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LAÍNA VOCHIKOVSKI

ALTERNATIVAS PARA REDUZIR A SENSIBILIDADE DENTAL NO CLAREAMENTO EM CONSULTÓRIO

PONTA GROSSA

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Tese apresentada como pré-requisito para obtenção do título de Doutora na Universidade Estadual de Ponta Grossa, no Programa de PósGraduação Stricto Sensu em Odontologia, Área de Concentração: Dentística Restauradora. Linha de Pesquisa: Pesquisa Clínica em Odontologia.
Orientadora: Profª. Drª. Alessandra Reis
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LAÍNA VOCHIKOVSKI

ALTERNATIVAS PARA REDUZIR A SENSIBILIDADE DENTAL NO CLAREAMENTO EMCONSULTÓRIO.

Tese apresentada ao Programa de Pós-graduação Stricto Sensu em Odontologia da Universidade Estadual de Ponta Grossa, como requisito parcial à obtenção do título de Doutora em Odontologia, área de concentração em Dentística Restauradora, linha de pesquisa dePesquisa Clínica.

Ponta Grossa, 25 de Fevereiro de 2022.

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Dedico este trabalho:

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DADOS CURRICULARES

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RESUMO

Vochikovski, L. **Alternativas para reduzir a sensibilidade dental no clareamento em consultório.** [Tese – Doutorado em Odontologia – Área de Concentração: Dentística Restauradora - Universidade Estadual de Ponta Grossa; 2022].

Os objetivos deste estudo foram: 1) Avaliar o efeito da aplicação do gel dessensibilizante experimental *vs* placebo antes do clareamento dental em consultório na redução da sensibilidade dental (SD) e mudança de cor. 2) Avaliar o efeito do *laser* de baixa potência na redução da SD advinda do clareamento em consultório e mudança de cor. Para o estudo 1, de boca-dividida, cinquenta participantes com os caninos na cor A2 ou mais escuros foram selecionados e randomizados em dois grupos: aplicação do gel dessensibilizante experimental (10% de gluconato de cálcio, 0,1% de acetato de dexametasona, 10% de nitrato de potássio e 5% de glutaraldeído) e aplicação do gel placebo antes do clareamento de consultório (peróxido de hidrogênio 35%, 1x50 min), durante 10 min. A SD foi avaliada imediatamente e 1 h, 24 h e 48 h após o clareamento e registrada pelos próprios participantes por meio de escala numérica (NRS) de 5 pontos e visual analógica (VAS 0-10). A cor foi avaliada através de escalas visuais e espectrofotômetro inicialmente, uma semana após cada sessão e trinta dias após o término do clareamento. Para o estudo 2, oitenta participantes foram randomizados em dois grupos. Os participantes do grupo laser/controle receberam a terapia de *laser* de baixa potência após cada sessão de clareamento em consultório (peróxido de hidrogênio 35%, 1x50 minutos). A SD e a cor foram avaliadas da mesma maneira que foi descrita para o estudo 1. Após trinta dias, em ambos os ECR realizados, clareamento significativo e semelhante entre os grupos ($p > 0,32$ para estudo 1 e $p < 0,22$ para estudo 2) e em relação à SD, não houve diferença estatisticamente significativa entre os grupos, sendo OR= 0,65; 0,10 to 4,09; $p = 1,0$ para o estudo 1 e risco relativo de 1,03 (IC 95%; 0,94 a 1,11; $p = 1,0$) para estudo o 2. Pode-se concluir que a aplicação prévia do agente dessensibilizante experimental não foi eficaz na redução do risco e da intensidade de SD e, não influenciou a mudança de cor do clareamento em consultório. Além disso, a aplicação do *laser* de baixa potência não reduziu o risco e a intensidade da SD e não afetou a mudança de cor.

Palavras-chave: Clareamento Dental. Peróxido de hidrogênio. Sensibilidade da dentina. Laserterapia de baixa potência. Gluconato de Cálcio. Dexametasona. Glutaral.

ABSTRACT

Vochikovski, L. **Alternatives to reduce tooth sensitivity in in-office bleaching**. [Thesis - Doctorate in Dentistry - Concentration Area: Restorative Dentistry - Ponta Grossa State University; 2022].

The objectives of this study were: 1) To evaluate the effect of the application of experimental desensitizing gel *vs* placebo before in-office dental bleaching, on reducing tooth sensitivity and color change. 2) To evaluate the effect of low power *laser* in reducing tooth sensitivity resulting from in-office bleaching and color change. For study 1, split mouth, fifty participants with A2 or darker canines were selected and randomly into two groups: application of experimental desensitizing gel (10% calcium gluconate, 0.1% dexamethasone acetate, 10% potassium and 5% glutaraldehyde) and application of placebo gel before in-office bleaching (35% hydrogen peroxide, 1x50 min), for 10 min. TS was assessed immediately and 1 h, 24 h and 48 h after bleaching and recorded by the participants them selves using a 5-point numerical scale (NRS) and visual analogue (VAS 0-10). Color was assessed using visual scales and spectrophotometer initially, one week after each session and thirty days after the completion of bleaching. For study 2, eighty participants were randomized into two groups. Participants in the laser/control group received low-level *laser* therapy after each in-office bleaching session (35% hydrogen peroxide, 1x50 minutes). SD and color were evaluated in the same way as described for study 1. It was observed after thirty days, in both RCTs performed, significant and similar bleaching between the groups ($p > 0.32$ for study 1 and $p < 0.22$ for study 2) and in relation to TS, there was no statistically significant difference between the groups. groups, with OR= 0.65; 0.10 to 4.09; $p = 1.0$ for study 1 and relative risk of 1.03 (95% CI; 0.94 to 1.11; $p = 1.0$) for study 2. It can be concluded that the previous application of the experimental desensitizing agent was not effective in reducing the risk and intensity of SD and did not influence the color change of in-office bleaching. Furthermore, the application of the low power *laser* did not reduce the risk and intensity of SD and did not affect the color change.

Keywords: Tooth Bleaching. Hydrogen peroxide. Dentin sensitivity. Low-Level Light Therapy. Calcium Gluconate. Dexamethasone. Glutaral.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

a*	Eixo vermelho-verde
b*	Eixo azul-amarelo
c*	Croma
COEP	Comissão de Ética em Pesquisa
ΔE	Variação de cor
ΔUEV	Variação de unidades na Escala Vita
cm	Centímetro
h	Hora (s)
ECR	Ensaios Clínicos Randomizados
J	Joule
L*	Luminosidade
min	Minuto (s)
mm	Milímetro (s)
N	Número amostral
nm	Nanômetro
NRS	*Numerical rating scale* (Escala de Classificação Numérica)
Mw	Miliwatts
ReBEC	Registro Brasileiro de Ensaios Clínicos
s	Segundo (s)
Sem	Semana
SD	Sensibilidade Dental
PH	Peróxido de Hidrogênio
TCLE	Termo de Consentimento Livre e Esclarecido
UEPG	Universidade Estadual de Ponta Grossa
UEV	Unidades na Escala Vita
VAS	*Visual Analogic Scale* (Escala Visual Analógica)
Vs	Versus

LISTA DE SÍMBOLOS

=	Igual
±	Mais ou menos
<	Menor
>	Maior
≤	Menor ou igual
α	Alfa
P	Significância estatística
®	Marca registrada
Δ	Delta

SUMÁRIO

INTRODUÇÃO

Alguns estudos nos mostram que grande parte da população está insatisfeita com a cor dos dentes (Bonafé et al.[1] 2021, Goettems et al.[2] 2021), o que explica a alta procura pelo clareamento dental, tanto pelo protocolo caseiro como de consultório, sendo amplamente indicado pelos clínicos e aceito pelos pacientes para obter sorrisos esteticamente agradáveis (Heymann[3] 2005, Perdigão[4] 2010).

Diferentemente do clareamento caseiro, o clareamento em consultório requer o uso de altas concentrações de peróxido de hidrogênio (PH) (de Geus et al.[5] 2016, Maran et al.[6] 2020). No entanto, o mesmo PH que clareia os dentes oxidando o componente orgânico da estrutura dental também pode se difundir rapidamente na câmara pulpar (Kwon et al.[7] 2015). Isso pode desencadear um processo inflamatório (Roderjan et al.[8] 2015), com liberação de vários mediadores químicos inflamatórios (Caviedes-Bucheli et al.[9] 2008, Cintra et al.[10] 2013). Esse processo modifica a microcirculação local, gerando pressão sobre as fibras nervosas periféricas e ativando nociceptores. A maioria dos pacientes apresenta sensibilidade dentária (SD) induzida pelo clareamento como consequência clínica. Essa dor é caracterizada como aguda e transitória, comumente relatada pelos pacientes nas primeiras 24 horas após o clareamento dental em consultório (Piknjač A et al.[11] 2021).

Para minimizar esse efeito colateral, alguns autores investigaram a administração oral preventiva de analgésicos e opioides (Coppla et al.[12] 2018, de Oliveira et al.[13] 2018), antiinflamatórios (Charakorn et al.[14] 2009, de Paula et al.[15] 2013, Fernandes et al.[16] 2017, Peixoto et al.[17] 2019), antioxidantes (de Paula et al.[18] 2014) e corticoides (Rezende et al.[19] 2016, de Costa Poubel et al.[20] 2019). Ainda assim, esses medicamentos não conseguiram minimizar o risco ou a intensidade de SD, como mostrado na revisão sistemática de Santana et al.[21] (2019). Até agora, as abordagens mais bem-sucedidas para reduzir a SD foram a aplicação tópica de dessensibilizantes contendo glutaraldeído (Mehta et al.[22] 2013, Parreiras et al.[23] 2018), nitrato de potássio (Martini et al.[24] 2020, Martini et al.[25] 2021) ou agentes com cálcio (Mehta et al.[26] 2018, Oldoini et al.[27] 2018).

O mecanismo de ação desses agentes tópicos é diferente, sendo que o nitrato de potássio previne a repolarização das fibras nervosas bloqueando a transmissão de estímulos dolorosos (Martini et al.[24] 2020, Martini et al.[25] 2021, Rezende et al.[28] 2020), o glutaraldeído coagula proteínas do esmalte e dos túbulos dentinários, reduzindo a fácil passagem do PH para a polpa (Parreiras et al.[23] 2018, Arrais et al.[29] 2004, Ibrahim et al.[30] 2011) e agentes contendo cálcio também podem reduzir o risco e a intensidade da SD principalmente pela saturação de seus componentes na superfície do esmalte (Parreiras et al.[31] 2020). Quando os produtos contendo cálcio são aplicados, eles interagem com a superfície dental e podem ser retidos, fornecendo grandes quantidades de cálcio e fosfatos para interação tecidual, o que pode reduzir a passagem do PH para a polpa (Mehta et al.[26] 2018, Oldoini et al.[27] 2018, Kossatz et al.[31] 2012, Maghaireh et al.[32] 2014, Parreiras et al.[33] 2020, de Araújo et al.[34] 2021).

A dexametasona também é um possível agente que pode diminuir a intensidade da SD, esta droga já foi testada por via oral (Rezende et al.[19] 2016, de Costa Poubel et al.[20] 2019), mas ainda não foi investigada sob a forma tópica. Embora esse fármaco tenha sido utilizado principalmente na Odontologia por via oral para cirurgias bucais (Oksa et al.[35] 2021, Momesso et al.[36] 2021, Oliveira et al.[37] 2021) e tratamentos endodônticos (Aksoy et al.[38] 2021, Kumar et al.[39] 2021) devido aos seus potentes efeitos anti-inflamatórios e pela sua baixa massa molar (392 g/mol-1), podemos sugerir que a dexametasona possa penetrar até a região pulpar, através do esmalte e da dentina.

Outra alternativa para reduzir esse efeito é a terapia com *laser* de baixa potência. Ela já é utilizada em vários campos da Odontologia para regenerar tecidos danificados (Dantas et al.[40] 2010), promover analgesia e reduzir a inflamação tecidual (Reddy[41] 2004, Albertini et al.[42] 2007, Silveira et al.[43] 2007, Fabre et al.[44] 2015). Estudos têm mostrado bons resultados para regeneração neural em parestesia (de Oliveira et al.[45] 2015, Bittencourt et al.[46] 2017) controle de neuralgia pós-herpética (Chen et al.[47] 2016), dor pós-operatória após exodontia de terceiros molares retidos (Amarillas-Escobar et al.[48] 2010, Ferrante et al.[49] 2013, Eshghpour et al.[50] 2016, Raiesian et al.[51] 2017) e para alívio dos sintomas de disfunção temporomandibular (Salmos-Brito et al.[52] 2013, Ayyildiz al.[53] 2015, Madani et al.[54] 2020). Relata-se que os componentes

da cadeia respiratória das células podem absorver os comprimentos de onda do *laser* infravermelho, aumentando o metabolismo celular (Karu[55] 1989, Silveira et al.[43] 2007). Consequentemente, espera-se que ocorram efeitos analgésicos, antiinflamatórios e biomoduladores, auxiliando os processos de reparo tecidual (Reddy[56] 2004, Silveira et al.[43] 2007).

Recentemente, a terapia com *laser* de baixa intensidade foi apresentada como uma alternativa para reduzir a SD induzida pelo clareamento (Farhat et al.[57] 2014, Moosavi et al.[58] 2016, Calheiros et al.[59] 2017, Mayer-Santos et al.[60] 2017, Alencar et al.[61] 2018, de Paula et al.[62] 2019, Pompeu et al.[63] 2021), embora ainda haja um número baixo de ensaios clínicos randomizados (ECRs) avaliando esse protocolo. Como existem muitas variações nos parâmetros do *laser*, marcas comerciais, técnicas e áreas de aplicação, o efeito do *laser* de baixa potência na SD induzida pelo clareamento merece uma investigação mais abrangente. Em alguns estudos, a fotobiomodulação foi associada a outros protocolos de dessensibilização, como nitrato de potássio (de Paula et al.[62] 2019), dentifrício fluoretado (Alencar et al.[61] 2018) e cloreto de estrôncio (Pompeu et al.[63] 2021), dificultando a avaliação de um protocolo específico de laserterapia de baixa potência.

O mecanismo da SD induzida pelo clareamento ainda não é totalmente conhecido, por isso, vários mecanismos de ação de alguns agentes ativos juntos poderiam produzir um efeito dessensibilizante mais potente do que o seu uso individual e que a aplicação do *laser* de baixa potência, seguindo as recomendações do fabricante, poderia reduzir o risco e a intensidade da SD. Portanto, o objetivo foi avaliar o impacto da aplicação tópica deste gel dessensibilizante experimental (10% de gluconato de cálcio, 0,1% de acetato de dexametasona, 10% de nitrato de potássio e 5% de glutaraldeído) e a aplicação do *laser* de baixa potência no risco absoluto e na intensidade de SD induzida pelo clareamento e a mudança de cor após clareamento em consultório com PH 35%.

2 PROPOSIÇÃO

2.1 ESTUDO 1

2.1.1 Proposição geral

O objetivo deste ensaio clínico randomizado, boca-dividida, duplo-cego foi avaliar o efeito da aplicação do gel dessensibilizante experimental *vs* placebo antes do clareamento dental em consultório na redução da sensibilidade dental e mudança de cor.

2.1.2 Proposição específica

1. Avaliar o risco absoluto da sensibilidade dental imediatamente, 1h, 24h e 48h após o clareamento dental em consultório com aplicação prévia do gel dessensibilizante experimental ou placebo através da escala visual analógica (VAS) e escala numérica de 5 pontos (NRS).
2. Avaliar a intensidade da sensibilidade dental imediatamente, 1h, 24h e 48h após o clareamento dental em consultório com aplicação prévia do gel dessensibilizante experimental ou placebo através da escala visual analógica (VAS) e escala numérica de 5 pontos (NRS).
3. Avaliar a eficácia do clareamento dental em consultório com aplicação prévia do gel dessensibilizante experimental ou placebo nos períodos: inicial, após a 1ª sessão de clareamento, após a 2ª sessão de clareamento e 30 dias após o término do tratamento através da escala Vita Classical, Vita Bleachedguide 3D-MASTER e espectrofotômetro Vita Easyshade.

2.2 ESTUDO 2

2.2.1 Proposição geral

O objetivo deste ensaio clínico randomizado, paralelo, duplo-cego foi avaliar o efeito do *laser* de baixa potência na redução da sensibilidade dental advinda do clareamento em consultório e mudança de cor.

2.2.2 Proposição específica

1. Avaliar o risco absoluto da sensibilidade dental imediatamente, 1h, 24h e 48h após o clareamento dental em consultório com e sem a aplicação do *laser* de

baixa potência após o procedimento clareador em consultório através da escala visual analógica (VAS) e escala numérica de 5 pontos (NRS).

2. Avaliar a intensidade da sensibilidade dental imediatamente, 1h, 24h e 48h após o clareamento dental em consultório com e sem a aplicação do *laser* de baixa potência após o procedimento clareador em consultório através da escala visual analógica (VAS) e escala numérica de 5 pontos (NRS).

3. Avaliar a eficácia do clareamento dental em consultório com e sem a aplicação do *laser* de baixa potência nos períodos: inicial, após a 1ª sessão de clareamento, após a 2ª sessão de clareamento e 30 dias após o término do tratamento através da escala Vita Classical, Vita Bleachedguide 3D-MASTER e espectrofotômetro Vita Easyshade.

3 MATERIAL E MÉTODOS

As informações detalhadas deste item são encontradas nos artigos referentes a cada estudo.

3.1 ESTUDO 1

O projeto deste ensaio clínico randomizado, duplo-cego, de “boca-dividida” foi aprovado pela Comissão de Ética em Pesquisa (COEP) (Anexo 1) da Universidade

Estadual de Ponta Grossa (UEPG) através do parecer nº 3.893.891. O estudo foi registrado no site eletrônico http://www.ensaiosclinicos.gov.br/, sob o número de identificação RBR-7T7D4D. A metodologia detalhada destes experimentos está descrita no ARTIGO 1.

3.1.1 Seleção dos pacientes

Cinquenta voluntários que tiveram interesse em realizar o clareamento dental e que se enquadraram nos critérios de inclusão e exclusão do estudo foram selecionados (Figura 1). Os caninos superiores deveriam ser classificados como cor A2 ou mais escuro, de acordo com a escala Vita Classical (VITA Zahnfabrik, Bad Sackingen, Alemanha) (Figura 2).

Figura 1 - Diagrama de fluxo das fases de desenho do estudo, incluindo critérios de exclusão e alocação para a análise do resultado primário. Abreviaturas: p – participantes; ha – hemiarcas.

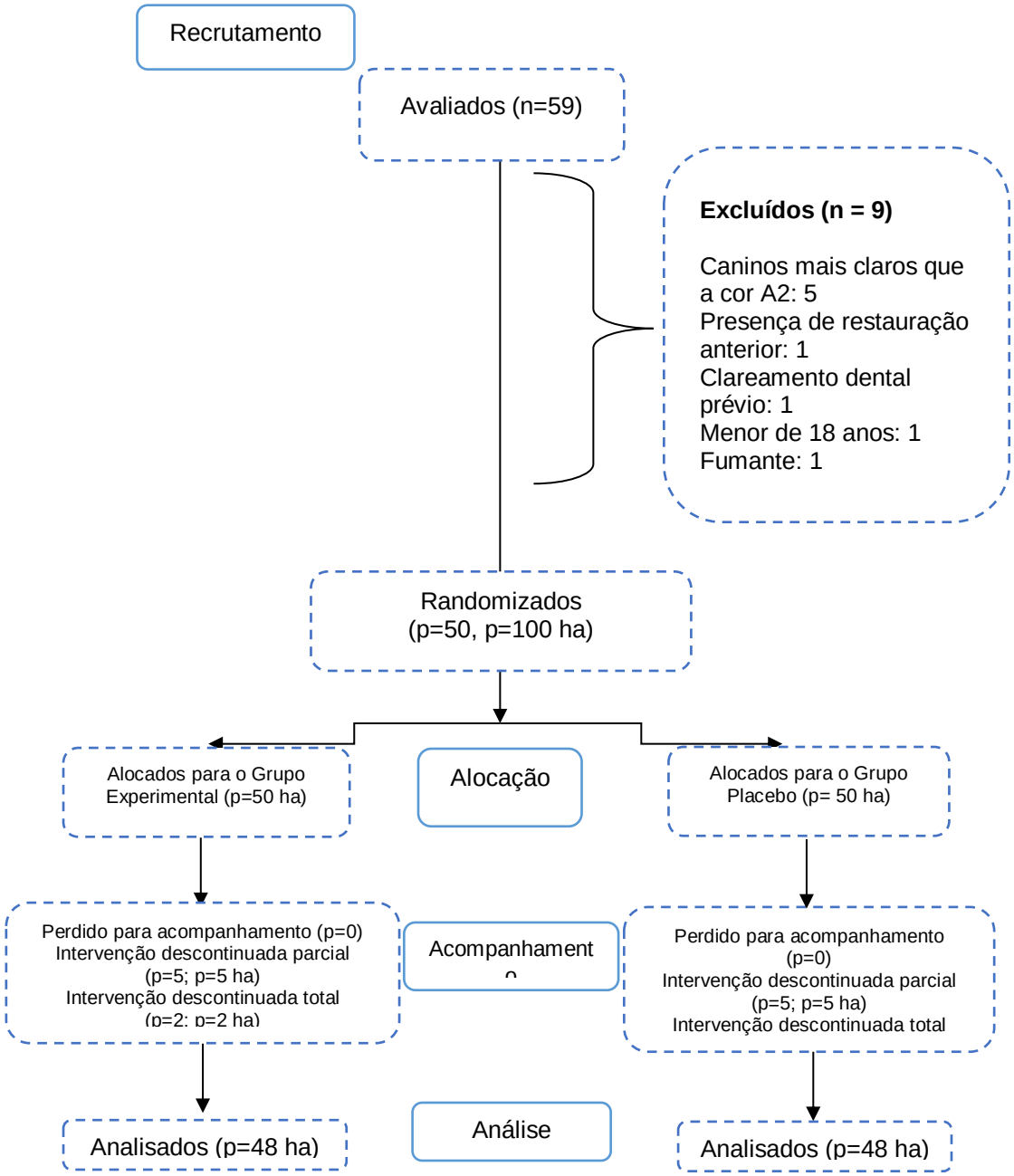

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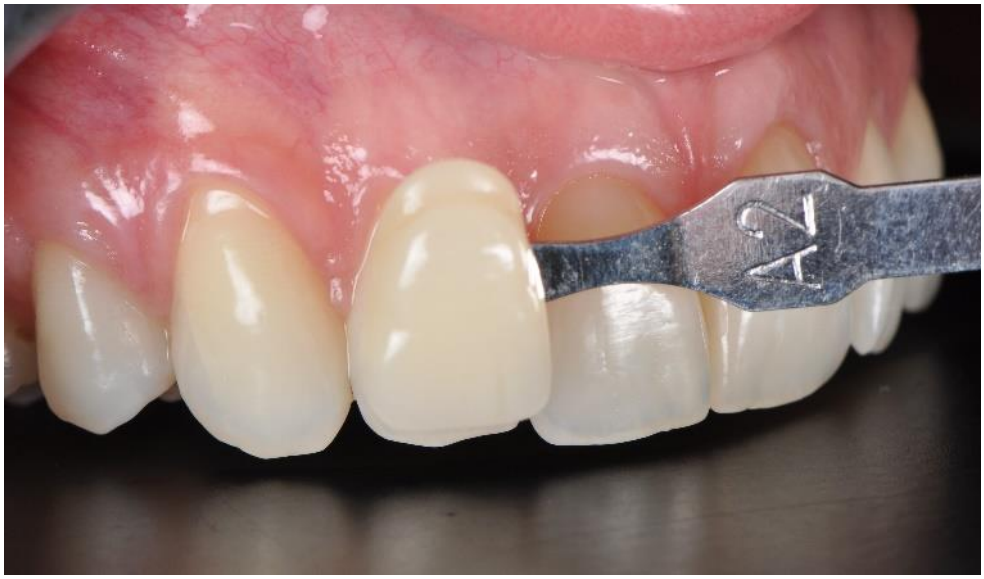
Figura 2 - Avaliação da cor inicial dos caninos superiores com a escala Vita Classical (Vita Zahnfabrik).



3.1.2 Protocolo experimental/intervenção

A randomização foi realizada no site www.sealedenvelope.com, por uma terceira pessoa, não envolvida nas etapas de implementação e avaliação dos pacientes. A distribuição do grupo a ser alocado foi registrada em cartões numerados sequencialmente e colocados em envelopes opacos e selados. As informações contidas no envelope determinaram o tratamento a ser atribuído nas hemi-arcadas do lado direito, enquanto os outras hemi-arcadas receberam o tratamento alternativo.

Foi preparado um gel dessensibilizante experimental contendo 10% de gluconato de cálcio, 0,1% de acetato de dexametasona, 10% de nitrato de potássio e 5% de glutaraldeído. Utilizando o propilenoglicol e hidroxietilcelulose como espessantes e o metilparabeno como conservante. O gel placebo foi composto pelos mesmos espessantes e conservantes sem os componentes ativos para manter a mesma viscosidade e aparência. Embora todas as tentativas tenham sido feitas para produzir um gel placebo semelhante ao gel experimental, o produto final apresentou transparência diferente, impossibilitando o cegamento do operador.

Após profilaxia dental, foi instalado o afastador labial (Arcflex, FGM) e aplicada a barreira gengival (Top Dam, FGM) nos dentes que receberiam o clareamento (segundo pré-molar esquerdo ao segundo pré-molar direito do

arco superior e inferior). A barreira gengival foi fotopolimerizada por 10 segundos (Radii Cal, SDI). Em seguida, o gel dessensibilizante experimental ou placebo foi aplicado topicamente na superfície vestibular dos dentes (Figura 3). Ele foi mantido por 10 min sem agitação (Figura 4) e após foi realizada uma aplicação ativa do gel por 10 s com microescova descartável (Figura 5) e então o gel foi removido com um sugador de saliva. Os dois arcos foram clareados com um gel de peróxido de hidrogênio a 35% (Whiteness HP AutoMixx, FGM) (Figura 6). O gel clareador foi mantido por 50 min e removido com sugador de saliva, gaze e enxágue com água. Foram realizadas duas sessões de clareamento em consultório com intervalo de 1 semana entre elas.

Figura 3 - Aplicação do gel dessensibilizante experimental ou gel dessensibilizante placebo previamente ao clareamento de consultório.

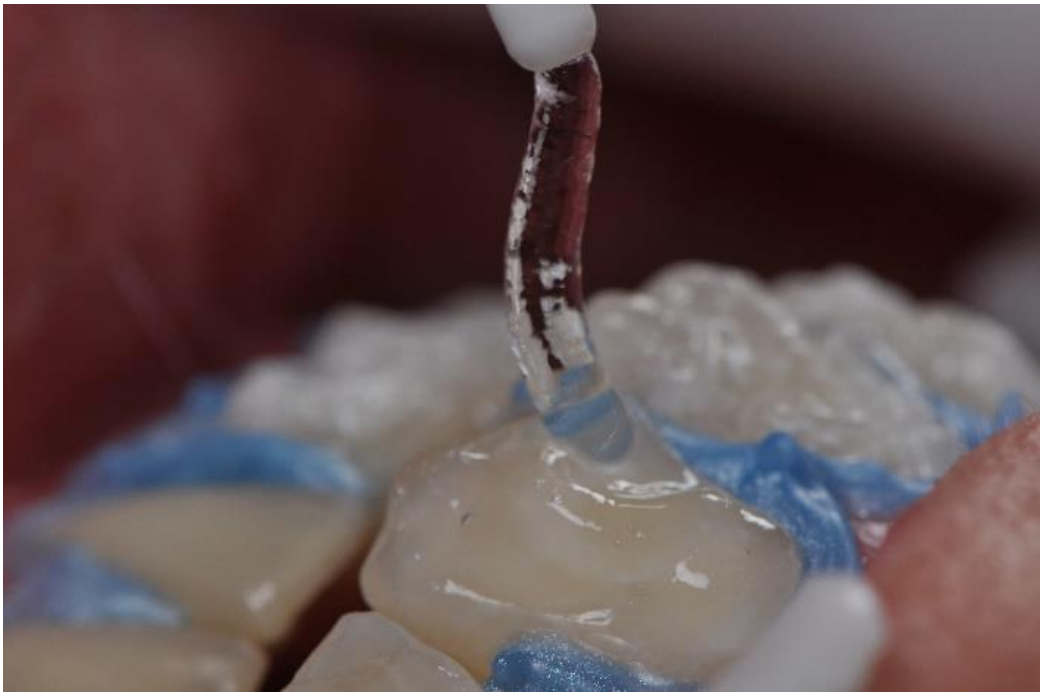


Figura 4 - Gel dessensibilizante experimental e gel dessensibilizante placebo na superfície vestibular do dente.

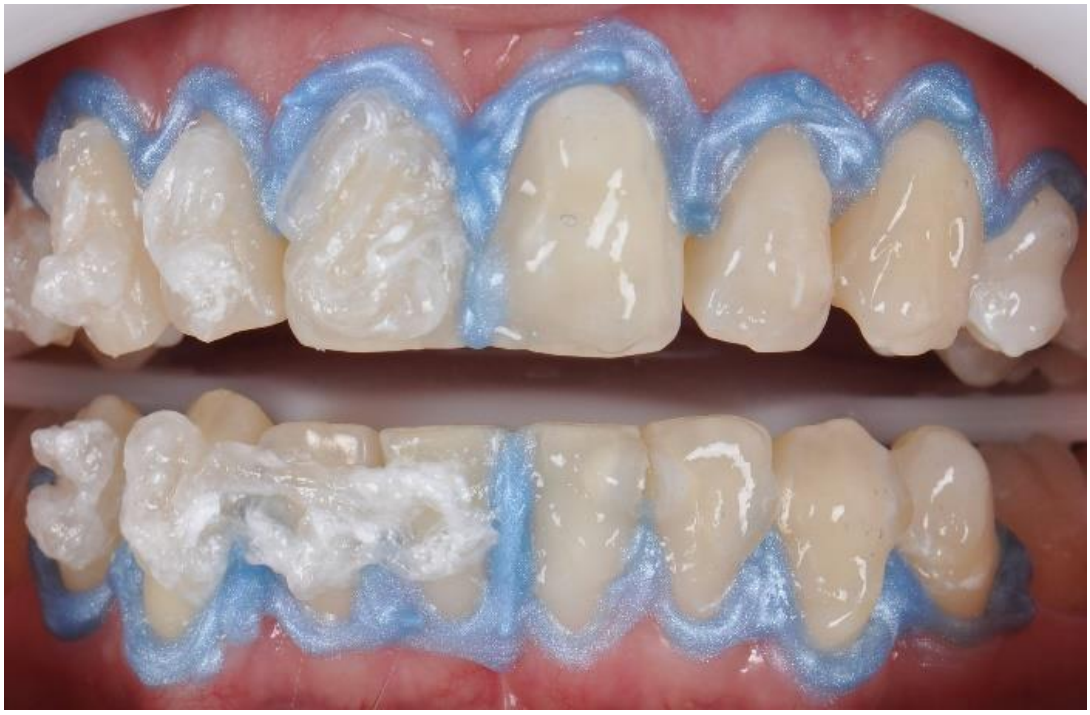


Figura 5 - Ativação do gel dessensibilizante experimental e gel dessensibilizante placebo com microescova descartável.

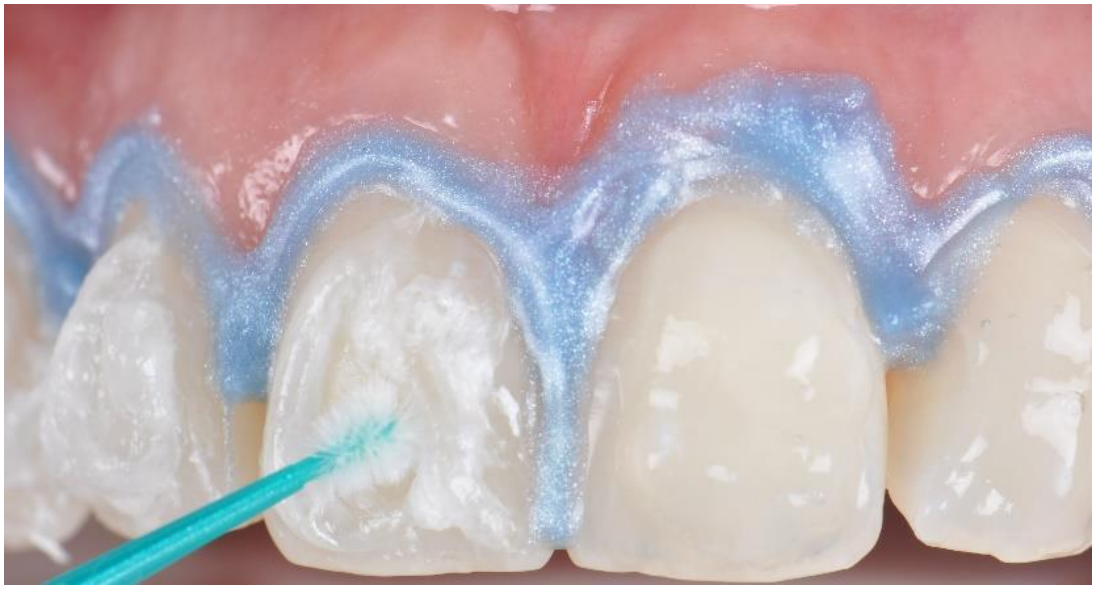
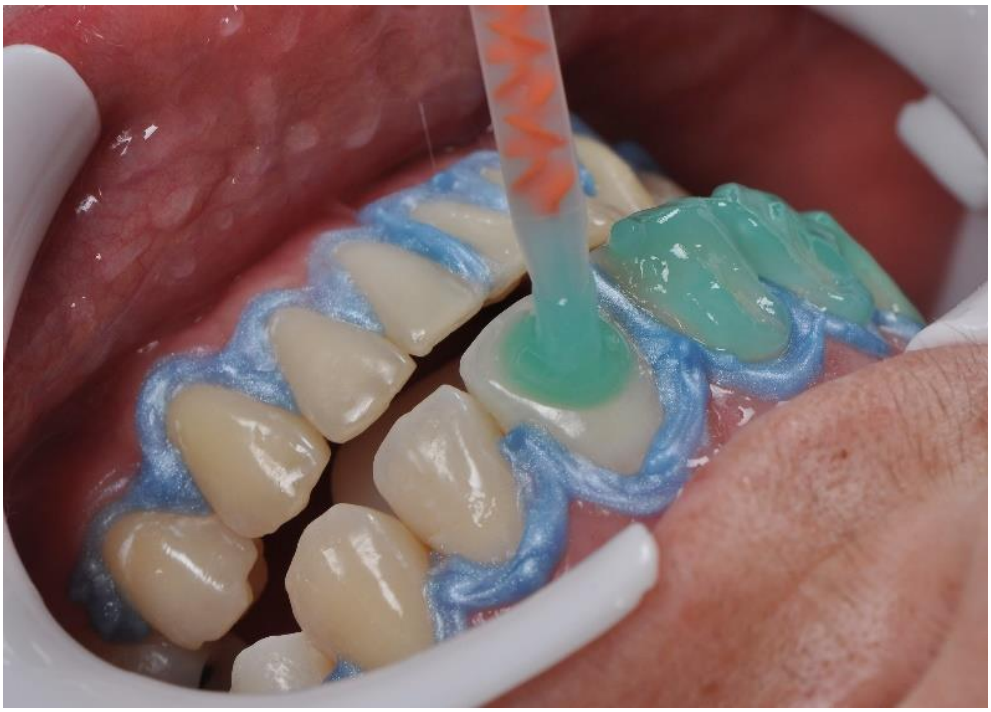
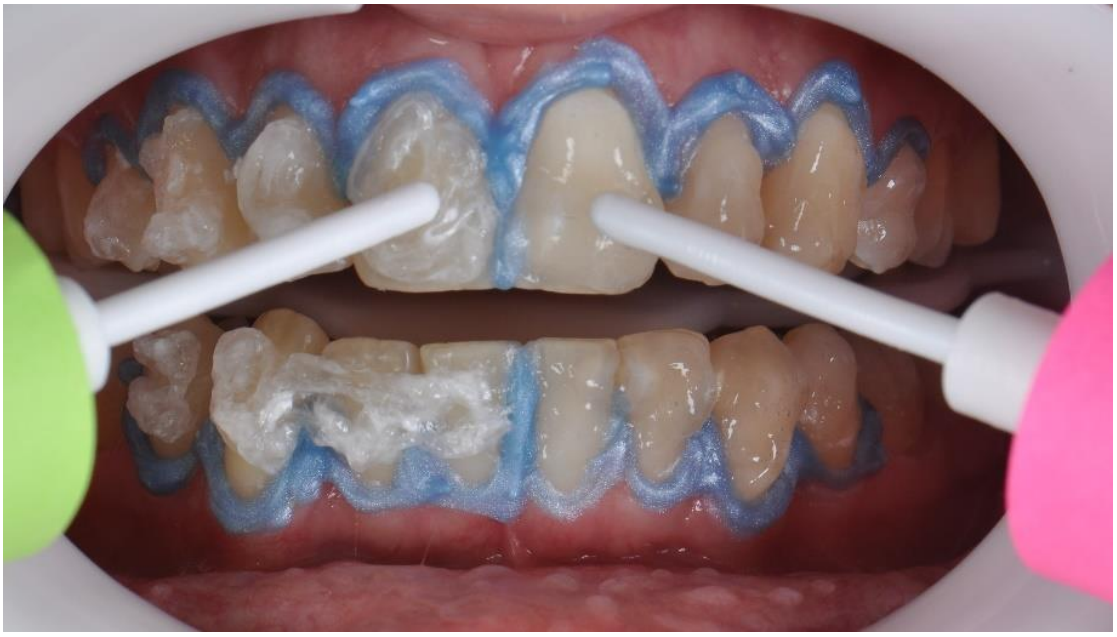


Figura 6 – Aplicação do gel de peróxido de hidrogênio 35% (Whiteness HP AutoMixx, FGM) na superfície vestibular dos dentes.



Um terceiro pesquisador, não envolvido no processo de implementação e na avaliação, foi o responsável pela randomização e entrega dos géis acondicionados em seringas específicas no momento da implementação, somente ele conhecia o sistema de codificação e sabia qual seringa correspondia ao gel experimental e ao gel placebo. Ambos foram entregues aos operadores em seringas brancas idênticas codificadas como A (seringa verde) e B (seringa rosa) (Figura 7), que seriam aplicadas antes do gel clareador. Ambos os géis tinham odor semelhantes.

Figura 7 - Gel dessensibilizante experimental e gel dessensibilizante placebo acondicionados em seringas brancas idênticas codificadas como A (seringa verde) e B (seringa rosa).



3.1.3 Avaliação da sensibilidade e cor

A SD foi avaliada imediatamente, 1 h, 24 h e 48 h após o clareamento em consultório. Os pacientes avaliaram em uma escala numérica de 5 pontos (NRS) (Anexo 5) de 0 a 4 na qual 0 = “nenhuma dor” e 4 indicando a “pior dor” e na escala visual analógica (VAS) (Anexo 6) de 0 a 10.

A cor foi avaliada em quatro períodos: anteriormente ao tratamento, após uma semana da 1ª e 2ª sessão e 30 dias após o término do tratamento. Para a análise subjetiva da cor foram utilizadas escalas de cor Vita Classical e Vita Bleachedguide (Vita Zahnfabrik) e para a análise objetiva, foi utilizado o Espectrofotômetro Vita Easyshade (Vita Zahnfabrik), de acordo com o sistema Vita e CIEL*a*b*. Dois cálculos diferentes foram realizados: 1) usando a fórmula tradicional CIELab* 1976 (ΔE76) (De L’eclairage[66] 1978) e 2) a fórmula CIEDE 2000 (ΔE00) (Luo et al.[67] 2001). Também calculamos o Índice de Clareamento para Odontologia (WID) (Pérez et al.[68] 2016).

3.1.4 Análise estatística

O estatístico estava cego para os grupos. Foi realizado tanto a análise de intenção de tratar quanto a análise por protocolo. Todos os participantes randomizados foram incorporados ao conjunto de dados na análise de intenção de tratar. Em contrapartida, na análise por protocolo, os pacientes que não realizaram as duas sessões de clareamento foram excluídos.

Os riscos absolutos de SD de ambos os grupos foram comparados pelo teste exato de McNemar ($\alpha = 0,05$, teste para proporção de razão de dados dependentes). Calculou-se o risco de odds e o intervalo de confiança (IC) de 95%.

Os pressupostos de distribuição normal (teste de Kolmogorov-Smirnov) e variância igual (teste de Barlett) dos conjuntos de dados contínuos foram inspecionados. Foi utilizado o teste de Wilcoxon para comparar a intensidade de SD na escala NRS e utilizado o teste t pareado para comparar os dados da escala VAS. A avaliação subjetiva da cor (ΔUEV) e a avaliação objetiva da cor (ΔEab, ΔE00 e ΔWID) foram comparadas com o teste t pareado. A diferença média e o IC de 95% também foram calculados como medidas de efeito para os resultados contínuos.

Foi calculada a correlação de Spearman entre os dados pareados do risco de SD e a correlação de Pearson entre os dados da intensidade de SD de ambos os grupos nas diferentes arcadas dentárias. A análise estatística foi realizada no software (SigmaPlot 14.0, Systat Software Inc. San Jose, CA, EUA) com nível de significância de 5%

3.1.5 Síntese dos resultados

A sensibilidade após o clareamento foi observada nos dois grupos, para as escalas VAS e NRS. A proporção de pacientes que apresentaram sensibilidade no lado em que o dessensibilizante experimental foi aplicado foi muito semelhante ao lado em que o dessensibilizante placebo foi aplicado, não havendo diferença estatisticamente significativa entre os grupos. O clareamento foi considerado eficaz em ambos os grupos de tratamento e nenhuma diferença significativa de mudança de cor foi observada entre eles.

3.2 ESTUDO 2

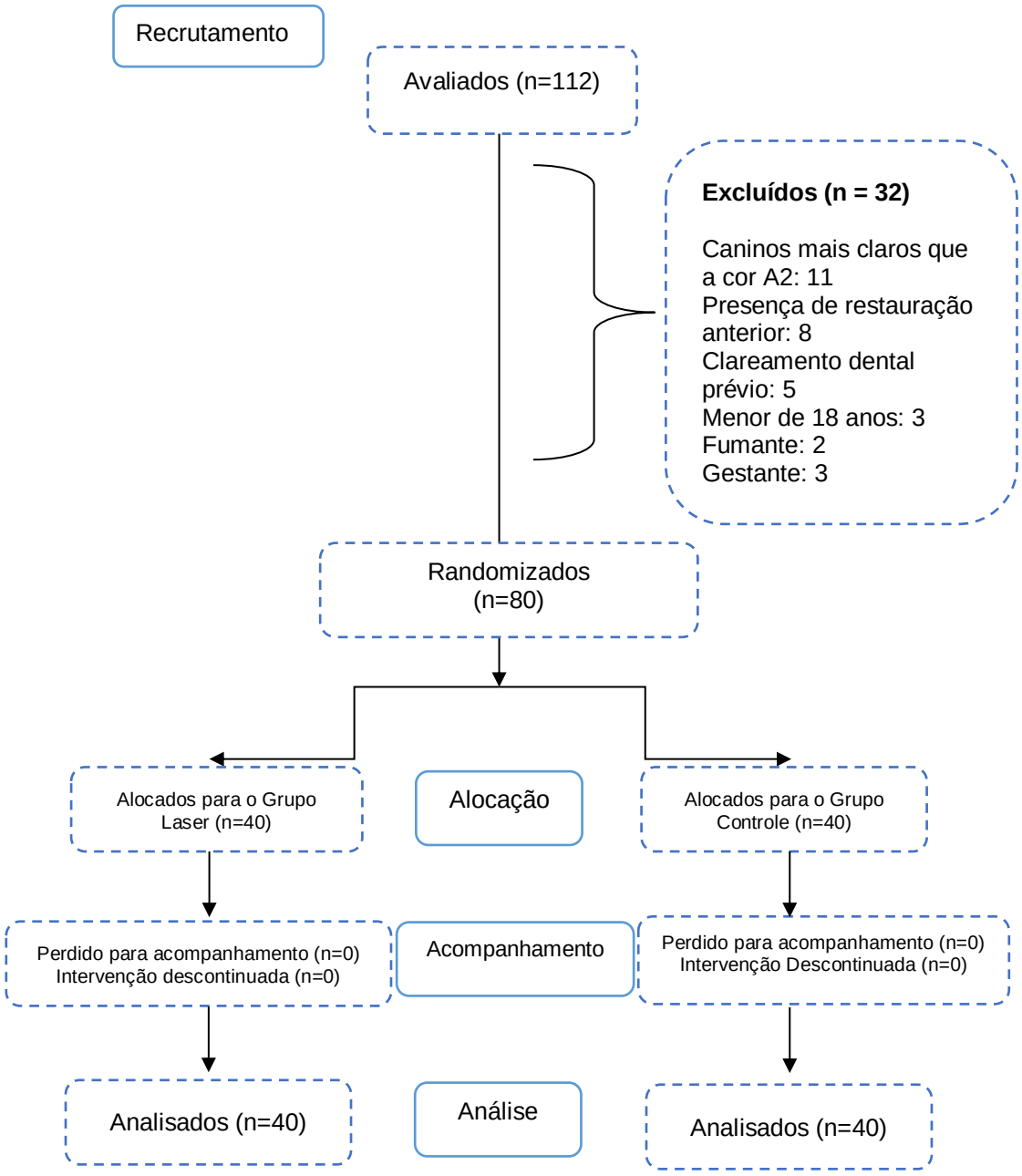
O projeto deste ensaio clínico randomizado, paralelo, duplo-cego foi aprovado pela Comissão de Ética em Pesquisa (COEP) (Anexo 2) da Universidade Estadual de Ponta Grossa (UEPG) através do parecer nº 3.056.864. O estudo foi registrado no site eletrônico http://www.ensaiosclinicos.gov.br/, sob o número de identificação RBR-4HCVSG.

A metodologia detalhada destes experimentos está descrita no ARTIGO 2.

3.2.1 Seleção dos pacientes

Oitenta voluntários que tiveram interesse em realizar o clareamento dental e que se enquadraram nos critérios de inclusão e exclusão do estudo foram selecionados (Figura 8). O canino superior direito deveria ser classificado como cor A2 ou mais escuro, de acordo com a escala Vita Classical (VITA Zahnfabrik, Bad Sackingen, Alemanha).

Figura 8 - Diagrama de fluxo das fases de desenho do estudo, incluindo critérios de exclusão e alocação para a análise do resultado primário.



3.2.2 Protocolo experimental/intervenção

Foi confeccionada uma guia com silicone de condensação (Profil Cub, Vigodent) envolvendo os incisivos, caninos e pré-molares superiores e inferiores dos lados direito e esquerdo (Figura 9) para a mensuração da cor com o espectrofotômetro Vita Easyshade (Vita Zahnfabrik, Bad Säckingen) e para a aplicação do *laser* de baixa potência (Laser Duo, MMOptics) (Figura 10). Em seguida foi obtido um orifício circular de 6 mm de diâmetro (Biopsy Punch, Miltex) no terço médio da coroa de cada dente envolvido (Figura 11). Esta guia é capaz de reduzir a quantidade de luz que pode ser vista pelo participante durante o procedimento. Além disso, todos os participantes foram orientados a utilizar fones de ouvido com uma *playlist* aleatória para que não ouvissem o som emitido pelo aparelho a *laser*. Esses procedimentos foram previamente testados em um grupo de 8 participantes, e se mostraram eficazes em reduzir a consciência do participante sobre a tarefa grupal a que se submeteram. Todos os participantes deste estudo clínico usaram óculos de proteção fornecido pelo fabricante durante as sessões de terapia a *laser*.

Figura 9 - Guia de silicone confeccionada para a avaliação de cor e para a aplicação do laser de baixa potência.

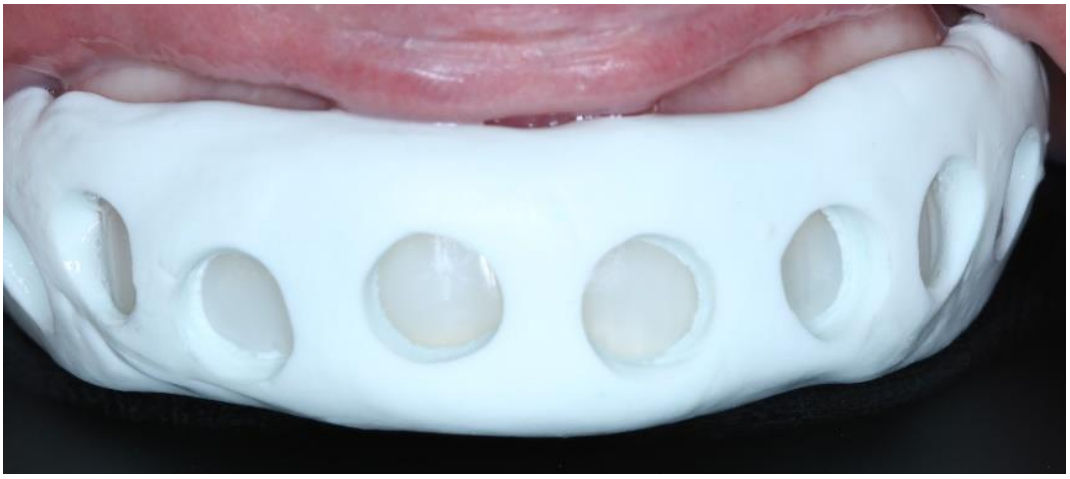


Figura 10 - Com a guia de silicone os pacientes não enxergavam a luz emitida pelo laser de baixa potência.

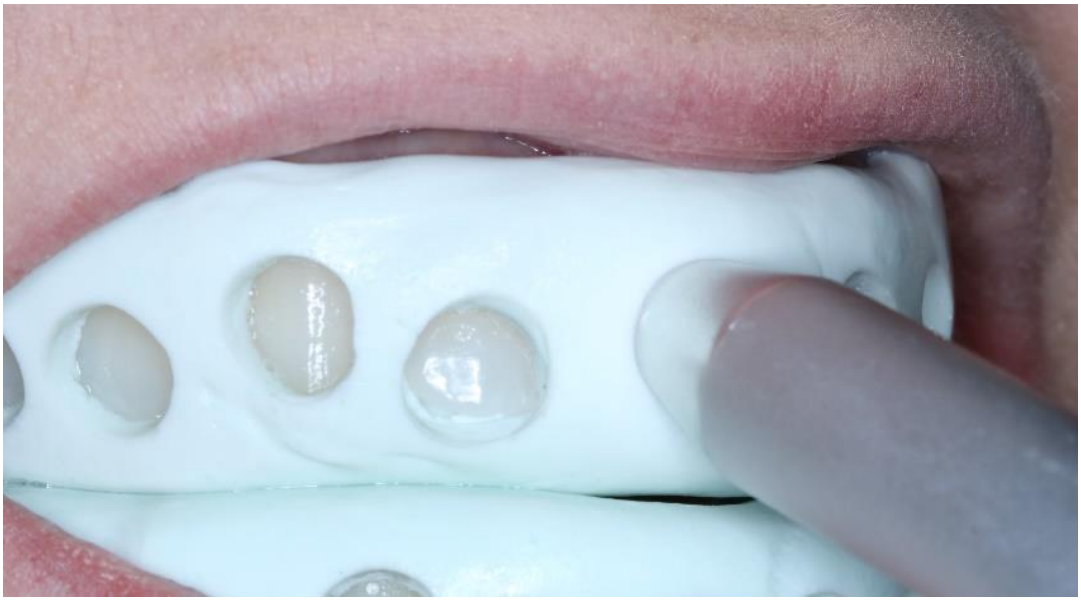


Figura 11 - Perfuração da guia de silicone com o bisturi circular de 6 mm de diâmetro.

Após profilaxia dental, foi instalado o afastador labial (ArcFlex, FGM) e aplicada a barreira gengival (Top Dam, FGM) nos dentes que receberiam o clareamento dental (segundo pré-molar esquerdo ao segundo pré-molar direito do arco superior e inferior). A barreira gengival foi fotopolimerizada por 10 min (Radii Cal, SDI). Em seguida, o gel de peróxido de hidrogênio 35% (Whiteness Automixx, FGM) foi aplicado e mantido por 50 min e removido com sugador de saliva, gaze e enxágue com água. Foram realizadas duas sessões de clareamento em consultório com intervalo de 1 semana entre elas.

Após cada sessão de clareamento em consultório, os pacientes do grupo *laser* (n = 40) foram submetidos a laserterapia de baixa potência com o *laser* infravermelho (Laser Duo, MMOptics, São Carlos, São Paulo, Brasil) (Figura 12). O dispositivo possui um meio semicondutor ativo de arsenato de gálio-alumínio (Ga-As-Al), emitindo um comprimento de onda de 808 nm. O *laser* operou a uma potência de 100 mW. A energia fornecida para cada dente foi de 3 J no terço médio por 30 s com densidade de energia de 100 J/cm^2. A região coronária submetida à irradiação foi padronizada com o auxílio da guia de silicone. Todos os procedimentos foram repetidos para o grupo controle (n = 40), mas o aparelho a *laser* foi mantido desligado.

Figura 12 - Aparelho Laser Duo MMOptics.

3.2.3 Avaliação de sensibilidade e cor

A SD foi avaliada imediatamente, 1 h, 24 h e 48 h após o clareamento em consultório. Os pacientes avaliaram em uma escala numérica de 5 pontos (NRS) (Anexo 5) de 0 a 4 na qual 0 = “nenhuma dor” e 4 indicando a “pior dor” e na escala visual analógica (VAS) (Anexo 6) de 0 a 10.

A cor foi avaliada em quatro períodos: anteriormente ao tratamento, após uma semana da 1ª e 2ª sessão e 30 dias após o término do tratamento. Para a análise subjetiva da cor foram utilizadas escalas de cor Vita Classical e Vita Bleachedguide (Vita Zahnfabrik) e para a análise objetiva, foi utilizado o Espectrofotômetro Vita Easyshade (Vita Zahnfabrik), de acordo com o sistema Vita e CIEL*a*b*. Dois cálculos diferentes foram realizados: 1) usando a fórmula tradicional CIELab* 1976 (ΔE76) (De L’eclairage[66] 1978) e 2) a fórmula CIEDE 2000 (ΔE00) (Luo et al.[67] 2001). Também calculamos o Índice de Clareamento para Odontologia (WID) (Pérez et al.[68] 2016).

3.2.4 Análise estatística

A análise seguiu o protocolo de intenção de tratar e envolveu todos os participantes divididos aleatoriamente. O estatístico também estava cego para os grupos.

Os riscos de SD de ambos os grupos foram comparados usando o teste exato de Fisher. O risco relativo e o intervalo de confiança (IC) de 95% também foram calculados. A intensidade de SD de ambos os grupos na escala de dor

NRS foi comparada usando o teste de Mann-Whitney e na escala VAS foi avaliada com o teste t para amostras independentes. A eficácia do clareamento, com dados de avaliação subjetiva da cor (ΔUEV) e avaliação objetiva da cor (ΔEab, ΔE00 e ΔWID), foi avaliada com o teste t para amostras independentes. A diferença média e o IC de 95% também foram calculados. Em todos os testes estatísticos, o nível de significância foi de 5%.

3.2.5 Síntese dos resultados

A sensibilidade após o clareamento foi observada nos dois grupos, para as escalas VAS e NRS. A proporção de pacientes que apresentaram sensibilidade no grupo experimental foi muito semelhante ao grupo controle, não havendo diferença estatisticamente significativa entre os grupos. O clareamento foi considerado eficaz em ambos os grupos de tratamento e nenhuma diferença significativa de mudança de cor foi observada entre eles.

4 ARTIGOS

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

4.2 Effect of low-power laser for reduction of bleaching-induced tooth sensitivity after in-office bleaching

4.1 ARTIGO 1

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

STATUS: Aceito.

REVISTA: Clinical Oral Investigations.

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

L. Vochikovski, M. Rezende, R.O. Terra, K. L. da Silva, M. Favoreto, P. V. Farago, A. D. Loguercio, A. Reis.

Abstract

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

Methods: In a split-mouth, double-blind, placebo-controlled study, 50 participants with canines that were color A2 or darker had their upper hemiarches randomized into experimental and placebo groups. Desensitizing and placebo gels were applied for 10 min before in-office bleaching (35% hydrogen peroxide, 1x50 min; two bleaching sessions; one-week interval). TS was recorded immediately after bleaching, 1, 24, and 48 h after each session, with a 0-10 visual analogue scale (VAS) and a five-point numerical rating scale (NRS). The color was recorded at baseline, one week after each session, and one month after the end of bleaching using shade guide units (ΔSGUs) and a spectrophotometer (ΔEab, ΔE00, and ΔWID).

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

Conclusion: The desensitizing experimental gel applied before in-office bleaching did not reduce the risk and the intensity of tooth sensitivity and did not affect color change.

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

Keywords: Tooth Bleaching. Dentin Sensitivity. Dentin Desensitizing Agents. Hydrogen Peroxide.

Introduction

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

Unlike at-home bleaching, in-office bleaching requires the use of high concentrations of hydrogen peroxide (HP).[5, 6] However, the same HP that whitens teeth by oxidizing the dental structure's organic component can also quickly diffuse into the pulp chamber.[7] This can trigger an inflammatory process[8] with the release of several inflammatory chemical mediators.[9, 10] This process modifies the local microcirculation, generating pressure over the peripheral nerve fibers and activating nociceptors. Most patients experience bleaching-induced tooth sensitivity (TS) as a clinical consequence. This pain is characterized as acute and transient pain, with patients commonly reporting it within the first 24 hours after in-office dental bleaching.[11]

The preventive effect of analgesics and opioids,[12, 13] anti-inflammatories,[14-16] antioxidants,[17] and corticosteroids[18-20] has previously been investigated, and they could not mitigate bleaching-induced TS.[21] So far, the most successful approach to reducing TS has been the topical application of desensitizers, such as those containing glutaraldehyde,[22, 23] potassium nitrate,[24, 25] and calcium agents.[26, 27]

These topical agents' mechanisms of action are different. Potassium nitrate prevents the repolarization of nerve fibers blocking the transmission of painful stimuli.[24, 25, 28] Meanwhile, glutaraldehyde was reported to coagulate proteins from enamel and dentinal tubules, reducing the easy passage of HP to the pulp.[23, 29, 30] Calcium-containing agents can also reduce the risk and intensity of TS mainly through the saturation of components on the enamel surface.[31]

When calcium-containing products are applied, they interact with the dental surface.[31] They can be retained on the teeth, thus providing large amounts of calcium and phosphates for tissue interaction, which may reduce the passage of HP to the pulp.[26, 27, 31-34] Another possible agent is dexamethasone; this drug has already been tested orally[18, 19] but has not yet been investigated in topical form. This drug has primarily been used in dentistry via the oral route for oral surgeries[35-37] and endodontic treatments[38, 39] due to its potent anti-inflammatory effects. However, its relatively lower molar mass (392 g/mol^{-1}) suggests that it can penetrate enamel and dentin as well.

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

Material and methods

Ethics approval and protocol registration

This clinical investigation received approval (protocol 3.893.891) from the Ethics Committee of the local university. This study was registered in the Clinical Trials Registry under “7T7D4D.” The preparation of this article followed the protocol established via the Consolidated Standards of Reporting Trials statement with extension for within-person designs.[40]

Trial design, settings, and location of data collection

This study was a randomized, split-mouth, placebo-controlled, and double-blind controlled trial (RCT). This study was performed from November 2019 to January 2020 in the clinics of the school of dentistry at the local university.

Recruitment

Recruitment was performed by placing written advertisements on the university walls and using social media to obtain a convenient sample. The

volunteers were informed about the study's objectives, and they all signed an informed consent form before being enrolled in the study.

Eligibility criteria

Participants included in this RCT were at least 18 years old, had good general and oral health, and did not report any type of TS. The participants were required to have six caries-free maxillary anterior teeth without restorations and periodontal disease. The canines had to be shade A2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical, Vita Zahnfabrik). Participants with anterior restorations, dental prostheses, orthodontic apparatuses, and severe internal tooth discoloration (tetracycline stains, fluorosis, and pulpless teeth) were not included. In addition, pregnant or lactating women, smokers, participants who had bruxism and had undergone tooth bleaching procedures, and any other condition that could cause sensitivity (such as recession, dentin exposure, or the presence of visible cracks in the teeth) were also excluded.

Sample size estimation

This study's primary outcome was the absolute risk of TS. The absolute risk of TS was reported to be approximately 93% for the bleaching product Whiteness Automixx (FGM).[13] For detecting an absolute risk difference of 25% between the control and experimental groups, a minimum sample size of 40 patients with a power of 80% and an alpha of 5% was required. Due to the high cost of the search for study participants, we included 50 participants.

Randomization

We performed blocked randomization (block sizes of 2 and 4) to guarantee equalsized groups with an equal allocation ratio at www.sealedenvelope.com. A third party not involved in the study implementation prepared consecutively numbered, opaque, and sealed envelopes containing information identifying the groups. The group identified in the envelope corresponded to the treatment performed on the right upper hemiarch, and the left hemiarch received the alternate treatment.

Blinding

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

Study intervention

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

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

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

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

Evaluation of tooth sensitivity (TS)

Participants had to record their pain intensity in the following time intervals: (1) during the treatment; (2) up to 1 h after each bleaching session; (3) between 1 and 24 h after each bleaching session; and (4) between 24 and 48 h. After both bleaching sessions, these measurements were performed using the five-point numerical rating scale (NRS; 0=none, 1=mild, 2=moderate, 3=considerable, and 4=severe)[41, 42] and 0-10 visual analog scale (VAS).[20, 25] The VAS scale is a 10-cm horizontal line with scores of zero and 10 at their ends, in which zero means no sensitivity and 10 means severe tooth sensitivity. The patient had to mark with a vertical line across the horizontal line of the scale the intensity of the TS. Then, the distance in millimeters from the zero end was measured with the aid of a millimeter ruler.

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

Color change

Two calibrated operators performed color evaluation before the bleaching session, one week after the first bleaching session, one week after the second treatment, and one month after the bleaching treatment. The color evaluation was never performed immediately after each bleaching session so that the effect of dehydration and demineralization on color measures could be avoided. The color evaluation was performed with the value-oriented shade guide Vita Classical (Vita Zahnfabrik) and the Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik).

In addition, an objective color evaluation was performed with the spectrophotometer Vita Easyshade (Vita Zahnfabrik). The 16 shade guide tabs from the Vita Classical shade guide were arranged from the highest (B_1) to the lowest (C_4) value for the subjective examination. Although this scale is not linear

in the truest sense, we treated the changes as representing a continuous and approximately linear ranking for analysis as already performed in published studies.[20, 23, 25, 41] The Vita Bleachedguide 3D-MASTER contains lighter shade tabs and is organized from the highest (0M1) to the lowest (5M3) value.

The middle third of the right upper canine was used as the tooth-matching area. Color changes were calculated from the beginning of the active phase up to the individual recall times by calculating the difference in the number of shade guide units (ΔSGUs), which occurred toward the lighter end of the value-oriented list of shade tabs. In the event of disagreement between the operators, the operators had to reach a consensus before the patient was dismissed.

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

The objective color change was measured after the CIELab parameters of L* (luminosity), a* (green to red axis), and b* (blue to yellow axis) were obtained from the spectrophotometer. The difference between the baseline and 30 days after the end of the bleaching treatment was computed using the following CIELab formula[43]: $\Delta Eab = [(\Delta L^*)^2+(\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$. In addition, the color change was also calculated based on the CIEDE 2000 formula[44]: $\Delta E00 = [(\Delta L /kLSL)^2 + (\Delta C/ kCSC)^2 + (\Delta H/kHSH)^2 + RT (\Delta C^*\Delta H/SC^*SH)]^{1/2}$ and Whiteness Index[45]: $\Delta WID = (0.511L^*) - (2.3424a^*) - (1.100b^*)$.

Statistical analysis

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

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

The assumptions of the normal distribution (Kolmogorov–Smirnov test) and equal variance (Barlett's test) of the continuous data sets were inspected. We used the Wilcoxon signed-rank test to compare the TS intensity in the NRS scale, and we used the paired t-test to compare data from the VAS scale. The subjective color assessment (ΔSGUs) and objective color assessment (ΔEab, ΔE00, and ΔWID) were compared with a paired t-test. The mean difference and 95% CI were also calculated as the effect measures for the continuous outcomes.

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

Results

Of the 50 participants, two did not return to recall evaluations after the first bleaching session, whereas five did not return after the second session. For the analysis of color change (intention-to-treat analysis), missing data from the color change were imputed using the last-outcome-carried-forward (LOCF) approach. These seven patients were excluded from the data set in the per-protocol analysis. Both analyses yielded similar conclusions, and we presented data from the per-protocol analysis. The intention-to-treat analysis can be seen in Supplementary Table 1.

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

These seven participants returned to their home cities and reportedly lost interest in doing the bleaching protocol. The final color measurement was

planned to be collected 30 days after bleaching. However, because the end of the present study was coincident with the rise of the COVID 19 pandemic, 23 patients had their final color changes evaluated within 2 to 6 months. Demographic features of the participants Fifty-nine participants were examined, and a total of 50 participants were included in the clinical study (Figure 1). The baseline color of canines in the Vita Classical shade guide units was very similar for both groups (experimental gel: 9.7 ± 2.8; placebo: 9.8 ± 2.8). The participants were predominantly young adults with a mean age of 23.4 ± 7.5 years. Most participants were female (60.5%).

Risk of tooth sensitivity

The majority of the participants (96%) felt some discomfort during treatment. Forty-five participants reported pain on the experimental arch side, and all of them also reported pain on the placebo hemiarch side. Two participants did not report pain on either hemiarch side. In relative terms, the odds ratio for pain was 0.65 (0.1 to 4.1; p = 1.0; Table 2). The Spearman correlation coefficient for the pairs of binary data was strong and significant (r = 0.80; p-value < 0.001).

Intensity of tooth sensitivity (TS)

The statistical analysis did not show any significant difference in the intensity of TS between the groups for any of the pain scales (p = 0.77 for NRS, and p = 0.25 for VAS; Table 3). The mean difference of the pain intensity on the VAS scale was, on average, 0.35 units lower, which is unlikely to be clinically important. The pain was positively correlated in both groups (Table 3). The correlation was strong and significant for both pain scales.

For the NRS, the Spearman correlation was 0.76 (p < 0.001), and for the VAS, the Pearson correlation was 0.77 (p < 0.001).

Color evaluation

A significant color change occurred in all groups after bleaching, which was approximately, and on average, five units on the Vita Classical scale, five units on the Vita Bleachedguide, 15 units on the ΔEab, nine units on the ΔE00, and nine units on the ΔWID (Table 4). No significant difference in color change was observed between the groups (Table 4; p > 0.32).

Discussion

The conducting of this clinical trial was met with some challenges in the final phase of the data collection. The color change analysis performed 30 days after bleaching coincided with the emergent COVID-19 pandemic, which prevented us from evaluating the last color change in this specific time assessment period. Thus, the final color assessment had to be done 2 to 6 months after bleaching for some patients. Still, it is unlikely to have introduced bias because the comparison of the immediate results (approximately 30 days after bleaching) and those obtained 3 to 12 months after bleaching did not report any statistical and clinical differences between these assessment periods.[46-50]

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

Contrary to our expectations, the experimental desensitizing gel did not cause any reduction of the risk and intensity of TS. Although the exact mechanism of bleaching-induced TS has not yet been explained, it is likely due to the damage that HP causes to living tissues from pulp tissue. In the case of injury, an acute inflammatory response begins to remove damaged tissue components to allow the body to begin the healing process. Due to increased blood flow, blood vessels dilate and eventually increase their permeability, thus allowing fluid, proteins, and white blood cells to migrate from the circulation to the site of the tissue damage.

A study[51] found a higher density of macrophages, collagen degradation, and infiltrate inflammatory in the pulps that underwent in-office bleaching with 38% HP.[51] Macrophages are involved in the degradation of the extracellular

matrix, the recruitment of leukocytes and pro-inflammatory cytokines, neovascularization, and fibroblast proliferation, among others.[52, 53]

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

It was already demonstrated that HP could reach the pulp tissue 15 min after being applied on the buccal enamel.[54, 55] This may occur because HP is a small molecule with a molecular mass of 35.01 g/mol^{-1}. The molecular mass of calcium gluconate (430.37 g/mol^{-1}), dexamethasone acetate (392 g/mol^{-1}), potassium nitrate (101.10 g/mol^{-1}), and glutaraldehyde (100.11 g/mol^{-1}) are higher than that of HP. They, therefore, may take longer to reach the pulp.

However, earlier clinical trials showed the beneficial effects of the desensitizing agents included in the experimental gel when used alone.[22, 23, 26, 27, 56] Most of these RCTs used low sample sizes (low study power) and a parallel design that did not control for intra-individual variability. The high correlation of the risk and TS intensity values between the dental hemiarches suggests that the split-mouth design can reduce the sample size while keeping the study power high enough to detect clinically meaningful differences.

When a total of 16 studies evaluating potassium-nitrate desensitizers were collected in a systematic review of the literature,[24] a significant and positive effect in favor of the potassium nitrate was observed. Still, this effect was subtle and not clinically significant. Similarly, a recent RCT that evaluated the impact of the topical application of a corticoid-containing product did not find any significant reduction in the risk and intensity of TS.[13, 20]

Altogether, this means that it is unlikely that the topical application of desensitizers can minimize bleaching-induced TS. More recently,[32] another RCT showed promising results by associating topical bioactive desensitizers

with intraoral drug prescription (acetaminophen/codeine),[32] but further studies should confirm these findings.

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

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

An objective evaluation is less clinically tangible but allows for the collection of more information. Using the same parameters of L*, a*, and b* parameters, we could calculate color change using the conventional CIELab 76 system (ΔE_{ab}), the CIEDE2000 system (ΔE_{00}), and the Whiteness Index for Dentistry (ΔWI_D).[43, 44 45] The CIEDE2000 system has been more recently employed, as it better estimates the visual perception of color.[57] The Whiteness Index provided more information on the direction of the bleaching effect[45] and has been added to recent RCTs about bleaching. [20, 46, 50, 58]

To translate the ΔE values to the clinical scenario, clinicians should compare them with the 50:50 perceptibility (PT) and 50:50 acceptability (AT) thresholds.[59] The PT value is the minimal color difference that human eyes can distinguish. On the other hand, the AT value is more comprehensive, representing an existing difference acceptable for most people. The 50:50 PT and AT values for ΔEab were reported to be 1.2 and 2.7, respectively,59 whereas for ΔE00, the values were 0.8 and 1.8, respectively.[59] By looking at Table 3, one can see that the difference in the means between the study groups did not reach these thresholds, so they are clinically unimportant. On the other hand, these thresholds were exceeded in all of the time assessment periods, which is evidence of effective whitening.

Conclusions

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

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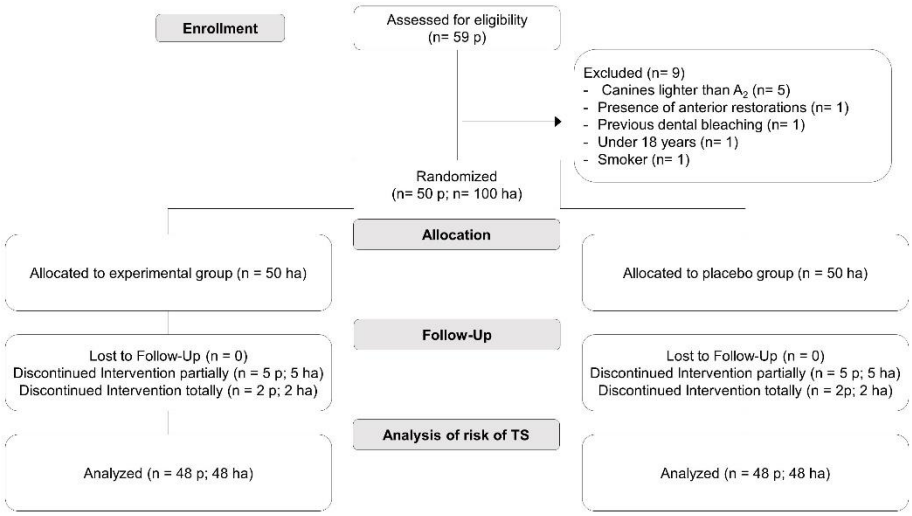

Fgure 1 - Flow diagram of study design phases, including enrollment and allocation criteria for the analysis of the primary outcome. Abbreviations: p – participants; ha – hemiarches.

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

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

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

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

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

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

Table 3. Means and standard deviations of ΔSGU (Classical and Bleachedguide), ΔE_{ab}, ΔE_{00}, and ΔWI_D between baseline vs. 30 days for both groups along with the mean difference (95% CI) in the per protocol analysis* (n = 43 hemi arches).

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

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

4.2 ARTIGO 2

TÍTULO: Effect of low-level laser therapy for reduction of bleaching-induced tooth sensitivity after in-office bleaching: A double-blind, randomized controlled trial.

STATUS: Aceito.

REVISTA: Lasers in Medical Science.

Effect of low-level laser therapy for reduction of bleaching-induced tooth sensitivity after in-office bleaching: A double-blind, randomized controlled trial

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Abstract

Objectives: To evaluate infrared low-level laser therapy (LLLT) to reduce bleaching-induced tooth sensitivity (TS) after in-office bleaching.

Methods: Eighty-three participants were randomized in blocks into two groups. In the experimental group, the patients received an LLLT application after each session of in-office bleaching (35% hydrogen peroxide, 1 x 50 min; 2 sessions with 1-week interval), while the laser application was simulated in the control group. The infrared LLLT system was operated in continuous mode, using 3 J of energy. A dose of 100 J/cm^2 was applied for 30 s with 808 nm infrared light (100 mW of power) in the middle third of the crown. The risk and intensity of TS were recorded immediately after bleaching, 1 h, 24 h, and 48 h after each dental bleaching session with a Visual Scale Analog (0-10) and five-point Numerical Scale (0-4). The color was recorded at the beginning, one week after each session, and one month after the end of the bleaching (VITA Classical, VITA Bleachedguide, and digital spectrophotometer).

Results: The risk of TS was 98% (95% CI 88 to 99%) for the laser group (n = 43) and 95% (95% CI 83to 99%) for the control (n = 40; RR = 1.03; 95% CI 0.94 to 1.12; p = 1.0). Similarly, no difference in the intensity of TS was detected for both pain scales (p > 0.65). Improvement in color change, regardless of the group, was observed (p > 0.15).

Conclusion: The application of an infrared LLLT did not reduce the risk and intensity of TS when applied after the procedure using the parameters recommended by the manufacturer.

Clinical Relevance: No relevant evidence was obtained in the study to recommend the application of an infrared LLLT after in-office bleaching to reduce the risk or intensity of bleaching-induced TS.

Clinical trials registry: RBR-4HCVSG

Keywords: Tooth Bleaching. Dentin Sensitivity. Low-Level Light Therapy.

Introduction

Dental bleaching is an effective cosmetic treatment that can increase patients' satisfaction with their smiles [1-3]. However, tooth sensitivity (TS) is the most common reported adverse effect, affecting 49 to 100% of the patients submitted to the in-office protocol [4-6]. The TS starts during bleaching and usually takes up to 24 h after the procedure [7].

Hydrogen peroxide (HP) and its free radicals can oxidize the organic component of the dental structure, producing a whitening effect [8]. However, these agents are not limited to hard dental tissues. Due to low molecular weight (34.01 g/mol^{-1}), HP can diffuse through enamel and dentin and penetrate the pulp tissue [9, 10]. An inflammatory reaction, thus, takes place in the pulp tissue [11-13], resulting in an unpleasant but transient bleaching-induced TS [14]. To minimize this side effect, authors have investigated the preventive administration of oral analgesics [15, 16], anti-inflammatories [15-23], and antioxidants [24]. Still, they failed to minimize either the risk or the intensity of TS, as shown in a systematic review on this topic [25].

Low-level laser therapy (LLLT) describes red and infrared laser (coherent, monochromatic, polarized light) at an intensity that stimulates biological processes [26]. LLLT was already used in several fields of dentistry to regenerate damaged tissues [26], promote analgesia, and reduce tissue inflammation [27-29]. Some studies showed LLLT was effective for neural regeneration for paresthesia [30, 31], control of postherpetic neuralgia [32], postoperative pain after retained third molar extraction [33-36], and for symptom relief from temporomandibular disorders [37, 38]. It is reported that cell respiratory chain components can absorb the visible red and near-infrared laser wavelengths, increasing cellular metabolism [28, 39, 40]. Consequently, analgesic, anti-inflammatory, and biomodulatory effects are expected to occur, thus helping tissue repair processes [26, 28].

LLLT, recently described as photobiomodulation, can be presented as an alternative to reduce bleaching-induced TS [41]. However, there is still a reduced number of randomized controlled trials (RCTs) evaluating this protocol [42-48]. Due to many variations in the laser parameters, commercial brands, techniques, and application areas, the effect of infrared LLLT on bleaching-induced TS deserves a more comprehensive investigation. Additionally, as pointed out in a recent systematic review of literature [49], some studies did not evaluate the sole efficacy of infrared LLLT because the procedure was associated with other desensitizing protocols such as potassium nitrate [44], fluoride dentifrice [46], strontium chloride [47], and additional energy sources [48].

Therefore, this parallel, double-blind RCT aimed to investigate whether the use of infrared LLLT, following the manufacturer's recommendations, could reduce the risk and intensity of TS in patients submitted to in-office bleaching. The impact of this protocol on the color change was also evaluated.

Methods

Ethics approval and protocol registration

This clinical investigation received approval (protocol 3.056.864) from the Ethics Committee of the State University of Ponta Grossa). This study was registered in the Brazilian Clinical Trials Registry under RBR-4HCVSG. The preparation of this article followed the protocol described in the Consolidated Standards of Reporting Trials statement for parallel designs [50].

Trial design, settings, and locations of data collection

This study was a parallel, double-blind RCT. This study was performed from November 2019 to January 2020 in the clinics of the School of Dentistry at the State University of Ponta Grossa, Paraná.

Recruitment

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

Eligibility Criteria

The participants included in this RCT were at least 18 years old, had good general and oral health, and did not report any type of TS. The participants were required to have all six maxillary anterior teeth free of caries, restorations, and periodontal disease. The canines had to be shade A_2 or darker as judged by comparison with a value-oriented shade guide (Vita Classical, Vita Zahnfabrik). Participants with anterior restorations, dental prostheses, orthodontic apparatuses, and severe internal tooth discoloration (tetracycline stains, fluorosis, and pulpless teeth) were not included. In addition, pregnant or lactating women, smokers, participants who had bruxism and had undergone tooth-bleaching procedures, and any other condition that could cause sensitivity (such as recession, dentin exposure, or visible enamel cracks) were also excluded.

Sample Size Estimation

This study's primary outcome was the absolute risk of TS. The absolute risk of TS was reported to be approximately 90% for the bleaching product Whiteness Automixx 35% (FGM Dental Group, Joinville, SC, Brazil) [6]. For detecting an absolute risk difference of 25% between the control and experimental groups, a minimum sample size of 80 patients (power of 80%, alpha of 5%) was required.

Randomization

We performed blocked randomization (block sizes of 2, 4, and 6) using the website www.sealedenvelope.com. A third researcher not involved in the study implementation prepared consecutively numbered, opaque, and sealed envelopes containing information identifying the groups. Allocation concealment

was guaranteed by only opening the envelope when the eligible patient was ready in the dental office for the treatment implementation.

Blinding

To guarantee participants' blinding, we should prevent them from seeing the light and hearing the laser device's sound. We made an impression with condensation silicone (Cub Kit Perfil, Vigodent Coltene, Alstatten, Switzerland) that involved the upper and lower incisors, canines, and premolars from both arches' sides. Thus, we drilled a circular hole of 6 mm in diameter (Biopsy Punch, Miltex Instruments, USA) in the middle third of each involved tooth. The construction of this guide was able to reduce the amount of light that the participant could see during the procedure. In addition, all participants wore headphones with a playlist to prevent them from hearing the sound emitted by the laser device. These procedures were previously tested on a group of 8 participants, and it was shown to be effective in reducing the participant's awareness of the group assignment they underwent. All participants in this clinical study wore protective goggles provided by the manufacturer during laser therapy sessions. Operators were not blinded because they needed to activate the laser when necessary. However, the evaluators were blinded to the group allocation.

Study intervention

All participants underwent a prophylaxis and oral hygiene guidance procedure before the bleaching procedure. Three operators with more than 3 years of clinical experience performing the bleaching procedures. After placement of a lip retractor (ArcFlex, FGM Dental Group, Joinville, SC, Brazil) and protection of the gingival tissue with a light-cured resin dam (Top Dam, FGM Dental Group, Joinville, SC, Brazil), the 35% HP gel (Whiteness Automixx, FGM Dental Group, Joinville, SC, Brazil) was applied in a single 50-minute application for both groups. At the end of the recommended time, the bleaching gel was removed with a disposable surgical saliva ejector, cleaned with gauze, and washed with an air-water spray. Two bleaching sessions were performed at a

1-week interval. All participants were instructed to brush their teeth regularly with fluoridated toothpaste.

After each bleaching in-office session, the laser group (n = 43) underwent infrared LLLT (Laser Duo, MMOptics, São Carlos, SP, Brazil). The device is a laser with an active semiconductor medium of gallium-aluminum arsenate (Ga-As-Al), emitting a wavelength of 808 nm. The laser was operated at a power of 100 mW. The energy supplied for each tooth was 3 J, and we applied it in the middle third of the crown for 30 s with an energy density of 100 J/cm^2. The region for laser irradiation was standardized with the aid of the silicone guide. All procedures were repeated for the control group (n = 40), but the laser device was positioned but kept turned off.

Outcomes

Evaluation of Tooth Sensitivity

Participants had to record their pain intensity in the following time intervals: (1) during the treatment; (2) up to 1 h after each bleaching session; (3) between 1 and 24 h after each bleaching session; and (4) between 24 and 48 h. After both bleaching sessions, the measurements were performed using the five-point numerical rating scale (NRS; 0=none, 1=mild, 2=moderate, 3=considerable, and 4=severe) [5, 6, 15, 19, 22-24], and a 0-10 visual analog scale (VAS) [5, 6, 15, 19, 22-24]. The VAS scale is a 10-cm horizontal line with scores of zero and 10 at their ends, in which zero means no sensitivity and 10 means severe TS. The patient had to mark the TS intensity with a vertical line across the scale's horizontal line. Then, the distance in millimeters from the zero end was measured with the aid of a millimeter ruler.

The worst score (NRS) or numerical value (VAS) obtained from all-time recalls was used in the statistical analysis. A patient who was insensitive to bleaching needed to score zero (no TS) during all assessments from both bleaching sessions. In all other circumstances, participants were considered as having TS. This dichotomization made it possible to calculate the absolute risk

of TS, which represented the percentage of participants who reported TS at least once during treatment.

Color Change

Two calibrated operators performed color evaluation before the bleaching session, one week after the first bleaching session, one week after the second, and one month after the bleaching treatment. The color evaluation was never performed immediately after each bleaching session, so that the effect of dehydration and demineralization on color measures. The color evaluation was performed with the value-oriented shade guide Vita Classical (Vita Zahnfabrik, Bad Säckingen, Germany) and the Vita Bleachedguide 3D-MASTER (Vita Zahnfabrik, Bad Säckingen, Germany). In addition, an objective color evaluation was performed with the spectrophotometer Vita Easyshade (Vita Zahnfabrik, Bad Säckingen, Germany).

The 16 shade guide tabs from the Vita Classical shade guide were arranged from the highest (B_1) to the lowest (C_4) value for the subjective examination. The changes were treated as representing continuous and approximately linear color change ranking as performed in published studies [5, 6, 15, 19, 22-24]. The Vita Bleachedguide 3D-MASTER contains lighter shade tabs, organized from the highest (0M1) to the lowest (5M3) value.

The middle third of the right upper canine was used as the tooth-matching area. Color changes were calculated from the beginning of the active phase up to the individual recall times by calculating the difference in shade guide units (ΔSGUs), which occurred toward the lighter end of the value-oriented list of shade tabs. In case of disagreements between the operators, the operators had to reach a consensus before the patient was dismissed.

For the objective evaluation, a preliminary impression of the maxillary arch was made with high-putty silicon paste (Cub Kit Perfil, Vigodent Coltene, Alstatten, Switzerland) to serve as a standard guide for the tip of the spectrophotometer. The silicone guide was punched with a 6 mm window in the medium region of the right upper canine to create a window. A calibrated

evaluator measured the color in all participants using a spectrophotometer (VITA Easyshade Advance, Vita Zahnfabrik, Bad Säckingen, Germany) at the beginning of the first session and 30 days after the end of the bleaching treatment.

The objective color change was calculated with the CIELab parameters of L* (luminosity), a* (green to the red axis), and b* (blue to the yellow axis) obtained from the spectrophotometer. The difference between the baseline and 30 days after the end of the bleaching treatment was computed using the following CIELab formula [51]: $\Delta E_{ab} = [(\Delta L^*)^2+(\Delta a^*)^2+ (\Delta b^*)^2]^{1/2}$. In addition, the color change was also calculated based on the CIEDE 2000 formula [52]: $\Delta E_{00} = [(\Delta L /kLSL)^2 + (\Delta C/ kCSC)^2 + (\Delta H/kHSH)^2 + RT (\Delta C^*\Delta H/SC^*SH)]^{1/2}$ and Whiteness Index [53]: $\Delta WI_D= (0.511L^*) - (2.3424a^*) - (1.100b^*)$.

Statistical analysis

The statistician was blinded to the study groups. We performed the intention-to-treat analysis, including all randomized in the data analysis. Data analyses were conducted with the SigmaPlot version 11.0 software (Systat Software) with a significance level of 5%.

The risk of TS (reported at least once by participants) of both groups was compared using Fisher's exact test. The relative risk and 95% confidence interval (CI) were also calculated. The intensity of TS of both groups was compared with the Mann-Whitney test (NRS scale) and t-test for independent samples (VAS scale). The mean difference of TS intensity in the VAS scale (95% CI) was also reported. Subjective color assessment (ΔSGUs) and objective color assessment (ΔE_{ab}, ΔE_{00}, and ΔWI_D) were compared with t-test for independent samples. The mean difference and 95% CI were also calculated as the effect measures for the continuous outcomes.

Results

Characteristics of the eligible participants

One hundred and twelve participants were examined, and 83 were included in the clinical study (Figure 1). Forty-three participants were randomized to the laser group and forty to the control group. The baseline features of the participants for both groups were very similar, showing they were balanced for these baseline variables (Table 1).

Tooth sensitivity

The absolute risk of TS was 98% (95% CI 88 to 99) for the laser group and 95% (95% CI 83 to 99) for the control group. In comparative terms, the relative risk for TS was 1.03 (95% CI 0.94 to 1.12; Table 2) with no statistical difference ($p = 1.0$). Similarly, no significant difference in the intensity of TS was observed for both pain scales ($p > 0.05$). The mean difference in the TS intensity in VAS units was - 0.3 (95% CI, −1.6 to 1.0; Table 3).

Color evaluation

The final color measurement was intended to be done 30 days after the bleaching protocol. However, as the end of the study coincided with the rise of the COVID-19 pandemic, 32 patients had their final color change evaluated in a time frame between 3 and 6 months after bleaching.

A significant whitening was observed after bleaching for both groups. The color change was approximately 5 units in the Vita Classical scale, 5 units in the Vita Bleachedguide, 11 units in the ΔE_{ab}, 6 units in the ΔE_{00}, and 13 units in the ΔWI_D (Table 4). No significant difference in color change was observed between the laser and control groups (Table 4; $p > 0.15$).

Discussion

Hydrogen peroxide has a low molecular weight and reaches the pulp chamber a few minutes after its application [54]. In pulp tissue, HP reduces cell viability, causes damage to the cell membrane, activates proteolytic enzymes, and degrades the extracellular matrix [55-57]. In addition, inflammatory mediators such as neuropeptides, prostaglandins, adenosine triphosphate, and substance-P are released, whose functions are recognized in triggering the

inflammatory response, exciting the nerve endings responsible for pain perception [58, 59].

Due to this common side effect, several approaches have been investigated to eliminate or at least reduce the risk of bleaching-induced TS. The present study investigated the LLLT with an infrared laser (808 nm) and a power of 100 mW, following the manufacturer's recommendations. The energy supplied to each tooth was 3 J for 30 s with an energy density of 100 J/cm^2. Unfortunately, the LLLT therapy tested did not reduce the risk or the TS intensity. In both groups, a high risk of TS was observed affecting up to 95% of the participants, which agrees with previous studies in the literature that performed in-office dental bleaching [6, 60, 61].

Previous studies evaluated LLLT for bleaching-induced TS, but they do not provide strong evidence of efficacy [42-48]. For instance, Calheiros et al. [43] assessed the application of infrared laser (780 nm) at different periods and showed no reduction in TS. Moosavi et al. [42] comparing two different wavelengths (660 nm and 810 nm), reported that the infrared laser (810 nm) effectively reduced TS but only after 24 h. However, the TS risk and intensity are usually not an important clinical issue during this period as TS reduces significantly 24 h postbleaching [7].

Another study showed positive findings for the LLLT, but the laser was associated with other desensitizing agents such as topical sodium fluoride [46], and the authors did not include control groups. The lack of a comparator prevents us from differentiating real treatment efficacy from the placebo effect, the natural evolution of the disease, Hawthorne effect [62], and regression to the mean [63]. Thus, the findings of these two studies have a high risk of bias and should not be used to support a clinical recommendation.

The cellular response to the LLLP depends on the wavelength [64], radiant power, irradiated area, and exposure time. These parameters allow the calculation of the radiant exposure or energy dose (energy per irradiated area), irradiance, and total radiant energy, which are also essential parameters [65]. The published studies on LLLT for bleaching-induced TS show a considerable variation in irradiation, treatment parameters, and protocols (Table 5). In the studies listed in Table 5, one can see that the laser wavelengths varied between

660 to 810 nm, and power ranged from 40 mW to 200 mW. Differences in power density were even more pronounced than energy density and application time (Table 5).

For the LLLT to be effective, the irradiation parameters must be within certain ranges for the specific target living tissue [66, 67]. As there are many parameters, finding the correct association to be effective is challenging. For instance, Lanzafame et al., [68] showed that LED radiation at 660 nm on their murine pressure ulcer model produced very different effects when applied with an increasing power density (irradiance) and decreasing irradiation time, despite keeping energy density (J/cm^2) constant.

We do not know the most appropriate parameters of an LLLT to minimize bleaching-induced TS. Although we have followed the manufacturer's recommendation in this study, we have not found any RCT in the literature using the evaluated parameters that showed efficacy. Therefore, such a manufacturer's recommendation is not based on scientific evidence. Other manufacturers also sell LLLT devices with specific protocols for bleaching desensitization (Photon Laser III infrared device, DMC; and Thor DD2 Control, THOR) without evidence of efficacy (Table 6).

Applying a protocol without evidence support is not in line with practice-based evidence (PBE) principles [69]. Conceptually, PBE involves three fundamental principles: awareness of the best available evidence, guidance on the trustworthiness of the evidence and trade-offs between the benefits and risks, and burden and costs associated with the protocol. At least the first principle has been ignored when LLLT is indicated for bleaching-induced TS. The best evidence should come from systematic summaries of the evidence or from larger, high-power RCTs, which were not found in the available literature.

Another factor that we cannot rule out is that the laser therapy, within the parameters used, did not penetrate the pulp tissue. The literature reports that the diode laser, composed of an active semiconductor medium of gallium-aluminum arsenate (Ga-As-Al), emits light in the infrared spectral range with an estimated penetration depth of 2 to 3 cm [42, 70, 71]. This makes it a good alternative for treatments that require a high level of tissue penetration. However, other previously published studies reported that all wavelengths

emitted by the diode laser are absorbed mainly in the intraoral soft tissue, through melanin and hemoglobin, being poorly absorbed by hydroxyapatite and water present in dental enamel [72-74]. Further studies should be conducted to investigate this issue.

Regarding the color change, there was an effective whitening in both groups detected by the three color evaluation methods, which shows that the application of LLLT did not jeopardize whitening. At the end of the bleaching protocol, the color change was approximately 6 and 5.5 units whiter in the VITA Classical and VITA Bleachedguide scales, respectively. These results agree with previous clinical studies that also used high concentrate HP for in-office bleaching [6, 60, 61].

The objective color change evaluation demonstrated that both groups experienced effective and clinically perceptible tooth whitening with a color change of approximately 11, 6, and 13 units for ΔE_{ab}, ΔE_{00}, and ΔWI_D, respectively. Although the figures provided by objective evaluation are not easily understandable, we can compare them with the 50:50 perceptibility (PT) and acceptability (AT) thresholds [75, 76]. Paravina et al. [76] found that PT and AT values were 1.2 and 2.7, respectively, for the CIELab system and 0.8 and 1.8 for the CIEDE2000 system. Pérez et al. [75] found that PT and AT values were 0.7 and 2.6, respectively, for the Whiteness Index. In our study, the ΔE_{ab}, $\Delta E_{00,}$ and ΔWI_D figures after bleaching treatments were well above the 50:50 PT and 50:50 AT limits, indicating the color change was noticeable and clinically significant to most participants.

Conclusion

After in-office bleaching, the infrared LLLT (808 nm, continuous mode, 100 mW of power, 3 J of energy, 100 J/cm^2, 30 s) did not reduce the risk and intensity of TS and did not jeopardize color change.

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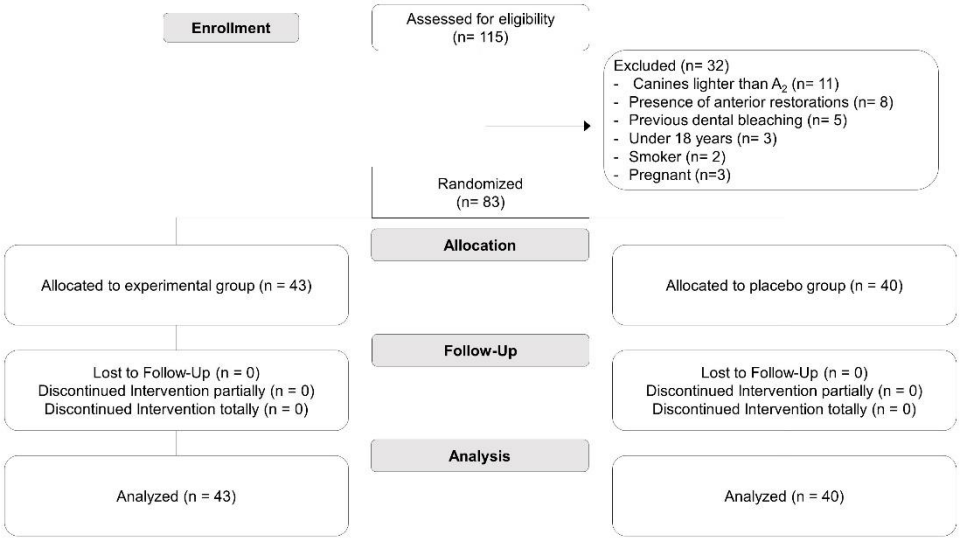

Figure 1. The CONSORT Flow diagram of study design phases including enrollment and allocation criteria.

Table 1. Baseline characteristics of the participants.

Groups (number of patients)	Laser group (n = 43)	Control group (n = 40)
Baseline color (SGU; mean ± SD)*	10.1 ± 3.1	10.1 ± 2.9
Age (years; mean ± SD)	25.7 ± 3.9	24.3 ± 3.6
Gender (female; %)	75	60

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

Table 2. Number of patients with TS during dental bleaching, and the absolute and relative risk of TS

Group	TS (number of patients)		Absolut Risk (95% CI)	Relative Risk (95% CI)*
	YES	NO		
Laser group	42	1	98% (88 to 99)	1.03 (0.94 to 1.12)
Control group	38	2	95% (83 to 99)	

Abbreviation: CI, confidence interval
*Fisher's exact test $p = 1.0$

Table 3. Intensity of TS in VAS scale (means and standard deviations) and NRS scale (medians and interquartile ranges).

	Laser group (n = 43)	**Control group (n = 40)**	**Mean difference (95% CI)**	**p-value**
VAS (0-10)	3.7 ± 2.8	4.0 ± 3.1	-0.3 (-1.6 to 1.0)	0.65*
NRS (0-4)	2.0 (1.0 - 3.0)	2.0 (1.0 - 3.0)	--	0.96**

* Student's t test for independent samples
** Mann–Whitney test

Table 4. Color change (means and standard deviations) between baseline *vs.* 30 days after bleaching procedure.

Color change instrument	Groups		Mean difference (95% CI)	p-value
	Laser (n = 43)	Control (n = 40)		
ΔSGU Vita Classical	5.1 ± 2.9	5.6 ± 2.8	-0.5 (-1.8 to 0.7)	0.42
ΔSGU Bleachedguide	4.9 ± 3.1	5.9 ± 2.9	-0.9 (-2.3 to 0.3)	0.15
ΔE_{ab}	11.4 ± 4.3	10.7 ± 3.7	0.7 (-1.1 to 2.5)	0.43
ΔE_{00}	6.7 ± 2.6	6.2 ± 2.2	0.4 (-0.6 to 1.5)	0.41
ΔWI_D	13.2 ± 6.5	13.7 ± 6.1	-0.5 (-3.3 to 2.3)	0.78

* Student's t test for independent samples.

Table 5. Laser parameters of LLLT used in clinical trials for desensitization of bleaching-induced TS.

Study	N per group	Commercial Name	Wavelengh (nm)	Power (mW)	Power density (W/cm^2)	Energy (J)	Energy density (J/cm^2)	Spot size area (cm^2)	Application time per point(s)	Application location
Farhat[50] 2014	N=16	Whitening Lase II, DMC	660 808	100	3.57	2.5	90	0.028	25	Cervical crown Apical root
Moosavi et al.[44] 2016	N=22	Thor DD2 Control Unit, Thor	660 810	200	0.8	3	12	0.25	15	Cervical crown
Calheiros et al.[45] 2017	N=10	MMOptics	780	40	1	0.4	10	0.04	10	Middle crown apical root
De Paula et al.[46] 2019	N=25	Photon Laser III, DMC	808	100	3.57	1.7	60	0.028	16	Cervical crown apical root
Alencar et al.[48] 2018	N=25	Photon Laser III, DMC	808	100	3.57	1.7	60	0.028	16	Cervical crown apical root
Pompeu et al.[49] 2021	N=25	Photon laser III, DMC	808	100	3.57	1.7	60	0.028	16	Cervical crown Apical rood
Present Study	N = 40	Laser Duo, MMOptics	808	100	3.33	3	100	0.03	30	Middle third crown

** These laser devices have two laser wavelengths available for bleaching-induced TS.*

Table 6. Description of protocols for desensitization after tooth bleaching with low power laser devices.

Commercial Name	Manufacturer	Composition	Wavelength (nm)	Power (mW)	Power Density W/cm^2)	Energy (J)	Energy Density (J/cm^2)	Application time (s)	Application Location
Photon Laser III infrared	DMC	Laser diode (ArGaAl)	808	100	3.57	1.7	60	16	Cervical crown and Apical root
Whitening Lase II	DMC	Laser diode (ArGaAl)	808	100	3.57	2.5	90	25	Cervical crown and Apical root
Thor DD2 Control	THOR	Laser diode (ArGaAl)	810	200	0.8	3	12	15	Cervical crown
Laser Duo	MMOptics	Laser diode (ArGaAl)	808	100	3.33	3-4	100	30 – 40	Middle or Cervical crown

5 DISCUSSÃO

Para a condução do Artigo 1, alguns desafios foram enfrentados na fase final da coleta de dados, pois a análise da mudança de cor de 30 dias após o clareamento, coincidiu com a pandemia emergente de COVID-19, que impediu a avaliação da última mudança de cor neste período específico de avaliação. Assim, a avaliação final da cor necessitou ser realizada dentro de 2 a 6 meses após o clareamento para alguns pacientes. Ainda assim, é improvável que tenha introduzido viés, pois a comparação dos resultados imediatos (aproximadamente 30 dias após o clareamento) e aqueles obtidos de 3 a 12 meses após o clareamento não relataram diferença estatística e clínica entre esses períodos de avaliação (Bersezio et al.[69] 2019; Kim et al.[70] 2020; Abrantes et al.[71] 2021; Martini et al.[72] 2021; Kury et al.[73] 2022).

Sete pacientes decidiram descontinuar o protocolo de clareamento e, para dois deles, nenhum dado foi coletado. Portanto, qualquer imputação pode ser enganosa. Como os dados ausentes foram balanceados entre os grupos (desenho de estudo pareado) e não no nível de randomização, excluímos esses dois pacientes da análise de dados. Essas duas exclusões explicam por que realizamos uma análise de intenção de tratar modificada para os resultados da SD. Nesta abordagem modificada, usamos dados apenas de pacientes que pudemos extrair dados de ambas as sessões de clareamento (n = 43) ou pelo menos da primeira sessão de clareamento (n = 5).

O PH possui baixo peso molecular e atinge a câmara pulpar em poucos minutos após sua aplicação (Bernadon et al.[74] 2010; Mondelli et al.[75] 2012; Soares et al.[76] 2013). No tecido pulpar, ele reduz a viabilidade celular, causa danos à membrana celular, ativa enzimas proteolíticas e degrada a matriz extracelular (Cook et al.[77] 2002; Trindade et al.[78] 2009; Sato et al.[79] 2013). Além disso, são liberados mediadores químicos como, neuropeptídeos, prostaglandinas, trifosfato de adenosina e substância-P, cujas funções são reconhecidas no desencadeamento da resposta inflamatória, excitando as terminações nervosas responsáveis pela percepção da dor (Huynh et al.[80] 2003; Cecarini et al.[81] 2007; Mounika et al.[82] 2018).

Dessa forma, um dos objetivos deste trabalho foi estudar a aplicação de um gel dessensibilizante (Artigo 1), contendo especificamente 10% de gluconato

de cálcio, 0,1% de acetato de dexametasona, 10% de nitrato de potássio e 5% de glutaraldeído, antes do clareamento em consultório. O resultado desse estudo mostrou que o agente dessensibilizante não reduziu o risco e a intensidade da SD induzida pelo clareamento. No entanto, já foi demonstrado que o PH pode atingir o tecido pulpar 15 minutos após ser aplicado no esmalte dental (Cooper et al.[83] 1992; Favoreto et al.[84] 2021). Isso pode ocorrer porque o PH é uma molécula pequena com massa molecular de 34 g/mol-1. A massa molecular de gluconato de cálcio (430,37 g/mol-1), acetato de dexametasona (392 g/mol-1), nitrato de potássio (101,10 g/mol-1) e glutaraldeído (100,11 g/mol-1) são maiores do que o de PH. Portanto, eles podem levar mais tempo para atingir a polpa.

Ensaios clínicos anteriores demostraram efeitos benéficos dos agentes dessensibilizantes incluídos no gel experimental quando eles foram avaliados individualmente. (Tay et al.[85] 2009; Mehta et al.[86] 2013; Mehta et al.[87] 2018; Oldoini et al.[88] 2018; Parreiras et al.[89] 2018). A maioria desses ECRs utilizou tamanhos de amostra baixos (baixo poder de estudo) e um desenho paralelo que não controla a variabilidade intra-individual. A alta correlação dos valores de risco e intensidade de SD entre hemiarcas dentárias sugere que o *design* de boca dividida pode reduzir o tamanho da amostra e diminuir a variabilidade interindividual, o que aumenta o poder do estudo para detectar diferenças clinicamente significativas.

A recente revisão sistemática de Martini et al.[24] (2021) coletou 16 estudos que avaliaram dessensibilizantes contendo nitrato de potássio, observando um efeito significativo e positivo do nitrato de potássio. Ainda assim, esse efeito foi sutil e não clinicamente significativo. Da mesma forma, um ECR também recente, avaliou o impacto de um produto contendo corticóide para aplicação tópica e não encontrou redução significativa no risco e na intensidade da SD (Favoreto et al.[90] 2021). Esses achados em conjunto, podem significar que é improvável que a aplicação tópica de dessensibilizantes possa minimizar a SD induzida pelo clareamento.

Outro aspecto que não devemos descartar é que a combinação desses agentes pode prejudicar a ação uns dos outros por mecanismos desconhecidos. No entanto, o gel experimental foi preparado e aplicado logo após o preparo, reduzindo a probabilidade dessa hipótese explicar os achados do estudo.

O outro objetivo avaliado neste estudo foi a aplicação do *laser* de baixa potência pós-clareamento em consultório para reduzir o risco e a intensidade de SD (Artigo 2). No entanto, a laserterapia de baixa potência aqui testada, não reduziu o risco ou a intensidade de SD. Um alto risco de SD foi observado, acometendo até 95% dos participantes, o que concorda com outros estudos anteriores da literatura que realizaram clareamento dental em consultório (Farhat[57] 2013; Moosavi et al. [58] 2016; Calheiros et al. [59] 2017; Rezende et al.[28] 2020).

Estudos anteriores avaliaram a laserterapia de baixa potência para SD induzida por clareamento, mas não forneceram fortes evidências de eficácia (Farhat et al.[57] 2014, Moosavi et al.[58] 2016, Calheiros et al.[59] 2017, Mayer-Santos et al.[60] 2017, Alencar et al.[61] 2018, de Paula et al.[62] 2019, Pompeu et al.[63] 2021). Calheiros et al.[59] (2017) avaliaram a aplicação do *laser* infravermelho (780 nm) em diferentes períodos e não mostraram redução da SD. Moosavi et al.[44] (2016) comparou dois comprimentos de onda diferentes (660 nm e 810 nm), e relataram que o *laser* infravermelho (810 nm) reduziu efetivamente a SD, mas somente após 24 h. Nesse período, no entanto, o risco e a intensidade de SD geralmente não são uma questão clínica importante, pois a SD reduz significativamente 24 h após o clareamento (González-Pacheco et al.[91] 2002).

Outro estudo mostrou achados positivos para a laserterapia, mas além da associação do *laser* com outro agente dessensibilizante, como o fluoreto de sódio tópico, o estudo não incluiu um grupo controle (Alencar et al.[61] 2018). Esse fato nos impede de diferenciar a real eficácia do tratamento com o efeito do placebo, a evolução natural da doença, o efeito Hawthorne (Sedgwick et al.[92] 2015) e a regressão à média (Bland et al.[93] 1994). Assim, os achados desse estudo têm alto risco de viés e não devem ser usados para apoiar uma recomendação clínica.

Outra característica importante é que a resposta celular depende do comprimento de onda do *laser* (Sommer[94] 2019), e de outros parâmetros de tratamento, como potência, área irradiada, energia e o tempo de exposição. Esses parâmetros permitem o cálculo da densidade de energia (energia por área irradiada) e densidade de potência (irradiância), que também são parâmetros essenciais (Peter et al.[95] 2011). Para que a terapia a *laser* seja eficaz, os parâmetros de irradiação devem estar dentro de certas faixas para o tecido vivo

alvo específico (Huang et al.[96] 2009; Huang et al.[97] 2011). Como existem muitos parâmetros, é muito difícil encontrar a associação correta para ser eficaz. Lanzafame et al.[98] (2007) mostraram que a radiação LED em 660 nm em seu modelo de úlcera por pressão murina produziu efeitos muito diferentes quando aplicada com uma densidade de potência crescente (irradiância) e tempo de irradiação decrescente, apesar de manter a densidade de energia (J/cm^2).

Desconhecemos os parâmetros mais adequados de um *laser* de baixa potência para minimizar a SD induzida pelo clareamento. Embora tenhamos seguido a recomendação do fabricante neste estudo, não encontramos nenhum ECR na literatura utilizando os parâmetros aqui avaliados que mostrassem evidência de eficácia. Portanto, tal recomendação do fabricante não é baseada em evidências científicas. A aplicação da laserterapia de baixa potência sem evidência de eficácia não está de acordo com os princípios da evidência baseada na prática (PBE) (Guyatt et al.[99] 2002). Conceitualmente, a PBE envolve três princípios fundamentais: conhecimento da melhor evidência disponível, orientação sobre a confiabilidade da evidência e *trade-offs* entre os benefícios e riscos, e encargos e custos associados ao protocolo. Pelo menos o primeiro princípio foi ignorado quando a laserterapia de baixa potência é indicada para SD induzida por clareamento. A melhor evidência deve vir de revisões sistemáticas ou de ECRs maiores e de alto poder, que não foram encontrados na literatura disponível.

Outro fator que não pode ser descartado é que o *laser*, dentro dos parâmetros utilizados, não penetrou no tecido pulpar. A literatura relata que o *laser* de diodo, composto por um meio semicondutor ativo de arsenato de gálio-alumínio (Ga-As-Al), emite luz na faixa espectral do infravermelho com profundidade de penetração estimada de 2 a 3 cm (Moosavi et al. 2016; de Freitas et al.[100] 2016; Mussttaf et al.[101] 2019), tornando-se uma boa alternativa para tratamentos que requerem um alto nível de penetração tecidual. No entanto, outros estudos publicados anteriormente relatam que todos os comprimentos de onda emitidos pelo laser de diodo são absorvidos principalmente no tecido mole intraoral, através da melanina e da hemoglobina, sendo pouco absorvidos pela hidroxiapatita e água presente no esmalte dentário (Hilgers et al.[102] 2004; Verma et al.[103] 2012; Derikvand et al.[104] 2016).

Em relação a eficácia do tratamento clareador, ela foi observada em ambos os estudos (1 e 2), independentemente dos grupos e instrumentos de avaliação de cor empregados. Em ambos os estudos, medimos a mudança de cor usando métodos subjetivos (unidades de guia de cores) e objetivo (espectrofotômetro), o que mostra que tanto a aplicação do gel dessensibilizante experimental, como a aplicação do *laser* de baixa potência não prejudicou o clareamento dental. Os resultados observados nos estudos concordam com estudos clínicos anteriores que também utilizaram o PH 35% para o clareamento em consultório (Martini et al. 2020[25]; Pompeu et al. 2021[63]; Vilela et al. 2021[105]; Maran et al. 2020[106]).

Embora os valores fornecidos pela avaliação objetiva não sejam facilmente compreensíveis, podemos compará-los com os limites de perceptibilidade (PT) e aceitabilidade (AT) de 50:50 (Della Bona et al. 2019[107]). Paravina et al.[108] 2015 verificaram que os valores de PT e AT foram 1,2 e 2,7, respectivamente, para o sistema CIELab e 0,8 e 1,8 para o sistema CIEDE2000. Em ambos os estudos, os valores de ΔEab e ΔE00 após os tratamentos de clareamento ficaram bem acima dos limites de 50:50 PT e 50:50 AT, indicando que a mudança de cor foi perceptível e clinicamente significativa para a maioria dos participantes.

6 CONCLUSÃO

(1) Com base nos resultados encontrados, a aplicação do gel dessensibilizante experimental (gluconato de cálcio, acetato de dexametasona, nitrato de potássio e glutaraldeído) antes do clareamento de consultório não reduziu o risco e a intensidade da sensibilidade dentária e não afetou a alteração de cor.

(2) A laserterapia de baixa potência (808 nm, modo contínuo, 100 mW de potência, 3 J de energia, 100 J/cm^2, 30 s), após o clareamento em consultório não reduziu o risco e a intensidade da sensibilidade dentária e não afetou a alteração de cor.

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ANEXO 1 - APROVAÇÃO DO ESTUDO CLÍNICO PELA COMISSÃO DE ÉTICA EM PESQUISA DA UNIVERSIDADE ESTADUAL DE PONTA GROSSA

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeito do gel dessensibilizante na sensibilidade induzida pelo clareamento dental em consultório

Pesquisador: Alessandra Reis

Área Temática:

Versão: 2

CAAE: 26996719.2.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.893.891

Apresentação do Projeto:

Projeto de Pesquisa:

Efeito do gel dessensibilizante experimental na sensibilidade induzida pelo clareamento dental em consultório. Antes da intervenção, será preparado o gel dessensibilizante experimental contendo gluconato de cálcio 10%, acetato de dexametasona 0,1%,

nitrato de potássio 10%, glutaraldeído 5% e um frasco contendo o placebo com as mesmas características de cor e viscosidade do gel

dessensibilizante, porém sem os componentes ativos.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o risco e a intensidade de sensibilidade dentária induzida pelo clareamento com a aplicação prévia do gel dessensibilizante experimental em

comparação com a aplicação prévia de um placebo.

Objetivo Secundário:Avaliar a efetividade do clareamento com a aplicação prévia do gel dessensibilizante experimental em comparação com a aplicação prévia de um

placebo.

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748, UEPG, Campus Uvaranas, Bloco M, Sala 115-B
Bairro: Uvaranas **CEP:** 84.030-900
UF: PR **Município:** PONTA GROSSA
Telefone: (42)3220-3108 **E-mail:** coep@uepg.br

ANEXO 2 - APROVAÇÃO DO ESTUDO CLÍNICO PELA COMISSÃO DE ÉTICA EM PESQUISA DA UNIVERSIDADE ESTADUAL DE PONTA GROSSA

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeito do laser de baixa potência para redução da sensibilidade dental após o clareamento em consultório

Pesquisador: Alessandra Reis

Área Temática:

Versão: 2

CAAE: 01598918.4.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.056.864

Apresentação do Projeto:

Efeito do laser de baixa potência para redução da sensibilidade dental após o clareamento em consultório. Intervenção/Experimental.

Objetivo da Pesquisa:

Objetivo Primário:Avaliar o risco e a intensidade da sensibilidade dental espontânea imediatamente, 1 hora, 24 horas e 48 horas após o clareamento dental em
consultório com e sem a aplicação do laser de baixa potência após o procedimento clareador através da Escala Visual Analógica (VAS 0-10) e
Escala de Classificação Numérica (NRS 0-4).

Objetivo Secundário:

Avaliar a eficácia do clareamento dental em consultório com e sem a aplicação do laser de baixa potência nos períodos inicial e um mês após o
término do tratamento através da escala Vita Classical, Vita Bleachedguide 3D-MASTER e espectrofotômetro Vita Easyshade.

Avaliação dos Riscos e Benefícios:

Riscos:

Ainda que devidamente informados, os participantes da pesquisa estão sujeitos a queimaduras,

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748, UEPG, Campus Uvaranas, Bloco M, Sala 116-B
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ANEXO 3 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO DO ESTUDO 1

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado(a) como voluntário(a) a participar da pesquisa: "*Efeito da aplicação pré-operatória do gel dessensibilizante na redução da sensibilidade dental decorrente do clareamento dental em consultório: estudo clínico randomizado, placebo-controlado, boca-dividida*".

Após o clareamento é muito comum que os pacientes relatem sensibilidade dental. No intuto de evitar esse efeito colateral, pretendemos com este estudo verificar a capacidade do gel dessensibilizante na prevenção da sensibilidade dental causada pelo clareamento de consultório.

Esta pesquisa clínica será realizada nas clínicas odontológicas da Universidade Estadual de Ponta Grossa, pela aluna de Doutorado Laína Vochikovski pelos alunos de Mestrado Michael Favoreto e Karine Leticia Silva sob orientação da professora Dra. Alessandra Reis. Para a execução da pesquisa serão necessários 80 voluntários que atendam aos critérios de seleção e que concordem com este Termo de Consentimento Livre e Esclarecido.

O clareamento dental será realizado nas clínicas odontológicas da UEPG, onde o cirurgião-dentista aplicará o produto clareador sobre os dentes do voluntário. Será utilizado um gel clareador contendo peróxido de hidrogênio 35% (Whiteness HP Automixx, FGM, Joinville, Santa Catarina, Brasil). Para proteger a gengiva, será utilizada uma resina (Top Dam, FGM) que funciona como uma barreira garantindo que apenas os dentes entrem em contato com o gel clareador, evitando possíveis queimaduras do gel na gengiva. Todo este procedimento leva aproximadamente 1 hora, e serão realizadas 2 sessões com intervalo de 1 semana entre elas. Antes da aplicação do gel clareador, será sorteado o lado direito ou esquerda da boca para a aplicação do gel dessensibilizante e do outro lado será aplicado o gel dessensibilizante placebo.

Durante todo o período da pesquisa você será acompanhado pelos pesquisadores para a verificação de qualquer efeito adverso, os quais serão tratados de forma gratuita e acompanhados.

Todo o material empregado no tratamento será fornecido pelos pesquisadores gratuitamente, portanto, você não terá nenhum custo e também não receberá qualquer vantagem financeira.

Alguns pacientes durante o clareamento apresentam sensibilidade dos dentes, que é ocasionada pela ação do produto. Se você apresentar sensibilidade muito forte, será aplicado um gel dessensibilizante (Dessensibilize® KF 2%, FGM) e se necessário, você será medicado com analgésicos e/ou anti-inflamatórios. Estes medicamentos serão fornecidos gratuitamente aos voluntários. A utilização de qualquer agente químico utilizado para o clareamento dental pode ocasionar efeitos adversos como sensibilidade, ardência, descamação e ulceração das mucosas bucais, dependendo da sensibilidade individual. Após o relato de qualquer efeito adverso (exceto sensibilidade), o tratamento com o clareador será imediatamente suspenso, com a sua retirada da pesquisa. Na presença de qualquer reação, os procedimentos serão suspensos e você receberá assistência médica gratuita.

Quanto aos benefícios, você terá seus dentes clareados e receberá gratuitamente o clareamento. Você terá a garantia de que receberá esclarecimento a qualquer dúvida, acerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa. Os pesquisadores responsáveis assumem o compromisso de proporcionar informação atualizada obtida durante o estudo, ainda que esta possa afetar a sua vontade em continuar participando dele. Você tem a liberdade de se recusar a participar da pesquisa ou de retirar seu consentimento a qualquer momento, sem sofrer qualquer tipo de prejuízo, ou represálias de qualquer natureza. Os pesquisadores se comprometem a resguardar todas as informações individuais, tratando-as com impessoalidade e não revelando a identidade do sujeito que as originou.

Eu, _____ (nome completo), portador(a) da Cédula de Identidade RG nº _____, inscrito(a) no CPF sob o nº _____, residente na (endereço completo) _____

CERTIFICO que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Laína Vochikovski, Michael Favoreto, Karine Leticia Silva e Dra. Alessandra Reis. Estou plenamente de acordo com a realização do experimento. Assim, eu concordo em participar como voluntário do trabalho de pesquisa, exposto acima

Ponta Grossa, _____ de _____ de 2020.

Assinatura: _____
Pesquisador responsável: _____

1ª via da instituição, 2ª via do sujeito da pesquisa.

ANEXO 4 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO DO ESTUDO 2

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado(a) como voluntário(a) a participar da pesquisa: *"Efeito do laser de baixa potência para redução da sensibilidade dental após o clareamento em consultório"*.

Após o clareamento é muito comum que os pacientes relatem sensibilidade dental. No intuito de evitar esse efeito colateral, pretendemos com este estudo verificar a capacidade do laser de baixa potência na prevenção da sensibilidade dental causada pelo clareamento de consultório.

Esta pesquisa clínica será realizada nas clínicas odontológicas da Universidade Estadual de Ponta Grossa, pelas alunas de Doutorado Laina Vochikovski, Alexandra Mara de Paula e pelas alunas de Mestrado Renata Terra e Karine Leticia Silva sob orientação da professora Dra. Alessandra Reis. Para a execução da pesquisa serão necessários 80 voluntários que atendam aos critérios de seleção e que concordem com este Termo de Consentimento Livre e Esclarecido.

O clareamento dental será realizado nas clínicas odontológicas da UEPG, onde o cirurgião-dentista aplicará o produto clareador sobre os dentes do voluntário. Será utilizado um gel clareador contendo peróxido de hidrogênio 35% (Whiteness HP Automixx, FGM, Joinville, Santa Catarina, Brasil). Para proteger a gengiva, será utilizada uma resina (Top Dam, FGM) que funciona como uma barreira garantindo que apenas os dentes entrem em contato com o gel clareador, evitando possíveis queimaduras do gel na gengiva. Todo este procedimento leva aproximadamente 1 hora, e serão realizadas 2 sessões com intervalo de 1 semana entre elas. Após a aplicação do gel clareador, os voluntários do grupo experimental receberão irradiação de um laser infravermelho de baixa potência (Laser Duo, MMOptics). Os voluntários do grupo placebo serão submetidos ao mesmo procedimento, porém para este grupo a irradiação será realizada com o aparelho desligado.

O aparelho é um laser de baixa potência com meio ativo semicondutor de Arsenato de Gálio-Alumínio (GaAsAl), emitindo um comprimento de onda de 808 nm. O laser operará com potência de 100 mW. A energia fornecida para cada dente será de 3 J na região coronária de cada dente por 30 segundos com densidade de energia de 100 J/cm^2. Durante todo o período da pesquisa você será acompanhado pelos pesquisadores para a verificação de qualquer efeito adverso, os quais serão tratados de forma gratuita e acompanhados.

Todo o material empregado no tratamento será fornecido pelos pesquisadores gratuitamente, portanto, você não terá nenhum custo e também não receberá qualquer vantagem financeira.

Alguns pacientes durante o clareamento apresentam sensibilidade dos dentes, que é ocasionada pela ação do produto. Se você apresentar sensibilidade muito forte, será aplicado um gel dessensibilizante (Dessensibilize® KF 2%, FGM) e se necessário, você será medicado com analgésicos e/ou anti-inflamatórios. Estes medicamentos serão fornecidos gratuitamente aos voluntários. A utilização de qualquer agente químico utilizado para o clareamento dental pode ocasionar efeitos adversos como sensibilidade, ardência, descamação e ulceração das mucosas bucais, dependendo da sensibilidade individual. Após o relato de qualquer efeito adverso (exceto sensibilidade), o tratamento com o clareador será imediatamente suspenso, com a sua retirada da pesquisa. Na presença de qualquer reação, os procedimentos serão suspensos e você receberá assistência médica gratuita.

Quanto aos benefícios, você terá seus dentes clareados e receberá gratuitamente o clareamento. Você terá a garantia de que receberá esclarecimento a qualquer dúvida, acerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa. Os pesquisadores responsáveis assumem o compromisso de proporcionar informação atualizada obtida durante o estudo, ainda que esta possa afetar a sua vontade em continuar participando dele. Você tem a liberdade de se recusar a participar da pesquisa ou de retirar seu consentimento a qualquer momento, sem sofrer qualquer tipo de prejuízo, ou represálias de qualquer natureza. Os pesquisadores se comprometem a resguardar todas as informações individuais, tratando-as com impessoalidade e não revelando a identidade do sujeito que as originou.

Eu, _____ (nome completo), portador(a) da Cédula de Identidade RG nº _____, inscrito(a) no CPF sob o nº _____, residente na (endereço completo) _____

CERTIFICO que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Laina Vochikovski, Alexandra Mara de Paula, Renata Terra, Karine Leticia Silva e Dra. Alessandra Reis. Estou plenamente de acordo com a realização do experimento. Assim, eu concordo em participar como voluntário do trabalho de pesquisa, exposto acima.

ANEXO 5 – ESCALA DE DOR (NRS)

Nome:					
Grupo:					
	0 NENHUMA	1 LEVE	2 MODERADA	3 CONSIDERÁVEL	4 SEVERA
Imediatamente após					
1 hora após					
24 horas após					
48 horas após					

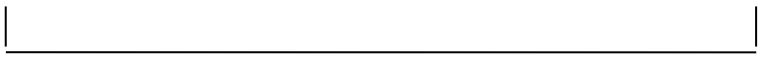
ANEXO 6 – ESCALA DE DOR (VAS)

NOME:

GRUPO:

Marque com uma linha vertical no lugar que você considera o nível de sensibilidade: Imediatamente após

Horário do término do clareamento: _____:_____



0 = Sem Dor 10 = Dor insuportável