety-eight patients were evaluated, but only 62 met the inclusion criteria (Figure 1). The baseline color of the patients and the distribution of gender are described in Table 1.

Adherence and Discontinuity to Protocol

One patient (ID 0045) discontinued the bleaching treatment after the first session, reporting considerable TS. This participant returned for a final color measurement appointment one week later, while the other participants attended recall appointments one week and one month after their bleaching treatments.

No adverse effect that could be attributed to the ibuprofen/arginine was reported by patients.

Risk of Tooth Sensitivity (TS)

Among the 62 participants, two did not experience TS in any of the experimental arches. A total of 16 patients did not report TS in the experimental arch side, and among these, only two patients did not report TS in the control side. A total of four patients did not present TS in the control arch side, and among these, two did not experience pain in the experimental side (Table 2). When considering relative figures, the odds ratio for TS was 0.14 (95% 0.02 to 0.6) meaning that the odds of experiencing TS in the experimental group was 86% lower (McNemmar test, $p = 0.004$).

From all hemi-arches treated, 58 out of 62 experienced TS in the placebo group (absolute risk of 94% [95% CI 85 to 97%]) but 46 of 62 presented TS in the desensitizing group (absolute risk of 74% [95% CI 62 to 83%]).

Intensity of tooth sensitivity (TS)

In the NRS scale, the desensitizing group exhibited lower TS intensity compared to the placebo group immediately, at the 1-h and 24-h periods (Table 3, $p < 0.05$). Within each group, TS was higher at the immediate and 1-h periods but decreased after 24 and 48 hours for both groups (Table 3, $p < 0.05$).

Likewise, in the VAS scale, the desensitizing group showed lower TS intensity than the placebo groups at all time assessments. On a 0-10 VAS scale, the average mean difference

between the groups was approximately 1.0 VAS unit up to 24 hours post bleaching (Table 4, $p < 0.05$). After 48 hours, TS intensity was very low for both groups (Table 4).

Color Evaluation

Regarding color change, groups were not different one another in any of the color change tools used (Table 5, $p > 0.05$).

DISCUSSION

In this current RCT, we applied ibuprofen and arginine topically to the enamel surface for 10 min prior to in-office bleaching treatment. This approach aimed to reduce inflammation, provide analgesic effects, and decrease tooth sensitivity (TS).

Numerous clinical studies and systematic reviews [26, 27, 29, 30] have indicated that drugs used to mitigate TS in dental bleaching treatments did not yield the desired effects when taken orally. Various factors, such as differences in administration, absorption rates, duration of action, and the underlying mechanisms of inflammation and pain, likely contributed to the lack of positive results observed with the oral administration of these drugs in previous studies. This led to the decision to use this combination as a topical gel, rather than administering it orally.

The ibuprofen gel were already extensively tested for safety and efficacy across healthcare domains and holds global approval [56-58]. Commercially available ibuprofen gels at our concentrations are known to be safe for humans [56-58]. As reported in the results section of this study, no adverse effect apart from bleaching-induced tooth sensitivity was reported, which lead us to conclude that ibuprofen/arginine for topical dental application is as safe as or safer than in other medical uses.

Although Ibuprofen and arginine are known for their ability to penetrate various tissues in the body [37, 59-61], its ability to reach the pulp tissue in the dental structure is limited. In a recent in vivo study conducted in rats, the authors demonstrated that ibuprofen-loaded hydrogel and nanogel, doped with rhodamine B, were visualized on the inner enamel and dentin, reaching the dental pulp [62].

Inside the pulp tissue of bleached teeth, ibuprofen reduced the inflammation caused by the bleaching agents. Bleached teeth that were topically administered with ibuprofen-loaded gel displayed reduced inflammatory infiltrate scores and a lack of necrotic areas, in contrast to bleached teeth without this treatment [62].

This explains the substantial 86% reduction in the odds of experiencing TS observed in the hemi-arches treated with the ibuprofen and arginine compound in our study. Additionally, the intensity of TS was approximately 1 VAS unit lower in the experimental group compared to the placebo group. This reduction highlights the efficacy of ibuprofen and arginine, administered topically, as a treatment option for reduction of the undesirable bleaching-induced TS.

The reduction of TS observed in this study appears to be superior to those reported in studies employing potassium nitrate, traditionally seen as one of the main options for treating TS. Recent clinical studies and a systematic review [63-65] suggests that, although potassium nitrate significantly reduces the risk and intensity of TS during bleaching, the clinical impact of this reduction is subtle. Potassium nitrate primarily acts by reducing nerve excitability but does not directly address inflammation, a key component of TS induced by bleaching agents [63, 65]. This contrast highlights ibuprofen and arginine, which not only relieve pain but also reduces inflammation, offering a more comprehensive approach to managing TS.

Ibuprofen, as a non-steroidal anti-inflammatory drug, primarily operates by inhibiting prostaglandin synthesis, thereby alleviating pain and inflammation. It also exerts a neural effect [66, 67], when it accumulates at nerve endings in the periphery [32, 68] by lowering the sensory neuron threshold in the pulp, which is particularly advantageous for post-bleaching analgesia [32, 68].

Arginine is an amino acid that plays a role in the production of nitric oxide, a molecule with vasodilatory properties. Nitric oxide helps to relax blood vessels, improving blood flow to the affected area. This increased blood flow can help reduce inflammation and enhance the delivery of immune cells and nutrients to the site of inflammation, promoting healing and reducing pain.

When ibuprofen and arginine are combined, they may have a synergistic effect in reducing pain during an inflammatory reaction [60, 61, 69, 70]. Ibuprofen targets the inflammatory pathways, while arginine supports better blood circulation and nutrient delivery to the inflamed tissue [71]. This combination can lead to improved pain relief and a quicker resolution of the inflammatory response. This synergistic effect was observed in a recent study that compared the combination of ibuprofen/arginine vs ibuprofen alone for the pain relief, edema and trismus in patients submitted to surgery of impacted third molar [72] as well other RCTs [37-39, 73-75].

For both groups, a significant decrease in tooth sensitivity (TS) intensity was observed within the first 24 hours after treatment with ibuprofen/arginine. Previous research has shown that various inflammatory mediators, including interleukin-10, interleukin-1 β , substance P, COX-1, and bradykinin, exhibit their highest levels of immunostaining during immediate periods post bleaching (Gallinari et al. 2019; Moura et al. 2022) being reduced significantly as passes [62, 76].

Although the combination of ibuprofen and arginine for pain control in dental procedures is not unprecedented, its use for the management of bleaching-induced tooth sensitivity has never been previously tested. Additionally, the topical application of products for dental sensitivity, irrespectively of the drug type or function has not either been explored in the dental field. Therefore, apart from introducing a potential new treatment combination for TS, this study also opens the door for further investigations into topical treatments for dental sensitivity, a significant and under-addressed issue in cosmetic dentistry.

Unfortunately, we have not found in the consulted literature any study that evaluated the penetration and release profiles of this drug combination applied on the dental structures. Further basic studies should focus on this aspect as it would provide invaluable findings to further elucidate the underlying mechanisms behind the observed clinical effects.

The color change resulting from dental bleaching remained unaffected by the application of the ibuprofen/arginine gel, thus demonstrating that topical use of ibuprofen and arginine does not reduce the effectiveness of bleaching. Subjective evaluation using the VITA Classical scale and VITA Bleach guide revealed an average color change of 7 to 10 shade guide units. This objective evaluation demonstrated that bleaching outcomes were comparable for both groups and clinically discernible from baseline.

To assess bleaching efficacy, we also employed spectrophotometers and the Lab^* values were analyzed according to the CIEL_{ab} system [23, 65]. Additionally, the CIE₀₀ and WI_D calculations were employed to evaluate color changes. These methods for color evaluation are commonly employed in dental bleaching studies [23, 52, 65, 77, 78]. The color values observed in both groups between baseline vs 1-month post-bleaching surpassed the 50:50% perceptibility/acceptability threshold ($\Delta E^*_{ab} > 6.4$; $\Delta E_{00} > 4.0$), indicating effective bleaching in both groups [79]. Similar results using high concentration hydrogen peroxide gels was observed [23, 30, 80].

The split-mouth design is a valuable approach in dentistry because it effectively controls inter-individual variability, utilizing each participant as their own control. This design not only

ensures efficient resource utilization but also enhances statistical power, particularly beneficial in pain studies where robust control for confounding factors is essential. However, it is important to acknowledge potential limitations, such as the risk of carry-over effects and central pain perception interference for some patients. An early investigation (Bonafe et al. 2013) [81] showed that participants could accurately identify teeth experiencing pain, addressing concerns about their ability to distinguish between the two halves of their dental arches in the present study.

Therefore, the topical application of the ibuprofen/arginine compound successfully reduced the bleaching-induced TS intensity and risk. As a recommendation for future research, it would be beneficial to explore the potential of alternative analgesics or anti-inflammatory drugs, as well as higher concentrations of the ibuprofen and arginine compound, to verify their potential for even more effective reductions in the absolute risk and intensity of dental sensitivity.

CONCLUSION

The topical application of ibuprofen in combination with arginine has demonstrated the ability to reduce the risk and intensity of tooth sensitivity, while preserving the efficacy of the bleaching process.

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TABLES

Table 1 - Baseline characteristics of the participants

Baseline Color (SGU; mean ± SD)	8.8 ± 2.6	
Baseline Whiteness Index (mean ± SD)	7.8 ± 11.9	
Age (years; mean ± SD)	24.3 ± 7.5	
Gender (%)	Female	69
	Male	31

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

Table 2 – Matched tabulation of the absolute risk of TS for both groups along with the odds ratio and 95% confidence interval (CI) ^a

		Placebo			Odds ratio (95% CI) ^a
		Positive	Negative	Total	
Desensitizing	Positive	44	2	46	0.14 (0.02 to 0.6)
	Negative	14	2	16	

Total 58 4 62

^a McNemar test ($p = 0.004$)

Table 3 – Comparison of the medians (interquartile range) of the TS intensity between groups in the different recall times using the Numerical Rating Scale.

Recall Times	Groups		p-value ^a
	Experimental	Placebo	
During bleaching	0 (0-2) A	1 (0-2) a	0.01
1 hour after	1 (0-2) A,B	1 (1-2) a	0.01
24 hours after	1 (0-1) A,B	0 (0-2) b	0.02
48 hours after	0 (0-0) C	0 (0-0) c	1.00

Within each column, significant differences are represented by distinct uppercase letters (Friedman test; $\alpha = 0.05$). ^b p-values were obtained from group comparison by Wilcoxon Signed Rank test.

Table 4 – Comparison of the means ($\pm$ SD) of TS intensity between groups in the different recall times using the 0-10 visual analog scale.

Recall Times	Groups		p-value ^b	Mean Difference (IC 95%)
	Desensitizing	Placebo		
During bleaching	1.4 $\pm$ 2.2 A	2.3 $\pm$ 2.5 a	0.02	-0.8 (-1.52 to -0.12)
1 hour after	2.1 $\pm$ 2.5 A	3.1 $\pm$ 2.4 a	< 0.001	-1.0 (-0.41 to -1.58)
24 hours after	1.9 $\pm$ 2.7 A	2.6 $\pm$ 3.0 a	0.03	-0.7 (-1.36 to 0.00)
48 hours after	0.3 $\pm$ 1.5 B	0.5 $\pm$ 1.4 b	0.04	-0.2 (-0.01 to -0.35)

Within each column, significant differences are represented by distinct uppercase letters (One-way repeated measures ANOVA and Tukey's test; $\alpha = 0.05$). ^b p-values were obtained from paired t-test.

Table 5 – Means and standard deviations, p-values and mean differences (IC 95%) of color change (baseline vs. one-month postbleaching) measured with different tools.

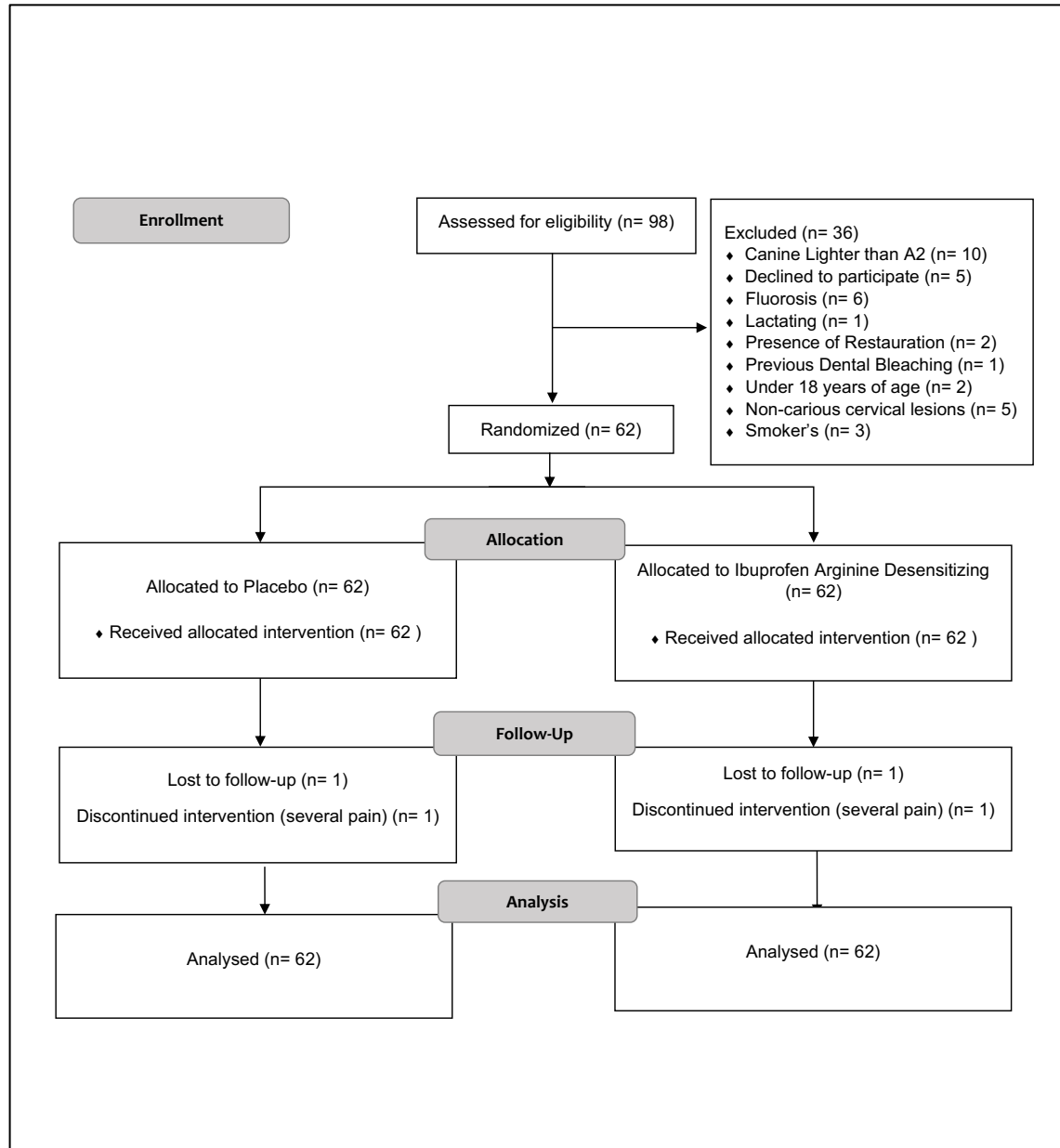
Color Evaluation	Groups		p-value ^a	Mean Difference (95 % IC)
	Desensitizing	Placebo		
Vita Classical	7.1 $\pm$ 2.5	7.1 $\pm$ 2.5	0.66	0.05 (-0.27 to 0.17)
Vita Bleachedguide	10.0 $\pm$ 2.7	10.1 $\pm$ 2.6	0.40	-0.1 (-0.33 to 0.13)
ΔE_{ab}	10.7 $\pm$ 3.8	10.5 $\pm$ 4.1	0.71	0.20 (-0.89 to 1.29)

ΔE_{00}	6.9 ± 2.8	6.8 ± 2.8	0.76	0.12 (-0.66 to 0.91)
ΔWI_D	14.0 ± 6.1	15.2 ± 7.6	0.19	-1.2 (-3.0 to 0.62)

^a paired t-test

FIGURES

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



4.2 IN-OFFICE BLEACHING AFTER A DESENSITIZING PROTOCOL: A 4.5-YEAR FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL

Diego Hortkoff ^a DDS, MSc, PhD Student, e-mail: drdiegohk@outlook.com, Paulo Vitor Farago ^b BS Pharm, PhD, e-mail: pvfarago@gmail.com, João Carlos Gomes ^a DDS, MSc, PhD, e-mail: gomesjoãocarlos@uol.com.br, Alessandra Reis ^a DDS, PhD, e-mail: reis_ale@hotmail.com, Giovana Mongrue Gomes ^a DDS, MSc, PhD, e-mail: giomongrue@gmail.com.

^a Department of Dentistry, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil.

^b Department of Pharmacy, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil.

Corresponding author:

Giovana Mongrue Gomes. State University of Ponta Grossa, Department of Dentistry. Av. General Carlos Cavalcanti, 4748, Uvaranas - Ponta Grossa, PR, Brazil. Zip code: 84030-900; Telephone: +55 42 3220-3740; E-mail: giomongrue@gmail.com.

Clinical Trial Registration Number: RBR-9v2xz6

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ABSTRACT

Objectives: This clinical trial aims to evaluate the bleaching efficacy and longevity of in-office bleaching after 4.5 years with or without ibuprofen/arginine desensitization.

Methods: Sixty-two patients, canines darker than A2 and in good general and oral health were selected and their hemi-arches randomized to receive an ibuprofen-arginine or placebo

desensitizing gels before in-office dental bleaching. Two bleaching sessions (35% hydrogen peroxide gel; 1-week) were performed. Color change was evaluated using the Vita Classical, Vita Bleachedguide (Δ SGU), and Vita EasyShade spectrophotometer (ΔE_{ab} , ΔE_{00} , WI_D) before dental bleaching, one month and 4.5 years after the bleaching procedure. Data was evaluated by paired t-test ($\alpha = 0.05$). Long-term dental tooth sensitivity, patient satisfaction and desire for a new bleaching procedure were evaluated.

Results: After 4.5 years, no significant difference in color change was found between the desensitizing and placebo sides ($p > 0.05$). A significant color rebound was observed (mean Δ SGU Classical 2.1 units, per-protocol analysis), though bleaching effects remained clinically relevant. Long-term tooth sensitivity was reported by 25.5% of participants. Patient satisfaction was moderate (mean VAS 6.7 ± 2.6), with 85.1% expressing interest in additional bleaching.

Conclusions: In-office dental bleaching showed sustained whitening effects after 4.5 years, despite a mild color rebound.

Clinical relevance: In-office bleaching maintains clinically acceptable whitening for over 4 years despite slight color rebound.

INTRODUCTION

Dental bleaching is a safe and effective procedure for improving smiles by removing stains and yellowing from teeth. Among the available bleaching techniques, in-office bleaching provides quicker results compared to at-home methods [1, 2], and does not require patient compliance with at-home protocols [3].

In-office bleaching typically uses highly concentrated hydrogen peroxide gels [1, 4], which can increase the risk and intensity of tooth sensitivity (TS), reported to affect over 80% of patients in many randomized controlled studies [5-9]. In the pulp tissue, hydrogen peroxide can trigger an inflammatory response and activate pain receptors [10, 11], leading to bleaching-induced TS. Various alternatives have been proposed to reduce this TS, with prior application of desensitizing agents showing promise [12-17]. The most effective agent appears to be ibuprofen-arginine gel applied before in-office bleaching [18], resulting in a reduction of the odds for bleaching-induced TS of 86%. However, the long-term effects on TS and color change are not investigated deeply, as most studies only assess sensitivity up to 48 hours post-procedure, without reports on subsequent months.

Additionally, although it is known that dental bleaching can whiten teeth and improve patient's quality of life and self-esteem [19-23], comprehensive analysis of the long-term impact on patient perception is lacking. Studies on the long-term efficacy of in-office bleaching protocols rarely extend beyond 24 months post-procedure [24, 25], and some suggest a potential color rebound within weeks after treatment [26-28]. Due to limited research, the stability of color change over prolonged post-bleaching periods is very welcomed as long as the patient's perceptions of the bleaching outcome [29].

Therefore, this study aimed to evaluate tooth sensitivity, long-term color change, and patient perception after 4.5 years in patients submitted to in-office bleaching with and without prior application of an ibuprofen-arginine desensitizer.

MATERIAL AND METHODS

Ethics approval and study protocol registration

This study represents a 4.5 years (55-month) follow-up of a prior investigation [18], conducted as a randomized controlled trial (RCT). Approval for the study (protocol number 3.067.235) was granted by the Scientific Review Committee for the Protection of Human Participants at the State University of Ponta Grossa, Brazil. Additionally, it was registered in the Brazilian Clinical Trials Registry (ReBEC) with the identification number RBR-9v2xz6. The preparation of this article adhered to the guidelines outlined in the Consolidated Standards of Reporting Trials statement, with a focus on within-person designs [30].

Trial design, settings, and locations of data collection

This study was conducted as a triple-blind, split-mouth, placebo-controlled randomized trial (RCT). It ensured that neither the patient, operator, nor evaluator knew which product was being applied. The study was conducted between July 2019 and September 2019 at the Dental Clinics of the local university's School of Dentistry.

Recruitment and eligibility criteria

Recruitment for the study involved posting written advertisements on university notice boards and using social media to gather a convenient sample. Volunteers needed to be at least 18 years old and in good oral and overall health. They also had to have no restorations or cavities in their six upper front teeth and upper canines with a shade of A2 or darker according to the Vita Classical shade guide.

Exclusion criteria included volunteers with dental issues that could cause sensitivity, such as tooth cracks, receding gums, or exposed dentin, as well as those with anterior dental

restorations, dental appliances, or severe tooth discoloration (like fluorosis or tetracycline stains). Pregnant or nursing women, smokers, people with bruxism, and those who had previously undergone dental bleaching were also ineligible to participate.

Sample size estimation

The previous report of this study [18] focused on determining the absolute risk of tooth sensitivity (TS) with or without ibuprofen-arginine desensitizer. To detect a significant a 25% difference between the control and experimental groups, a minimum of 48 patients were needed (80% power, 5% alpha) considering a previous report [18] of absolute risk of TS of 93% for Whiteness HP 35% Automixx (FGM, Joinville, SC, Brazil). Accounting for a 15% dropout rate, the final sample size was 55 participants. To ensure robustness, we assumed no correlation between mouth sections, allowing for a larger sample size.

Random sequence generation and allocation concealment

Randomization was conducted in blocks of 2 and 4. A third researcher, not involved in the treatment implementation, generated the randomization list via www.sealedenvelope.com and placed the assignments in opaque, sealed, individually labeled envelopes. These envelopes opened just before treatment, determining the right-side treatment, with the opposite side receiving the alternate treatment.

Blinding and experimental groups

This triple-blind RCT ensured that patients, operators, and evaluators were unaware of which dental arch received the ibuprofen/arginine or placebo. Both gels were dispensed in identical white syringes labeled with random codes, only decoded by the researcher who generated the randomization list.

An experimental desensitizing gel containing 5% ibuprofen and 10% arginine was formulated with propylene glycol and hydroxyethyl cellulose as thickening agents, along with methylparaben as a preservative. Additionally, a placebo gel was created using the same thickening agents and preservatives but without the active ingredients (ibuprofen/arginine), ensuring identical viscosity and appearance between the gels. This procedure was performed in the Pharmaceutical Laboratory of the local university.

Study intervention

Before beginning the bleaching procedure, all participants received informed consent and underwent dental prophylaxis using pumice and water in rubber cups.

Based on the randomization scheme, the experimental or placebo gel was applied to one side of each upper and lower hemi-arch (from the central incisors to the first premolars), with

the alternate gel applied to the opposite side. The assigned gel was gently applied to the enamel using disposable micro brushes (Cavibrush, FGM), left for 10 min, and then removed with clean gauze.

A lip retractor (ArcFlex, FGM) was placed, and gingival tissue protected with a light-cured resin dam (Top Dam, FGM), cured for 10 s on every two teeth using an LED-curing light unit at 1200 mW/cm² (Radii Cal, SDI, Victoria, Australia). The 35% hydrogen peroxide gel (Whiteness HP 35% AutoMixx, FGM) was then applied for 50 min according to the manufacturer's instructions, then removed with a saliva ejector, followed by water rinsing. Two bleaching sessions were performed one week apart, and participants were advised to brush their teeth regularly with fluoridated toothpaste.

Color change evaluation

Two trained operators performed color evaluations at baseline, one week after each bleaching session, one month after bleaching, and at 55 months post-treatment. Immediate post-session color assessment was not performed to prevent bias from dehydration or demineralization. The middle third of both upper canines was used for tooth-matching.

Color was assessed using the value-oriented Vita Classical (B1 to C4) [31-33], and Vita Bleachedguide 3D-MASTER (0M1–5M3) [34, 35] shade guides, along with objective color measurements from the Vita Easyshade spectrophotometer [32, 33, 36, 37] (Vita Zahnfabrik, Bad Säckingen, Germany). For both shade guides, color change was expressed in shade guide units (Δ SGU), representing the number of tabs shifted from baseline; thus, higher Δ SGU values reflect a greater whitening effect. In the case of Δ SGU Classical, each unit corresponds directly to one tab on the Vita Classical scale, and Δ SGU Bleachedguide refers to the number of tabs shifted on the Vita Bleachedguide 3D-MASTER scale.

To standardize objective color measurement, a silicone impression of the maxillary arch was made with a 6-mm window over the buccal canines. Vita Easyshade was positioned in the silicone matrix to collect L*, a*, b* parameters for calculation of ΔE_{ab} (CIELab 1976) [38], ΔE_{00} (CIEDE 2000) [39], and WI_D (Whiteness Index) [40, 41], where higher WI_D values indicate whiter teeth [40, 41].

TS and patient satisfaction evaluation

At the 4.5-year recall, participants reported whether their teeth got more sensitive (yes/no) after the bleaching procedure and rated their satisfaction with bleaching results on a 0-10 visual analog scale (VAS), where 0 means complete dissatisfaction, and 10 means complete

satisfaction. Additionally, they were asked if they would like to have additional bleaching (yes/no).

Statistical Analysis

Statistical analyses included both intention-to-treat (ITT) and per-protocol (PP) approaches. The ITT analysis reflects the primary principle of including all participants as originally allocated after randomization, regardless of follow-up status or protocol deviations. In contrast, the PP analysis includes only participants who fully adhered to the study protocol and completed the follow-up without additional bleaching procedures. ITT analyses included all 62 randomized participants, with missing data from patients lost to follow-up ($n = 15$) imputed using the last observation carried forward (LOCF) approach. The per-protocol analysis was performed in two stages: (1) excluding participants who did not attend the 4.5-year recall, and (2) further excluding those who reported undergoing additional bleaching sessions after the 1-month evaluation ($n = 8$), resulting in a final PP sample of 39 participants. Analyses were conducted using Statistics for Windows (IBM Corp., version 28.0, 2021, USA).

To check differences between hemi-arches treated with placebo or the desensitizing gel, we compared the baseline vs. 4.5-year color change from both sides for all color change parameters (ΔSGU , $\Delta\text{E}_{\text{ab}}$, ΔE_{00} , WI_D). If no differences were found, the mean of both sides from the same patient was used to assess color rebound.

Color rebound was evaluated by comparing immediate (baseline vs. 1-month) and long-term (baseline vs. 4.5-year) changes using paired t-tests across all parameters, with mean differences and 95% confidence intervals calculated.

Descriptive analyses described the percentage of patients reporting increased tooth sensitivity, desiring additional bleaching and satisfaction levels after 4.5 years, with 95% confidence intervals. These analyses were performed using the per-protocol analysis but including and excluding participants who underwent additional bleaching

RESULTS

Characteristics of the Participants

The baseline characteristics of the patients are described in **Table 1**. Of the 62 participants enrolled, 47 (76%) patients completed for the 4.5-year evaluation (**Figure 1**), resulting in a recall rate of 80%.

Adherence and Discontinuity to Protocol

Of the 15 patients who did not return for the 4.5-year recall, four we were unable to contact, five declined to return, and six had moved to other cities. Among the 47 participants who returned, eight reported having additional bleaching sessions after the last color evaluation (**Figure 1**), and one patient noted a color difference between the two dental arches.

Color Evaluation

Data collected by the spectrophotometer (L^* , a^* and b^*) and used to calculate ΔE_{ab} , ΔE_{00} and WI_D were found to be very unreliable at the 4.5-year follow-up. This limitation was primarily due to repositioning inconsistencies and potential device calibration drift over time, compromising the validity of long-term measurements. Therefore, these data were excluded from the main statistical analysis, and the primary color outcome analyses focus on visual shade guide units (SGU). However, all spectrophotometric results are provided in the **Supplemental Material** to ensure full transparency, and the issue is further addressed in the Discussion section.

As shown in **Table 2**, only the visual analysis data (color change in shade guide units) are reported. After 4.5 years, no significant differences in color change were found between hemi-arches treated with desensitizing or placebo gels across all evaluation methods ($p > 0.05$; **Table 2**). In the intention-to-treat analysis ($n = 62$), ΔSGU Classical was 5.7 ± 2.6 vs. 5.9 ± 2.5 ($p = 0.30$; mean difference: 0.13, 95% CI: -0.10 to 0.40), and ΔSGU Bleachedguide was 6.4 ± 3.8 vs. 6.5 ± 3.5 ($p = 0.90$; mean difference: 0.03, 95% CI: -0.40 to 0.40). Similar results were observed in the per-protocol analysis ($n = 39$): ΔSGU Classical was 5.0 ± 2.4 vs. 5.3 ± 2.3 ($p = 0.26$; mean difference: 0.24, 95% CI: -0.70 to 0.20), and ΔSGU Bleachedguide was 4.7 ± 3.6 vs. 4.8 ± 3.1 ($p = 0.69$; mean difference: 0.14, 95% CI: -0.80 to 0.50) (**Table 2**).

From this point forward, values from both sides were averaged per patient and comparisons were made between baseline vs. one-month and baseline vs. 4.5 years (**Table 3**). In the intention-to-treat analysis, color rebound was approximately 3.6 ± 3.7 units of SGU (Bleachedguide) and 1.3 ± 1.9 units of SGU (Classical), and this color rebound was slightly higher in the per protocol analysis (5.8 ± 3.1 units and 2.1 ± 2.0 units, respectively, **Table 3**).

Dental sensitivity and patient satisfaction

Regarding tooth sensitivity, 12 of 47 patients (25.5%; 95% CI 15.3 to 39.5%) reported increased tooth sensitivity post-bleaching (**Table 4**). When excluding patients who underwent additional bleaching, the risk was nearly the same (RR 25.6%; 95% CI 14.6% to 41.1%, **Table 4**).

Patient satisfaction was moderate, with a mean VAS score of 6.7 ± 2.6 (Table 4). Excluding the patients who underwent additional bleaching, the patient satisfaction was very similar (6.8 ± 2.4 VAS units). Most participants (85.1%; 95% CI 72.1 to 92.6) expressed interest in additional bleaching, with a similar rate of 84.6% (95% CI 70.3 to 92.8) after exclusion of those who undergo further bleaching (Table 4).

DISCUSSION

This 4.5-year follow-up is a continuation of a previously published study [18] that showed that a ibuprofen/arginine desensitizing gel reduced tooth sensitivity, compared to a placebo, without compromising whitening efficacy. In the present follow-up, no significant color differences were found between hemi-arches, indicating that the desensitizing treatment did not affect either immediate or long-term whitening efficacy.

While ibuprofen/arginine gel significantly reduced post-bleaching sensitivity in the short term [18], the lack of difference in color stability after 4.5 years suggests that its anti-inflammatory action did not influence peroxide diffusion, long-term enamel and dentin alteration or even secondary deposition of dentin. Since the gel was removed prior to bleaching and not left in place, its effect was likely limited to early-phase pulpal response without influencing structural or oxidative bleaching pathways.

Despite this important finding, the focus of this 4.5-year follow-up was to assess the long-term color stability of dental bleaching. While bleaching efficacy has been thoroughly investigated, few studies have addressed long-term outcomes. Assessing long-term stability helps clarify the procedure's durability and anticipate potential color rebound over time, improving patient communication and expectation management more effectively.

The longest follow-ups reported so far in the literature ranged from 1 year to 3 years [20, 23-25, 42-44] and within this period, a slight color rebound was reported by some authors. The present study is the longest follow-up of in-office bleaching reported so far in the literature with a recall rate of 80% after 4.5 years. Visual assessments showed an average color rebound of 1.3 units (ITT analysis) and 2.1 units (PP analysis) on the Vita Classical scale. A change of 1.3 units is generally considered imperceptible to the untrained eye, while a 2.1-unit difference may be noticeable to laypersons. Although there are no formal studies specifically establishing perceptibility thresholds for shade guide units, prior clinical calibration experiences suggest that subtle differences of approximately 1 SGU are generally detected only by trained and calibrated examiners, whereas differences of 2 SGU or more may be perceptible to untrained

observers. However, both values seem to be consistent with the expected gradual shade relapse over time due to the constant deposition of secondary dentin and enamel wear. Importantly, the teeth did not return to their original baseline color, indicating that the whitening effect remained perceptible and esthetically beneficial after 4.5 years.

We did not expect whitening outcomes to be permanent as some degree of tooth yellowing over time is a natural consequence of the aging process of the dental structure. However, there is currently limited evidence to predict when this yellowing begins or how rapidly it progresses. As teeth age, the outer layer of enamel gradually thins due to wear. As enamel becomes more translucent with wear, it reveals more of the underlying dentin which appears as a naturally yellowish hue. Additionally, the continued deposition of secondary dentin within the tooth further contributes to this yellowing effect. While this process is a normal part of dental aging, it remains unclear whether tooth bleaching accelerates the deposition of secondary dentin or alters the aging process of the dental structure. Further longitudinal studies, with a control group of unbleached patients would be needed to clarify these potential effects of whitening of the bleaching protocol on the aging process.

It is important to highlight that, despite the observed color rebound after 4.5 years, the overall color change from baseline remains high, with teeth much whiter than the baseline condition. This indicates that the teeth did not return to their original color and are unlikely to do so in the short term. Based on the observed 2.1 unit darkening over 4.5 years in the participants, one might estimate an average change of 0.47 shade guide units per year. However, this assumes a linear progression, which likely oversimplifies a multifactorial and non-linear process. Tooth color stability is influenced by a range of factors—including enamel wear, dentin changes, dietary habits, and oral hygiene, making long-term predictions inherently uncertain. Thus, while the data suggest a gradual trend of yellowing, individual outcomes may vary significantly.

Despite the occurrence of the slight color rebound after 4.5 years and participants expressing moderate satisfaction with the procedure (a mean of 6.7 ± 2.6 on a 0-10 VAS scale), over 80% of them reported interest in additional bleaching. This result suggests that, despite the bleaching effect remaining clinically evident, some patients may have perceived color rebound or developed higher aesthetic expectations over time. These findings highlight the importance of managing expectations when performing bleaching procedures, especially in the context of long-term outcomes. While previous studies have shown high satisfaction shortly after bleaching [28, 45, 46], the moderate VAS scores found after 4.5 years in our study may be

influenced by factors such as memory bias, adaptation to the post-bleaching tooth color, or increased aesthetic expectations. These dynamics underscore the need for setting realistic expectations with patients undergoing bleaching from the outset. Recording the patient's baseline tooth color can serve as a valuable reference during follow-up visits, helping them recall their original shade and avoid dissatisfaction driven by distorted perceptions—sometimes referred to in the literature as bleachorexia [47].

It is possible that participants may have largely forgotten their baseline color change over time. This phenomenon is known as "response shift" [48] where individuals' perceptions of their health or well-being adjust over time, making it challenging to accurately recall or compare their initial state. In the context of dental bleaching, participants may have gotten used to their post-bleaching tooth shade, leading them to focus more on the current appearance of their teeth rather than directly comparing it to their pre-bleaching color. Additionally, we must consider the significant influence of social media on individuals' self-evaluation. Idealized smiles, often enhanced by filters for a whiter appearance, may create unrealistic standards and increase desires for ongoing treatments.

One important issue to be discussed is that an overall TS risk of 25.5% was reported by participants who had undergone bleaching. This finding is somewhat unexpected, given that bleaching-induced TS is typically transient in nature and usually resolves within 48 hours following bleaching [7, 18, 49-52]. However, the absence of a control group, comprising individuals of similar age and other features who had not undergone bleaching limits our ability to attribute this sensitivity directly to the bleaching treatment. Nonetheless, the persistence of TS in a notable proportion of participants raises important questions and underscores the need for further research to investigate this issue more comprehensively.

One important limitation of the present study is that although we have measured L^* , a^* , and b^* parameters with the same spectrophotometer VitaEasyshade at the different time assessment periods, the results obtained at 4.5 years contrasted drastically with the visual evaluation (**Supplemental Material**). Although some differences between visual and instrumental evaluation can be seen in reported articles, with some color change parameters reaching statistical significance while others do not, both correlate well [53], and results do not diverge in the direction of the effect size [32, 50, 52, 54-56].

The values obtained from the spectrophotometer indicated a significant whitening of the dental structure after 4.5 years, a finding that lacks biological plausibility. Although we have used the same device in all time assessments and adhered strictly to the device's calibration

instructions, we believe the data collected is not reliable. In an earlier 30-month follow-up of bleaching performed in smokers and non-smokers [19], the same problem occurred, and we opted to omit the data from the Vita Easyshade, although this issue was not explored in that article.

We have further revised the Vita Easyshade spectrophotometer's user instructions but no mention of the need for regular calibrations or maintenance over time is reported. This is concerning given the device relies on electronic components and light sources, which may degrade over time, potentially compromising the accuracy of color parameter measurements.

As data collected from visual inspection does not rely on software or device calibration, it is less susceptible to this type of measurement error. This is why we chose to rely on visual inspection for the description of the results. Future research evaluating long-term dental bleaching should continue employing shade guides and start incorporating digital image methods, particularly those utilizing cross-polarization filters, to complement visual assessments [57] as they might be less prone to measurement errors [58].

Demonstrating color stability and long-term efficacy has important implications for clinical practice. It enables professionals to set realistic expectations with patients regarding the durability of whitening results, which can positively influence both treatment decisions and long-term satisfaction. While this study provides valuable evidence supporting the long-term efficacy of dental bleaching, it also highlights that slight yellowing may naturally occur over time. Future research should investigate additional factors that influence color stability and examine whether the bleaching process itself may contribute to accelerated dental aging and darkening. Comparative studies exploring different hydrogen peroxide concentrations, bleaching techniques, and the role of touch-up treatments could further optimize protocols for more long-lasting outcomes and enhanced patient satisfaction.

CONCLUSION

After 4.5 years, a slight color rebound of approximately 2.1 units was observed following in-office dental bleaching; however, the overall change from baseline remained clearly noticeable. The prior application of the ibuprofen-arginine desensitizing gel had no impact on the long-term bleaching efficacy. Around 25% of participants reported increased tooth sensitivity over time, expressed moderate satisfaction with the treatment, and the majority indicated a desire for additional bleaching.

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TABLES

Table 1 - Characteristics of all participants enrolled in the study (intention-to-treat) and of those who attended the 4.5-year recall.

Intention-to-treat analysis (n = 62)	Baseline color (SGU; mean ± SD)		8.8 ± 2.6
	Baseline whiteness index (mean ± SD)		7.8 ± 11.9
	Age (years; mean ± SD)		24.3 ± 7.5
	Gender (%)	Female	69
		Male	31
	Baseline color (SGU; mean ± SD)		8.9 ± 2.6

Per-protocol analysis (n = 47)	Baseline whiteness index (mean $\pm$ SD)		8.0 $\pm$ 12.8
	Age (years; mean $\pm$ SD)		28.7 $\pm$ 7.8
	Gender (%)	Female	68
		Male	32
Abbreviations: SGU, shade guide unit measured by Vita Classical; SD, standard deviation. Intention-to-treat analysis included all participants, with missing data imputed using the last observation carried forward. Per-protocol analysis excluded participants who did not attend the 4.5-year recall (n = 15).			

Table 2 – Means and standard deviations, p-values, and mean differences (95% CI) of color change (baseline vs. 4.5 years post-bleaching) measured with different color change tools.

Intention-to-treat analysis (n = 62)				
	Groups		p-value^a	Mean Difference (95% CI)
	Desensitizing	Placebo		
Δ SGU Classical	5.7 $\pm$ 2.6	5.9 $\pm$ 2.5	0.30	0.13 (-0.1 to 0.4)
Δ SGU Bleachedguide	6.4 $\pm$ 3.8	6.5 $\pm$ 3.5	0.90	0.03 (-0.4 to 0.4)
Per protocol analysis (n = 39)				
Δ SGU classical	5.0 $\pm$ 2.4	5.3 $\pm$ 2.3	0.26	0.24 (-0.7 to 0.2)
Δ SGU Bleachedguide	4.7 $\pm$ 3.6	4.8 $\pm$ 3.1	0.69	0.14 (-0.8 to 0.5)
Abbreviations: CI – confidence interval; ^a paired t-test Intention-to-treat analysis included all participants, with missing data imputed using the last observation carried forward. Per-protocol analysis excluded participants who did not attend the 4.5-year recall (n = 15) and those who underwent additional bleaching (n=8).				

Table 3 - Means and standard deviations, p-values, and mean differences (95% CI) for color change (one month vs. 4.5 years postbleaching) measured with shade guide units.

Intention-to-treat analysis (n = 62)				
	Baseline vs. one month	Baseline vs. 4.5 years	p-value^a	Mean difference (95% CI)
Δ SGU Classical	7.1 $\pm$ 2.5	5.9 $\pm$ 2.5	< 0.001	1.3 (0.8 to 1.9)
Δ SGU Bleachedguide	10.1 $\pm$ 2.6	6.5 $\pm$ 3.5	< 0.001	3.6 (2.7 to 4.5)
Per protocol analysis (n = 39)				
Δ SGU Classical	7.4 $\pm$ 2.3	5.3 $\pm$ 2.3	< 0.001	2.1 (1.5 to 2.8)
Δ SGU Bleachedguide	10.6 $\pm$ 2.4	4.8 $\pm$ 3.1	< 0.001	5.8 (4.8 to 6.9)
Abbreviations: CI – confidence interval; ^a paired t-test				

Intention-to-treat analysis included all participants, with missing data imputed using the last observation carried forward. Per-protocol analysis excluded participants who did not attend the 4.5-year recall (n = 15) and those who underwent additional bleaching (n=8).

Table 4 - Tooth sensitivity, patient satisfaction, and patient interest in additional bleaching after 4.5 years.

	Patient report	Outcome
Per-protocol* (n = 47)	Self-report of dental sensitivity (%)	25.5 (95% CI 15.3 to 39.5)
	Patient satisfaction (VAS 0-10; mean $\pm$ SD)	6.7 $\pm$ 2.6
	Interest in additional bleaching (%)	85.1 (95% CI 72.3 to 92.6)
Per-protocol** (n = 39)	Self-report of dental sensitivity (%)	25.6 (95% CI 14.6 to 41.1)
	Patient satisfaction (VAS 0-10; mean $\pm$ SD)	6.8 $\pm$ 2.4
	Interest in additional bleaching (%)	84.6 (95% CI 70.3 to 92.8)
<i>Abbreviations: VAS – visual analogue scale; SD – standard deviation; CI – confidence interval.</i> <i>*Analysis excluding only participants who did not attend the 4.5-year recall (n = 15); ** Analysis excluding the missing participants and those who underwent additional bleaching (n=8).</i>		

Supplemental Material

Supplementary Table 1- Means and standard deviations, p-values and mean differences (95% CI) of color change (intention-to-treat [ITT] vs per-protocol [PP]) measured with different color change tools.

Color change	Groups							
	Ibuprofen-arginine		p-value ^a	Mean Difference (95% CI)	Placebo		p-value ^a	Mean Difference (95% CI)
	ITT (n=62)	PP (n=47)			ITT (n=62)	PP (n=47)		
ΔSGU Classical	5.7 ± 2.6	5.3 ± 2.4	0.35	0.5 (-0.5 to 1.4)	5.9 ± 2.5	5.5 ± 2.4	0.42	0.4 (-0.5 to 1.3)
ΔSGU Bleached	6.4 ± 3.8	5.1 ± 3.6	0.08	1.3 (-0.1 to 2.8)	6.4 ± 3.5	5.5 ± 3.5	0.16	1.0 (-0.4 to 2.3)
ΔE _{ab}	14.0 ± 5.2	15.1 ± 5.2	0.27	-1.1 (-3.2 to 0.9)	14.0 ± 5.3	15.6 ± 5.0	0.11	-1.6 (-3.6 to 0.4)
ΔE ₀₀	9.5 ± 3.9	10.4 ± 3.7	0.24	-0.9 (-2.4 to 0.6)	9.4 ± 3.5	10.5 ± 3.1	0.08	-1.1 (-2.4 to 0.1)

Abbreviations: CI – confidence interval; SGU – shade guide units. ^a Paired t-test

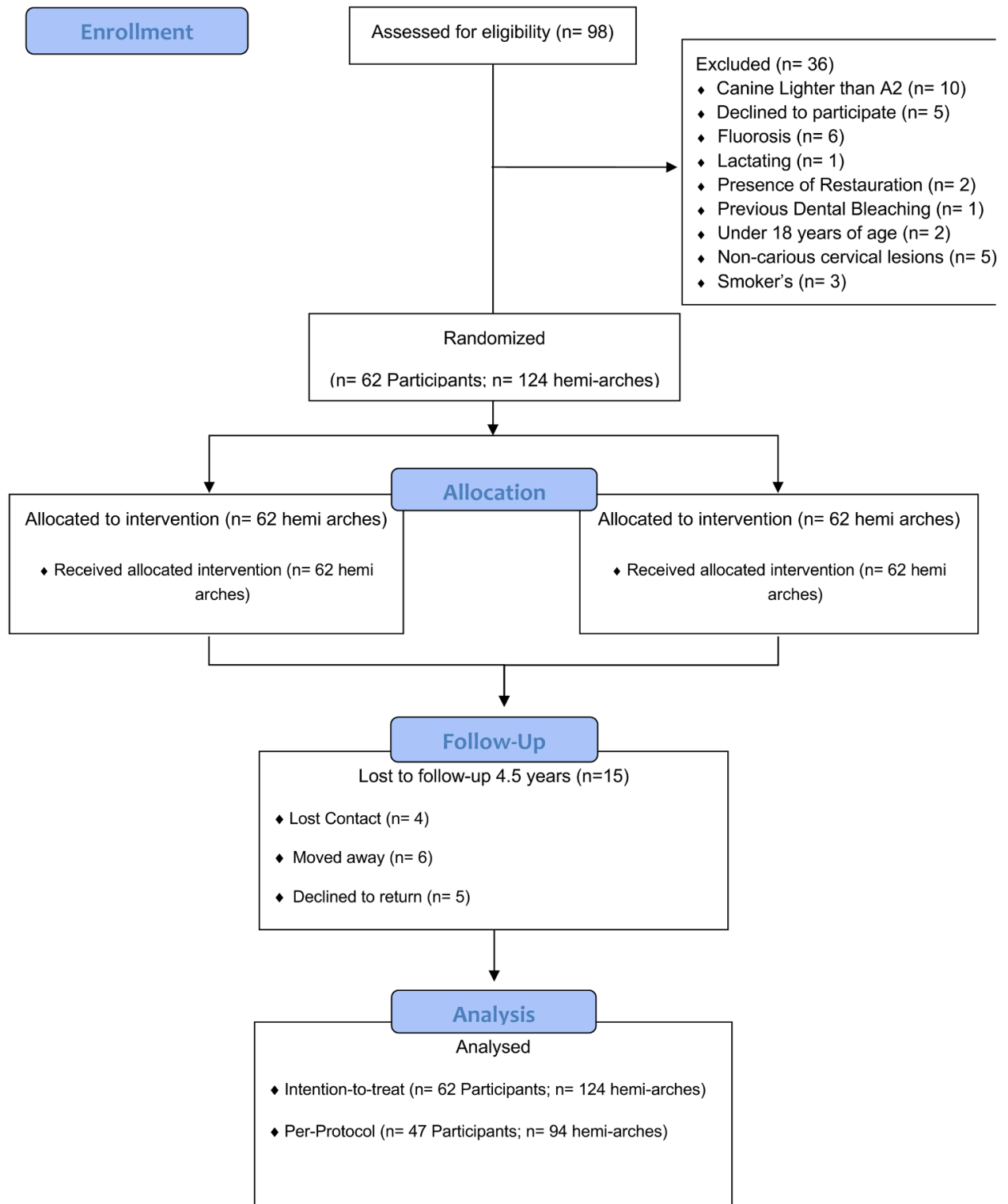
Per-protocol – Analysis excluding participants who did not attend the 4.5-year recall

Supplementary Table 2 - Means and standard deviations, p-values, and mean differences (IC 95%) of color change (one month vs. 55-month postbleaching) measured with different tools.

Color evaluation	Groups							
	Ibuprofen-arginine				Placebo			
	1-month	55-month	p-value ^a	Mean Difference (95% CI)	1-month	55-month	p-value ^a	Mean Difference (95% CI)
Δ SGU classical	7.1 $\pm$ 2.5	5.7 $\pm$ 2.6	<0.001	1.3 (0.8 to 1.7)	7.1 $\pm$ 2.5	5.9 $\pm$ 2.5	<0.001	1.3 (0.8 to 1.9)
Δ SGU bleached	10.0 $\pm$ 2.8	6.4 $\pm$ 3.8	<0.001	3.7 (2.7 to 4.6)	10.1 $\pm$ 2.6	6.5 $\pm$ 3.5	<0.001	3.6 (2.7 to 4.5)
ΔE_{ab}	10.7 $\pm$ 3.8	14.0 $\pm$ 5.2	<0.001	-3.6 (-4.7 to -2.4)	10.5 $\pm$ 4.1	14.0 $\pm$ 5.3	<0.001	-3.3 (-4.2 to -2.3)
ΔE_{00}	6.9 $\pm$ 2.8	9.5 $\pm$ 3.9	<0.001	-2.6 (-3.4 to -1.8)	6.8 $\pm$ 2.8	9.4 $\pm$ 3.5	<0.001	-2.6 (-3.3 to -1.8)
WI _D	21.4 $\pm$ 13.2	25.6 $\pm$ 10.7	0.002	-4.3 (-6.9 to -1.6)	22.1 $\pm$ 12.3	26.7 $\pm$ 9.3	0.001	-4.6 (-7.3 to -1.9)

Abbreviations: CI – confidence interval; SGU – shade guide units. ^a Paired t-test.

Figure 1 - CONSORT flowchart of the study design phases, including allocation and eligibility criteria



5 DISCUSSÃO

Nesta tese conduzimos dois estudos clínicos, onde aplicamos ibuprofeno e arginina topicamente na superfície do esmalte por 10 minutos antes do tratamento clareador em consultório, avaliamos a cor dental após 4,5 anos do tratamento clareador. Estas abordagens tiveram como objetivo reduzir a inflamação, proporcionar efeitos analgésicos e, em última análise, diminuir a sensibilidade dentária (SD), avaliar a longevidade do clareamento dental durante o tempo.

Numerosos estudos clínicos randomizados (ECRs) e revisões sistemáticas [25, 26, 36, 37] indicaram que os medicamentos utilizados para atenuar a ST em tratamentos de clareamento dentário não produziram os efeitos desejados quando tomados por via oral. Vários fatores, como diferenças na administração, taxas de absorção, duração de ação e mecanismos subjacentes de inflamação e dor, provavelmente contribuíram para a falta de resultados positivos observados com a administração oral desses medicamentos em estudos anteriores. Isto levou à decisão de utilizar esta combinação como um gel tópico, em vez de administrá-la por via oral.

Estudos mostram que o ibuprofeno e a arginina têm a capacidade de penetrar em vários tecidos do corpo [31, 38-40], porém a sua capacidade de atingir o tecido pulpar na estrutura dentária é limitada. Em um estudo *in vivo* recente, observou-se que os dentes clareados de ratos tratados topicamente com um gel contendo ibuprofeno apresentaram uma redução significativa nos escores de inflamação e ausência de áreas necróticas no tecido pulpar, comparados aos dentes clareados que não receberam este tratamento. [41]. Isso explica a redução substancial de 86% nas chances de sofrer SD observada nas hemiarçadas tratadas com o composto ibuprofeno e arginina em nosso estudo. Além disso, a intensidade da SD foi aproximadamente 1 unidade VAS menor no grupo experimental em comparação ao grupo placebo. Essa redução destaca a eficácia do ibuprofeno e da arginina, administrados topicamente, como opção de tratamento para redução da SD indesejável induzida pelo clareamento.

O ibuprofeno, é um anti-inflamatório não esteroidal, que atua principalmente inibindo a síntese de prostaglandinas, aliviando assim a dor e a inflamação. O ibuprofeno também exerce um efeito neural [42, 43], quando se acumula nas terminações nervosas periféricas [30, 44], diminuindo assim o limiar dos neurônios sensoriais na polpa, o que é particularmente vantajoso para analgesia após o clareamento [30, 44].

A arginina é um aminoácido que desempenha um papel na produção de óxido nítrico, molécula com propriedades vasodilatadoras. O óxido nítrico ajuda a relaxar os vasos sanguíneos, melhorando o fluxo sanguíneo na área afetada. Este aumento do fluxo sanguíneo pode ajudar a reduzir a inflamação e melhorar a entrega de células imunológicas e nutrientes ao local da inflamação, promovendo a cura e reduzindo a

dor. Quando o ibuprofeno e a arginina são combinados, podem ter um efeito sinérgico na redução da dor durante uma reação inflamatória [39, 40, 45, 46]. O ibuprofeno tem como alvo as vias inflamatórias, enquanto a arginina melhora a circulação sanguínea e entrega de nutrientes ao tecido inflamado [47].

Esta combinação pode levar a um melhor alívio da dor e a uma resolução mais rápida da resposta inflamatória. Este efeito sinérgico foi observado em um estudo recente que comparou a combinação de ibuprofeno/arginina versus ibuprofeno sozinho para o alívio da dor, edema e trismo em pacientes submetidos à cirurgia de terceiro molar impactado [48], bem como outros ECRs [31-33, 49-51]. Para ambos os grupos, foi observada uma diminuição significativa na intensidade da SD nas primeiras 24 horas após o tratamento com ibuprofeno/arginina. Pesquisas anteriores mostraram que vários mediadores inflamatórios, incluindo interleucina-10, interleucina-1 β , substância P, COX-1 e bradicinina, exibem seus níveis mais elevados de imuno-modulação durante os períodos imediatos após o clareamento sendo reduzido significativamente à medida que passa [41, 52]. Embora a combinação de ibuprofeno e arginina para controle da dor em procedimentos odontológicos não seja inédita, seu uso para o tratamento da sensibilidade dentária induzida pelo clareamento nunca foi testado anteriormente. Além disso, a aplicação tópica de produtos para sensibilidade dentária, independentemente do tipo de medicamento ou função, também não foi explorada na área odontológica. Portanto, além de introduzir uma nova combinação potencial de tratamento para ST, este estudo também abre portas para futuras investigações sobre tratamentos tópicos para sensibilidade dentária, uma questão significativa e ainda pouco abordada na odontologia estética.

A alteração de cor decorrente do clareamento dental não foi afetada pela aplicação do gel de ibuprofeno/arginina, demonstrando assim que o uso tópico de ibuprofeno e arginina não reduz a eficácia do clareamento. A avaliação subjetiva utilizando a escala VITA Classical e a guia VITA Bleach revelou uma mudança média de cor de 7 a 10 unidades da escala de cores. Esta avaliação objetiva demonstrou que os resultados do clareamento foram comparáveis para ambos os grupos e clinicamente discerníveis desde o início. Para avaliar a eficácia do clareamento, também utilizamos espectrofotômetros e os valores Lab* foram analisados de acordo com o sistema CIELab [22, 53]. Além disso, os cálculos CIE00 e WID foram empregados para avaliar as alterações de cor. Esses métodos para avaliação de cor são comumente empregados em estudos de clareamento dental [22, 53-56]. Os valores de cor observados em ambos os grupos entre o início e 1 mês pós-clareamento ultrapassaram o limite de perceptibilidade/aceitabilidade de 50:50% ($\Delta E^*_{ab} > 6,4$; $\Delta E_{00} > 4,0$), indicando clareamento eficaz em ambos os grupos [57].

Embora o clareamento dentário tenha sido extensivamente estudado, a eficácia do tratamento branqueador não se limita à mudança imediata na coloração do dente, mas também inclui a sua capacidade de manter esta mudança a longo prazo. Por esse motivo o desfecho primário do segundo estudo foi a

avaliação da estabilidade da cor no clareamento dental após 4,5 anos de tratamento. Esta análise de longo prazo contribui significativamente para a literatura ao preencher lacunas em relação ao desempenho e duração dos efeitos do clareamento dental.

Estudos anteriores cobriram um curto período na avaliação dos resultados do clareamento [58-64]. Nosso estudo aborda uma lacuna com uma avaliação de longo prazo de 4,5 anos de um ensaio clínico randomizado, além de termos alcançado uma taxa de retorno de 76% dos pacientes que foram tratados inicialmente. O presente acompanhamento, o mais longo já relatado para clareamento em consultório, demonstrou um discreto escurecimento médio entre 1,3 e 2,1 unidades da escala VITA Classical, mas ainda assim muito inferior ao valor basal, indicando que o efeito clareador foi mantido de forma clinicamente perceptível após 4,5 anos [58-64]. A literatura existente frequentemente relata uma regressão da cor nas primeiras semanas após o tratamento [65]. Embora tenha ocorrido um leve rebound de cor ao longo dos 4,5 anos, os valores observados permanecem dentro do esperado para o processo natural de envelhecimento dental, influenciado pelo desgaste progressivo do esmalte e pela deposição contínua de dentina secundária. Importante destacar que, apesar desse escurecimento gradual, os dentes não retornaram à cor basal, mantendo-se visivelmente mais claros do que antes do tratamento, o que demonstra que o efeito clareador pode ser sustentado no longo prazo.

O clareamento dental pode ter efeitos duradouros que são benéficos na autoestima e na qualidade de vida dos pacientes. Porém, em muitos casos, o desconforto aliado à sensibilidade dentária pode ser um fator determinante para o sucesso do atendimento ao paciente. Neste contexto, é fundamental compreender a percepção dos pacientes em relação ao clareamento dental, tanto antes, durante e após o procedimento. Compreender esses fatores pode melhorar a experiência geral, incluindo a satisfação com os resultados.

Portanto, a aplicação tópica do composto ibuprofeno/arginina reduziu com sucesso a intensidade e o risco de TS induzidos pelo clareamento. Como recomendação para pesquisas futuras, seria benéfico explorar o potencial de analgésicos ou anti-inflamatórios alternativos, bem como concentrações mais elevadas do composto ibuprofeno e arginina, para verificar o seu potencial para reduções ainda mais eficazes no risco absoluto e intensidade da sensibilidade dentária. E, embora este estudo forneça evidências valiosas sobre a estabilidade da cor e a eficácia do clareamento dental a longo prazo, pesquisas futuras deverão explorar o impacto de variáveis adicionais na sustentabilidade dos resultados. Além disso, estudos comparativos entre diferentes concentrações de peróxido de hidrogênio, técnicas de clareamento e possíveis retoques podem oferecer insights sobre a otimização de protocolos de tratamento para alcançar resultados ainda mais duradouros.

6 CONCLUSÃO

Conclui-se que:

A aplicação tópica de ibuprofeno em combinação com arginina demonstrou a capacidade de reduzir o risco e a intensidade da sensibilidade dentária, preservando a eficácia do processo de clareamento.

Após 4,5 anos do clareamento dental, a cor do dente ainda é satisfatória com altos valores de índice de brancura e baixos índices de amarelecimento.

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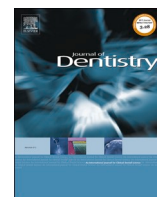
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**ANEXO A – EFFECT OF TOPICAL APPLICATION OF IBUPROFEN/ARGININE IN
THE IN-OFFICE BLEACHING-INDUCED TOOTH SENSITIVITY: A
RANDOMIZED, TRIPLE-BLIND CONTROLLED TRIAL**



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Effect of topical application of ibuprofen/arginine on the in-office bleaching-induced tooth sensitivity: A randomized, triple-blind controlled trial

Diego Hortkoff^a, Karine Letícia da Silva^a, Paulo Vitor Farago^b, João Carlos Gomes^a,
Alessandra Reis^a, Giovana Mongruel Gomes^{a,*}

^a Department of Dentistry, State University of Ponta Grossa – UEPG, 4748, Uvaranas - Ponta Grossa, Ponta Grossa, Paraná 84030-900, Brazil

^b Department of Pharmacy, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil

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ABSTRACT

Objective: The application of anti-inflammatories as topical desensitizers before dental bleaching is an approach to reduce bleaching-induced tooth sensitivity (TS). This randomized controlled trial compared the risk and intensity of TS and the color change resulting from in-office dental bleaching after using an experimental desensitizing gel containing ibuprofen and arginine.

Methods: Sixty-two participants with upper canine shades A2 or darker were randomly assigned to either the ibuprofen-arginine desensitizing group or the placebo group. The desensitizing gel was applied for 15 min before in-office bleaching with 35 % hydrogen peroxide gel for 50 min (2 sessions). To assess the absolute risk and intensity of TS, visual (0–10) and numeric rating (0–5) scales were used, and group comparisons were made using the McNemar test, Wilcoxon test, and paired Student *t*-test ($\alpha = 0.05$). Color change was evaluated using Vita Classical, Vita Bleachedguide (Δ SGU), and Vita EasyShade (ΔE_{ab} , ΔE_{00} , and ΔW_{ID}) before and one month after the bleaching procedure. Group comparisons for color change were done using a paired *t*-test ($\alpha = 0.05$).

Results: The odds ratio for TS was 0.14 [95 % CI 0.02 to 0.6], meaning lower odds of TS for the desensitizing gel. A lower intensity of TS was also observed for the experimental group ($p < 0.005$) up to 48 h after bleaching. All color evaluation tools demonstrated effective and similar whitening for both groups ($p > 0.05$).

Conclusions: Using the experimental desensitizing gel containing ibuprofen and arginine effectively reduced the risk and intensity of TS without compromising the bleaching efficacy.

Clinical relevance: The topical application of ibuprofen/arginine on the in-office bleaching reduced risk and intensity of bleaching-induced tooth sensitivity.

1. Introduction

Tooth bleaching is one of the most common cosmetic procedures patients seek due to dissatisfaction with color and teeth appearance [1]. Since the introduction of at-home bleaching by Haywood and Heymann in 1989, this technique has quickly gained popularity as an easy, practical, affordable, and conservative way to treat teeth that are discolored or intensely achromatized [2,3]. Additionally, the in-office bleaching protocol, which employs a high-concentration hydrogen peroxide, is also requested by patients who prefer not to use at-home bleaching trays and desire quicker results [4,5].

Despite the success of dental bleaching procedures, adverse effects such as gingival irritation and bleaching-induced tooth sensitivity (TS) are commonly observed. Among these, bleaching-induced TS is the most prevalent [6,7]. Studies have consistently shown that 67 to 100 % of patients undergoing in-office dental bleaching report experiencing TS at some point during treatment [8–12], mainly in the first hours following the procedure [6]. This sensitivity occurs because hydrogen peroxide, which has low molecular weight, penetrates dental tissues and reaches the pulp chamber approximately 15 min after application [13,14]. Its presence in pulp tissues can trigger inflammatory processes [15] and active pain-specific receptors [16], leading to an uncomfortable

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* Corresponding author.

E-mail address: giomongruel@gmail.com (G.M. Gomes).

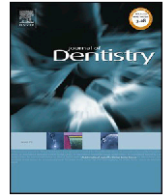
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**ANEXO B – IN-OFFICE BLEACHING AFTER A DESENSITIZING PROTOCOL: A
4.5-YEAR FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL**



In-office Bleaching After a Desensitizing Protocol: a 4.5-Year Follow-up of a Randomized Controlled Trial[☆]

Diego Hortkoff^{a,} , Paulo Vitor Farago^b, João Carlos Gomes^a, Alessandra Reis^a,
Giovana Mongrue Gomes^{a,}

^a Department of Dentistry, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil

^b Department of Pharmacy, State University of Ponta Grossa – UEPG, Ponta Grossa, Paraná, Brazil

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ABSTRACT

Objectives: This clinical trial aims to evaluate the bleaching efficacy and longevity of in-office bleaching after 4.5 years with or without ibuprofen/arginine desensitization.

Methods: Sixty-two patients, canines darker than A2 and in good general and oral health were selected and their hemi-arches randomized to receive an ibuprofen-arginine or placebo desensitizing gels before in-office dental bleaching. Two bleaching sessions (35% hydrogen peroxide gel; 1-week) were performed. Color change was evaluated using the Vita Classical, Vita Bleachedguide (Δ SGU), and Vita EasyShade spectrophotometer (Δ E_{ab}, Δ E₀₀, WI_D) before dental bleaching, one month and 4.5 years after the bleaching procedure. Data was evaluated by paired t-test ($\alpha = 0.05$). Long-term dental tooth sensitivity, patient satisfaction and desire for a new bleaching procedure were evaluated.

Results: After 4.5 years, no significant difference in color change was found between the desensitizing and placebo sides ($p > 0.05$). A significant color rebound was observed (mean Δ SGU Classical 2.1 units, per-protocol analysis), though bleaching effects remained clinically relevant. Long-term tooth sensitivity was reported by 25.5% of participants. Patient satisfaction was moderate (mean VAS 6.7 ± 2.6), with 85.1% expressing interest in additional bleaching.

Conclusions: In-office dental bleaching showed sustained whitening effects after 4.5 years, despite a mild color rebound.

Clinical relevance: In-office bleaching maintains clinically acceptable whitening for over 4 years despite slight color rebound.

1. Introduction

Dental bleaching is a safe and effective procedure for improving smiles by removing stains and yellowing from teeth. Among the available bleaching techniques, in-office bleaching provides quicker results compared to at-home methods [1,2], and does not require patient compliance with at-home protocols [3].

In-office bleaching typically uses highly concentrated hydrogen peroxide gels [1,4], which can increase the risk and intensity of tooth sensitivity (TS), reported to affect over 80% of patients in many randomized controlled studies [5–9]. In the pulp tissue, hydrogen peroxide

can trigger an inflammatory response and activate pain receptors [10, 11], leading to bleaching-induced TS. Various alternatives have been proposed to reduce this TS, with prior application of desensitizing agents showing promise [12–17]. The most effective agent appears to be ibuprofen-arginine gel applied before in-office bleaching [18], resulting in a reduction of the odds for bleaching-induced TS of 86%. However, the long-term effects on TS and color change are not investigated deeply, as most studies only assess sensitivity up to 48 hours post-procedure, without reports on subsequent months.

Additionally, although it is known that dental bleaching can whiten teeth and improve patient's quality of life and self-esteem [19–23],

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* Corresponding author at: State University of Ponta Grossa, Department of Dentistry, Av. General Carlos Cavalcanti, 4748, Uvaranas - Ponta Grossa, PR, Brazil. Zip code: 84030-900

E-mail addresses: drdiegohk@outlook.com (D. Hortkoff), pvfarago@gmail.com (P.V. Farago), gomesjoacarlos@uol.com.br (J.C. Gomes), reis_ale@hotmail.com (A. Reis), giomongrue@gmail.com (G.M. Gomes).

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