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EVELINE CLAUDIA MARTINI

MANEJO DA SENSIBILIDADE DENTAL ADVINDA DO CLAREAMENTO EM CONSULTÓRIO E DO PROTOCOLO DE CLAREAMENTO CASEIRO

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Tese apresentada como pré-requisito para obtenção do título de Doutora na Universidade Estadual de Ponta Grossa, no Programa de Pós-Graduação *Stricto Sensu* em Odontologia, Área de Concentração: Dentística Restauradora. Linha de Pesquisa: Pesquisa Clínica em Odontologia.

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EVELINE CLAUDIA MARTINI

Manejo da sensibilidade dental advinda do clareamento de consultório e do protocolo de clareamento caseiro.

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 Doutor em Odontologia, área de concentração em Dentística Restauradora, linha de pesquisa: Pesquisa clínica em Odontologia.

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Dedico este trabalho:

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DADOS CURRICULARES

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RESUMO

Martini, EC. **Manejo da sensibilidade dental advinda do clareamento em consultório e do protocolo de clareamento caseiro.** [Tese – Doutorado em Odontologia – Área de Concentração: Dentística Restauradora - Universidade Estadual de Ponta Grossa; 2020].

Os objetivos deste estudo foram: 1) Avaliar o efeito da aplicação de gel dessensibilizante a base de nitrato de potássio e fluoreto de sódio aplicado antes *vs* antes e após o clareamento em consultório na SD (sensibilidade dentária) e na efetividade do clareamento, através de um ensaio clínico randomizado (ECR) triplo-cego, boca dividida; 2) Responder à pergunta PICO através de uma revisão sistemática: "O risco e a intensidade da sensibilidade dentária e da eficácia do clareamento são diferentes entre pacientes adultos submetidos ao clareamento caseiro usando moldeiras com reservatórios e aqueles que usam moldeiras sem reservatórios?" e 3) Avaliar, através de um ECR cego e boca dividida, se o uso de reservatórios em moldeiras de clareamento caseiro é equivalente a moldeiras sem a presença dos reservatórios na mudança de cor, SD e irritação gengival. Para o estudo 1, 90 pacientes com os caninos de cor A2 ou mais escuros foram selecionados e divididos aleatoriamente em dois grupos: aplicação de gel dessensibilizante somente antes *vs* antes e depois do clareamento de consultório com PH (peróxido de hidrogênio) 35%, durante 10 min. A SD foi avaliada imediatamente e 1 h, 24 h e 48 h após o clareamento e registrada pelos próprios pacientes 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 um mês depois do término. Para o estudo 2, uma pesquisa abrangente foi realizada sem restrições, em bases de dados e literatura cinzenta, onde apenas ECR foram incluídos e avaliados através da ferramenta Risk of Bias (RoB) da Cochrane Collaboration. Devido a baixa qualidade dos estudos primários e alto risco de viés, não foi possível executar a metanálise e um ECR bem delineado foi sugerido para responder a essa pergunta de pesquisa, que foi realizado no estudo 3, onde 46 pacientes com dentes de cor A2 ou mais escuros foram selecionados para realizar o clareamento caseiro com gel de PC (peróxido de carbamida) 10%, sendo que em uma metade do arco as moldeiras tinham reservatórios e na outra metade não tinham. A SD durante o clareamento foi avaliada por escalas VAS e NRS, questionário sobre irritação gengival e a cor foi avaliada com escalas visuais e espectrofotômetro. Foi observado após um mês, em ambos os ECR realizados, clareamento significativo e semelhante entre os grupos ($p > 0,45$ para estudo 1 e $p < 0,01$ para estudo 3) e em relação a SD, não houve diferença estatisticamente significativa entre os grupos (sendo OR = 0,25; IC 95% 0,005 a 2,52; p = 0,37 para estudo 1 e OR = 0,8; IC 95% 0,2 a 3,0; p = 1,0 para estudo 3. Pode-se concluir que a aplicação de agente dessensibilizante não influenciou na eficácia do clareamento em consultório, mas não foi eficiente na redução da SD, quando aplicada antes do clareamento, ou antes e depois deste. Além disso, o protocolo de clareamento caseiro com PC 10% com reservatórios é equivalente em mudança de cor, SD e irritação gengival ao de não-reservatório, como observado através do ECR. Portanto, não há evidências para concluir sobre a eficácia da presença ou ausência de reservatórios nas moldeiras.

Palavras-chave: Clareamento Dental. Peróxido de hidrogênio. Peróxido de carbamida. Sensibilidade da dentina. Reservatórios

ABSTRACT

Martini, EC. **Management of dental sensitivity resulting from in-office bleaching and the at-home bleaching protocol**. [Thesis - Doctorate in Dentistry - Concentration Area: Restorative Dentistry - Ponta Grossa State University; 2020].

The objectives of this study were: 1) To evaluate the effect of the application of desensitizing gel based on potassium nitrate and sodium fluoride applied before vs before and after in office bleaching, on TS (tooth sensitivity) and on the effectiveness of bleaching, through a triple-blind randomized controlled trial (RCT), split mouth; 2) Answer the following PICO question through a systematic review: “Are the risk and intensity of tooth sensivity and bleaching efficacy different between adult patients undergoing at-home bleaching using trays with reservoirs and those using trays without reservoirs?” and 3) To evaluate, through a randomized, blinded, split mouth trial, whether the use of reservoirs in at-home bleaching trays is equivalent to trays without the presence of reservoirs in the color change, TS and gingival irritation. For study 1, 90 patients with canines of color A2 or darker were selected and randomly divided into two groups: application of desensitizing gel only before vs before and after in-office bleaching with HP (hydrogen peroxide) 35%, for 10 min. Dental sensitivity was assessed immediately and 1 h, 24 h and 48 h after bleaching and recorded by the patients themselves using a 5-point numerical scale (NRS) and visual analog (VAS 0-10). Color was assessed using visual scales and spectrophotometer initially, one week after each session and one month after the end of the procedure. For study 2, a comprehensive survey was conducted without restrictions, in databases and gray literature, where only RCTs were included and evaluated using the Cochrane Collaboration's Risk of Bias (RoB) tool. Due to the low quality of primary studies and high risk of bias, it was not possible to perform the meta-analysis and a well-designed RCT was suggested to answer this research question, which was carried out in study 3, where 46 patients with A2 or darker ones were selected to perform at-home bleaching with 10% CP (carbamide peroxide) gel, and in one half of the arch the trays had reservoirs and in the other half they did not. Tooth sensitivity during bleaching was assessed using VAS and NRS scales, a questionnaire on gingival irritation and the color was assessed using visual scales and a spectrophotometer. It was observed after one month, in both RCTs performed, significant and similar bleaching between groups ($p > 0.45$ for study 1 and $p < 0.01$ for study 3) and in relation to TS, there was no statistically significant difference between the groups (with OR = 0.25; 95% CI 0.005 to 2.52; $p = 0.37$ for study 1 and OR = 0.8; 95% CI 0.2 to 3.0; $p = 1.0$ for study 3). It can be concluded that the application of desensitizing agent did not influence the efficacy of in-office bleaching, but it was not efficient in reducing TS, when applied before the bleaching, or before and after it. In addition, the at-home bleaching protocol with 10% CP with reservoirs is equivalent in color change, TS and gingival irritation to that of non-reservoir, as observed through the RCT. Therefore, there is no evidence to conclude about the effectiveness of the presence or absence of reservoirs in the bleaching trays.

Keywords: Tooth Bleaching. Hydrogen peroxide. Carbamide Peroxide. De sensitivity. Reservoirs.

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LISTA DE ABREVIATURAS E SIGLAS

ECR	Ensaio clínico randomizado
RoB	*Risk of bias*
VAS	*Analogic visual scale*
NRS	*Numerical rating scale*
PC	Peróxido de carbamida
PH	Peróxido de hidrogênio
OR	*Odds ratio*
IC	Intervalo de confiança
PICO	Paciente/Intervenção/Comparação/"*Outcomes"*
MeSH	*Medical Subject Headings*
IADR	*International Dental Research Association*
PRISMA	Principais itens para relatar revisões sistemáticas e meta-análises
ReBEC	Registro Brasileiro de Ensaios Clínicos
CONSORT	*Consolidated Standards of Reporting Trials*
SD	Sensibilidade dental
IG	Irritação gengival
a *	Eixo cromático vermelho-verde
ADA	*American Dental Association*
ANOVA	Análise de variância
b *	Eixo cromático azul-amarelo
COEP	Comissão de Ética em Pesquisa
∆SGU	Variação de cor (escalas de cor)
∆E	Variação de cor nos parâmetros CIElab (espectrofotômetro)

g	Grama
h	Hora
L*	Luminosidade
Min	Minuto
mm	Milímetro
s	Segundo
TCLE	Termo de Consentimento Livre e Esclarecido
UEPG	Universidade Estadual de Ponta Grossa
Medline	Sistema online de busca e análise de literatura médica
Pubmed	Biblioteca nacional de medicina dos Estados Unidos
Lilacs	Literatura latino-americana e do Caribe em ciências da saúde
BBO	Bibliografia brasileira de odontologia

LISTA DE SÍMBOLOS

%	Porcentagem
±	Mais ou menos
α	Alfa
p	Probabilidade de significância
µ	Micro
OH^-	Íon hidroxila
°C	Graus Celsius
<	Menor
>	Maior
H_0	Hipótese nula

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1 INTRODUÇÃO

Um sorriso estético pode afetar fortemente a aparência facial, além de melhorar a autoestima e as relações sociais (Koidou et al.[1] 2018). Embora a atratividade do sorriso esteja relacionada a vários fatores, incluindo a forma e a posição dos dentes, a cor exerce um forte efeito sobre as percepções estéticas e sociais, pois os dentes mais claros geralmente estão relacionados ao bom estado de saúde bucal (Kershaw et al.[2] 2008).

Nas últimas duas décadas, o clareamento dental tornou-se um dos tratamentos dentários estéticos mais populares, já que se trata de um procedimento eficaz e não invasivo para a remoção da descoloração dentária (Dourado Pinto et al.[3] 2019). O efeito clareador é obtido devido aos radicais livres gerados pela quebra do peróxido, que degradam a estrutura orgânica do esmalte (Eimar et al.[4] 2012) e da dentina (Jiang et al.[5] 2018), promovendo o clareamento. Dentre as formas disponíveis, temos o clareamento caseiro supervisionado e realizado em consultório, aplicando agentes clareadores de alta concentração sobre os dentes pigmentados (de Geus et al.[6] 2016).

No entanto, apesar de ser um tratamento conservador, aproximadamente 60 a 100% dos pacientes em algum momento do tratamento clareador relatam sensibilidade dental (Bonafe et al.[7] 2013, Kielbassa et al.[8] 2015, Rezende et al.[9] 2016). A hipótese teórica mais aceita para explicar essa sensibilidade pós-operatória está relacionada à ação do peróxido de hidrogênio (PH) na polpa dental. O PH causa estresse oxidativo, danos celulares (Cooper et al.[10] 1992, Dias Ribeiro et al.[11] 2009, Trindade et al.[12] 2009, Lima et al.[13] 2013) redução da atividade enzimática, o que resulta em um processo inflamatório que ativa as fibras nervosas e deflagram o estímulo doloroso (Wang et al.[14] 2015).

Com intuito de reduzir ao máximo esses sintomas, os autores buscam entender a etiologia e o emprego de alternativas para o manejo da SD decorrente do clareamento (Martini et al.[15] 2019). Dentre as formas já testadas, podemos citar a escolha da técnica clareadora pelo profissional (caseira ou em consultório), tipo de agente clareador (peróxido de carbamida ou de hidrogênio) e concentração do agente, que podem ser baixas ou elevadas (ADA[16] 2009). Pode-se citar também a diminuição no tempo e frequência de aplicação do gel clareador visando a redução na taxa de penetração do PH na câmara pulpar (Cooper et al.[10] 1992), bem como modificações no pH dos géis (Acuña et al.[17] 2019).

No clareamento em consultório, alguns autores já investigaram o uso de agentes dessensibilizantes, como fosfopeptídeos de caseína/fosfato de cálcio amorfo e nanofosfato de cálcio (Giniger et al.[18] 2005, Giniger et al.[19] 2005, Borges et al.[20] 2012, Vano et al.[21] 2015), nitrato de potássio e fluoreto de sódio, quanto ao potencial de reduzir a sensibilidade advinda do clareamento (Wang et al.[14] 2015). A aplicação de dessensibilizantes a base de nitrato de potássio e fluoreto de sódio durante 10 min previamente ao clareamento feito em consultório já demonstrou capacidade de reduzir pela metade o risco da sensibilidade dental, bem como a intensidade com que a mesma ocorre (Tay et al.[22] 2009), mas também já foi testado e não apresentou diminuição do risco e nem da intensidade da sensibilidade (Kose et al.[23] 2011). Em virtude dos resultados controversos sobre a eficácia na aplicação prévia desses agentes, especula-se se a aplicação dupla, antes e após o clareamento poderia ser mais eficaz, porém, nenhum estudo clínico que investigasse essa abordagem foi encontrado na literatura.

No que se refere ao clareamento caseiro, encontramos um número alto de géis e protocolos diferentes de tratamento que são constantemente avaliados em ensaios clínicos randomizados (Monteiro et al.[24] 2019, Darriba et al.[25] 2019), isso dificulta os clínicos a chegarem em uma conclusão sobre qual protocolo apresenta maior eficácia, menor risco e intensidade de SD (de Geus et al.[5] 2016). Com objetivo de melhorar a eficácia do clareamento, algumas variações no desenho das moldeiras de clareamento podem ser encontradas na literatura, como o tipo de material termoplástico utilizado para sua fabricação, a espessura da moldeira e a presença ou ausência de reservatório. (Meireles et al.[26] 2010, Türkün et al.[27] 2010). Alguns autores relataram que as moldeiras com reservatórios aumentam a quantidade de gel disponíve permitem um melhor assentamento da moldeira de clareamento (Haywood et al.[28] 1993, Matis et al.[29] 2002).

No entanto, os benefícios desses reservatórios nas moldeiras de clareamento ainda não são claros, e diferentes resultados foram relatados. Enquanto os pesquisadores de um estudo observaram um grau significativamente maior de clareamento para as moldeiras de clareamento com reservatórios (Ishikawa[30] 2011), outros não observaram nenhum benefício (Matis et al.[29] 2002, Bosma et al.[31] 2000, Delgado et al.[32] 2000) e até mesmo efeito prejudicial nos tecidos moles devido ao risco aumentado de irritação gengival (Kirsten et al.[33] 2009).

Portanto, essa tese teve por objetivo investigar um protocolo de dessensibilização com nitrato de potássio e fluoreto de sódio aplicados antes e após o clareamento em consultório e investigar, por meio de uma revisão sistemática da literatura e de um ensaio clínico randomizado, o efeito do uso de reservatórios em moldeiras de clareamento caseiro.

2 PROPOSIÇÃO

2.1 ESTUDO 1

2.1.1 PROPOSIÇÃO GERAL

O objetivo deste ensaio clínico randomizado triplo-cego foi avaliar o efeito da aplicação de gel dessensibilizante a base de nitrato de potássio 5% e fluoreto de sódio 2% antes do clareamento em consultório *vs* aplicação antes e depois do procedimento, na sensibilidade dental e efetividade do clareamento.

2.1.2 PROPOSIÇÃO ESPECÍFICA

1. Avaliar o risco e a intensidade da sensibilidade dental após clareamento em consultório com a aplicação de agente dessensibilizante utilizando a escala numérica de 5 pontos e a escala visual analógica (0 – 10).

2. Avaliar a efetividade do clareamento em consultório com a aplicação de agente dessensibilizante após 1 mês do clareamento utilizando as escalas de cor Vita classical e Vita Bleachedguide e o espectrofotômetro Vita Easyshade.

2.2. ESTUDO 2

2.2.1 PROPOSIÇÃO GERAL

O objetivo deste estudo foi determinar, através de uma revisão sistemática, se existem diferenças na sensibilidade dental e no grau de mudança de cor do clareamento caseiro realizado em moldeiras com e sem reservatórios.

2.2.2 PROPOSIÇÃO ESPECÍFICA

1. Comparar o risco e a intensidade da sensibilidade dentária nos estudos clínicos que compararam moldeiras com e sem reservatórios.

2. Comparar a eficácia clareadora nos estudos clínicos que compararam moldeiras com e sem reservatórios.

2.3 ESTUDO 3

2.3.1 PROPOSIÇÃO GERAL

O propósito deste ensaio clínico randomizado cego foi avaliar se o uso de reservatórios em moldeiras de clareamento caseiro é equivalente a moldeiras sem reservatórios na mudança de cor.

2.3.2 PROPOSIÇÃO ESPECÍFICA

1. Verificar se há equivalência, após um mês, na eficácia do clareamento caseiro com PC 10% realizado com moldeiras com e sem reservatórios, utilizando as escalas de cor Vita classical e Vita Bleachedguide e o espectrofotômetro Vita Easyshade.

2. Comparar o risco e intensidade de SD e irritação gengival durante o clareamento caseiro com PC 10% realizada com moldeiras com e sem reservatórios, utilizando a escala numérica de 5 pontos e a escala visual analógica (0 – 10).

3 MATERIAL E METODOS

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

3.1 ESTUDO 1

O projeto deste ensaio clínico randomizado triplo-cego foi aprovado pela Comissão de Ética em Pesquisa (COEP) (Anexo A) da Universidade Estadual de Ponta Grossa através do parecer nº 2.455.095. O estudo foi registrado no sítio eletrônico http://www.ensaiosclinicos.gov.br/ sob o número de identificação RBR-5V6G7F. A metodologia detalhada destes experimentos está descrita no ARTIGO 1.

3.1.1 SELEÇÃO DOS PACIENTES

Noventa 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.

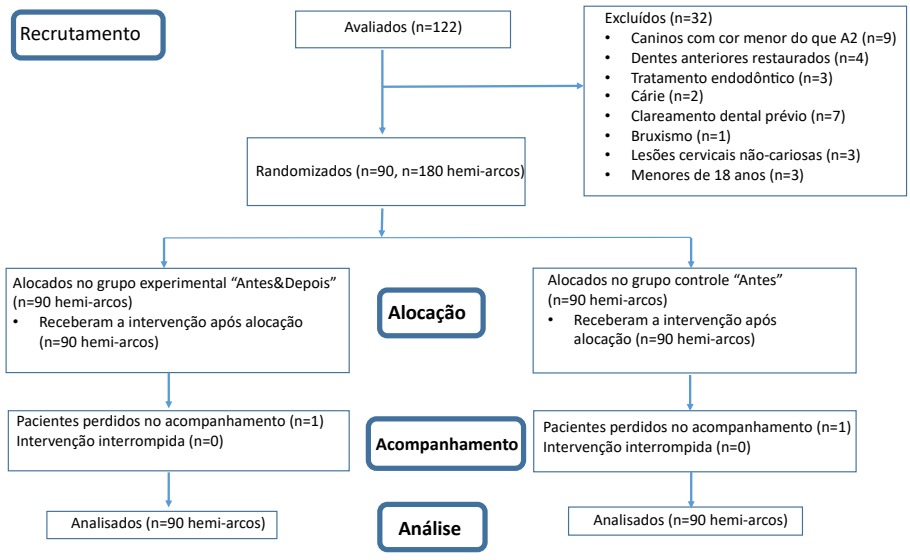


Figura 1 - Fluxograma das fases do ensaio clínico, incluindo o recrutamento, critérios de inclusão e alocação.

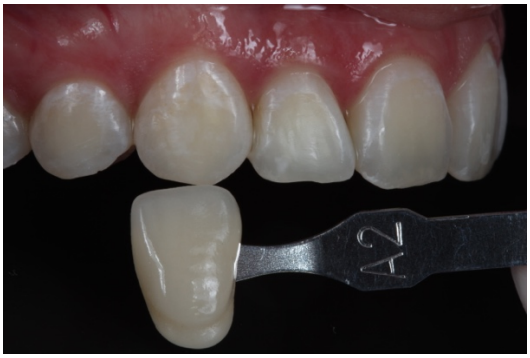


Figura 2 - Avaliação da cor inicial dos caninos superiores com a escala Vita Classical (Vita Zahnfabrik)

3.1.2 PROTOCOLO EXPERIMENTAL/INTERVENÇÃO

Um processo de randomização foi realizado 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 no arco superior direito, enquanto o outro arco recebeu o tratamento alternativo. Uma vez que o participante foi elegível para o procedimento e todas as avaliações iniciais foram concluídas, a atribuição de alocação foi revelada abrindo o envelope imediatamente antes da implementação.

Após profilaxia, foi instalado o afastador labial (Arcflex, FGM, Joinville, Brasil) 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 então fotoativada (Radii-Cal, SDI, Bayswater, Austrália) de acordo com as recomendações do fabricante.

Em seguida, o agente dessensibilizante (Desensibilize KF 2%, FGM) foi aplicado nas superfícies vestibulares de ambos os hemi-arcos dentários em uma camada de 2 mm. O gel foi mantido por 10 min sem agitação (Figura 3). Em seguida, o gel dessensibilizante foi removido com um sugador de saliva e os dois arcos foram clareados com um gel de peróxido de hidrogênio a 35% (Whiteness HP AutoMixx, FGM) (Figura 4). O gel clareador foi mantido por 50 min e removido com sugador de saliva, gaze e enxágue com água.

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 KF 2% e qual era o placebo. Ambos foram entregues aos operadores em seringas idênticas codificadas como BA (seringa vermelha) e BB (seringa verde) (Figura 5), que seriam aplicadas após a remoção do gel clareador. Ambos os géis tinham consistência e cor semelhantes.

Após a aspiração do gel clareador, em um dos hemi-arcos dentários foi aplicado o gel dessensibilizante e o outro lado recebeu o gel placebo (determinado pelo processo de randomização), ambos mantidos em contato com as superfícies vestibulares por 10 min e aspirados na sequência. Isso resultou em um grupo com aplicação do KF 2% antes e depois *vs* um grupo com a aplicação apenas antes. Duas sessões de clareamento foram realizadas da mesma maneira com intervalo de 1 semana entre elas.

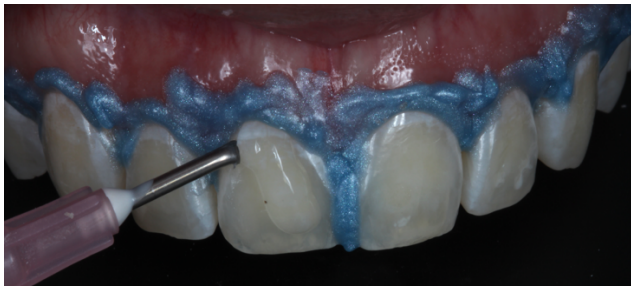


Figura 3 - Aplicação do gel dessensibilizante previamente ao clareamento de consultório.

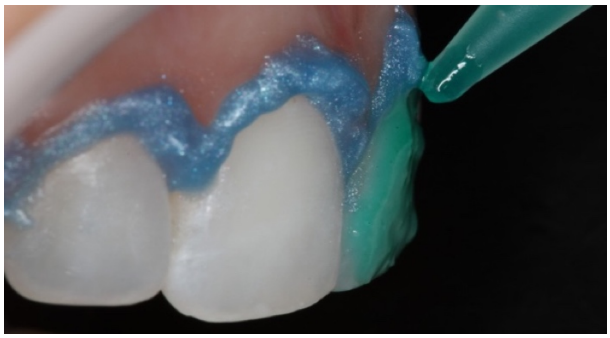


Figura 4 - Aplicação do gel clareador (Whiteness HP AutoMixx, FGM).

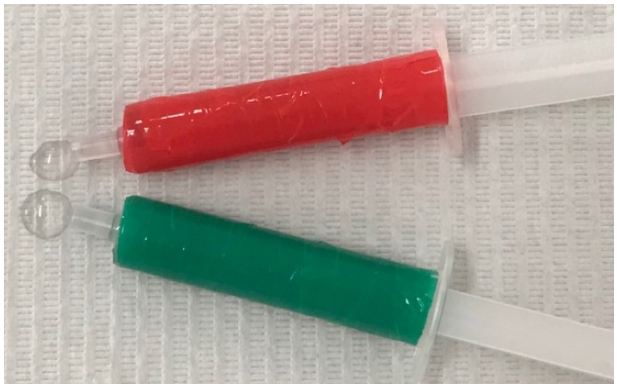


Figura 5 - Gel placebo e gel dessensibilizante acondicionados em seringas de cor diferente.

3.1.3 AVALIAÇÃO DA COR E SENSIBILIDADE

A sensibilidade foi avaliada durante o clareamento, 1 h, 24 h e 48 h após o clareamento. Os pacientes avaliaram numa escala (NRS) de 0 a 4 na qual 0 = “nenhuma dor” e 4 indicando a “pior dor” e na escala visual analógica (VAS) de 0 a 10.

A cor foi avaliada em quatro períodos: anteriormente ao tratamento, após uma semana da 1ª e 2ª sessão, e um mês depois do término do tratamento. Para a análise da cor subjetiva foram utilizadas escalas de cor Vita classical e Vita Bleachedguide (Vita Zahnfabrik). Para análise objetiva foi utilizado o espectrofotômetro Vita Easyshade (Vita Zahnfabrik), de acordo com o sistema Vita e CIEL*a*b* (Figura 6).

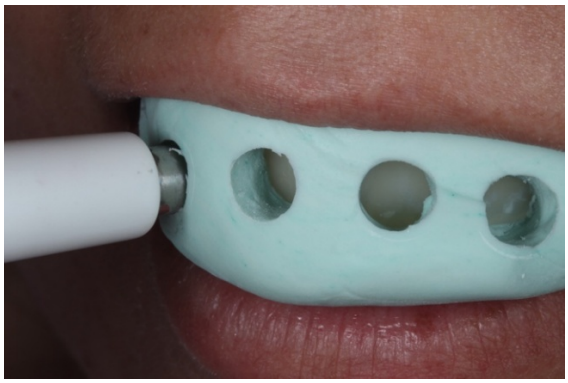


Figura 6 - Guia em silicona de condensação realizada para avaliação de cor dos dentes.

3.1.4 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 sensibilidade dentária de ambos os grupos foram comparados por meio do teste exato de McNemar, usado para comparar a proporção de dados

dependentes (α = 0,05). O *odds ratio* e o intervalo de confiança (IC) foram calculados.

Os dados de intensidade da sensibilidade dentária para as escalas VAS e NRS foram plotados em histogramas e inspecionados quanto à distribuição normal. Como não apresentaram distribuição normal, os grupos foram comparados pelo teste de Wilcoxon e pelo método de Student-Newman-Keuls (α = 0,05). Calculamos o coeficiente de correlação para pares de dados binários do risco de dor entre os dois grupos e o coeficiente de correlação de Spearman para os pares de dados de intensidade da sensibilidade dentária.

Foram calculadas as médias e desvios padrão da mudança de cor em ΔSGU e ΔE entre inicial e 30 dias após o clareamento. Para avaliar se os protocolos de clareamento foram eficazes, os dados de ambos os grupos foram comparados usando o teste de Mann-Whitney para os dados de ΔSGU e o teste t pareado para ΔE. O nível de significância de todos os testes foi estabelecido em 5%.

3.1.5 Síntese dos Resultados

A sensibilidade após o clareamento foi observada nos dois grupos, para as escalas VAS e NRS em todos os períodos avaliados. A proporção de pacientes que apresentaram sensibilidade no lado em que o dessensibilizante foi aplicado somente antes do clareamento foi muito semelhante ao grupo em que o dessensibilizante foi aplicado antes e depois do clareamento, 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

Este protocolo de estudo foi registrado no Registro Internacional Prospectivo de Revisões Sistemáticas (PROSPERO - CRD42016037628 – Anexo B) e seguiu as recomendações do PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) para responder a pergunta PICO: “O risco e a intensidade da sensibilidade dentária são diferentes entre pacientes adultos submetidos ao clareamento caseiro usando moldeiras com reservatórios e aqueles que usam moldeiras sem reservatórios?”

3.2.1 CRITÉRIOS DE ELEGIBILIDADE

Ensaios clínicos randomizados (ECR) paralelos e de boca divididos que compararam o clareamento caseiro em pacientes adultos de qualquer idade com e sem reservatórios foram incluídos. ECRs que avaliaram apenas uma das duas técnicas foram excluídos.

3.2.2 ESTRATÉGIA DE BUSCA E BASES DE DADOS ESCOLHIDAS

O vocabulário controlado (termos MeSH) e palavras-chave livres foram utilizados na estratégia de busca, com base nos elementos da questão PICO abordados nos objetivos do estudo. Os desfechos primários foram o risco e a intensidade da sensibilidade dentária durante o clareamento dental e a alteração da cor, medida em unidades de cor (ΔSGU) ou com um espectrofotômetro (ΔE). Também coletamos os dados sobre o risco de inflamação gengival (desfecho secundário).

A busca detalhada encontra-se no Artigo 2 e foi feita em bases de dados eletrônicos (MEDLINE via *PubMed*, *LILACS, BBO, Cochrane Library* e bancos de dados de citações (*Scopus* e *Web of Science*); sem restrições de data e idioma. As listas de referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais.

A literatura cinzenta também foi pesquisada. Os resumos da conferência anual da Associação Internacional de Pesquisa Odontológica (IADR) e suas divisões regionais (1990-2018), banco de dados do Sistema de Informação sobre Literatura Cinzenta na Europa (*OpenSigle*), dissertações e teses (*ProQuest Dissertations* e Periódicos Capes Teses) também foram examinados. Sempre que um resumo da reunião da conferência era encontrado, tentávamos encontrar se o texto completo já havia sido publicado através de busca na literatura ou através de contato com os autores do estudo.

Os ensaios não publicados e em andamento foram pesquisados nos registros de ensaios clínicos: *Current Controlled Trials* (https://www.isrctn.com/), *International Clinical Trials Registry Platform* (http://apps.who.int/trialsearch/), *ClinicalTrials.gov* (www.clinicaltrials.gov), ReBEC (http://www.ensaiosclinicos.gov.br) e *EU Clinical Trials Register* (https://www.clinicaltrialsregister.eu).

3.2.3 Coleta de dados e seleção dos estudos

Após a busca nas bases de dados, os artigos foram exportados para o software gerenciador de referência *EndNote (X6, Thomson Reuters, EUA*). As duplicatas foram removidas inicialmente por uma ferramenta específica do *EndNote*. Na segunda etapa, os artigos foram organizados em ordem alfabética por título e as duplicatas foram identificadas e removidas manualmente, já que a ferramenta do *EndNote* pode manter alguma devido a diferenças no processo de indexação usado nas diferentes bases de dados.

Em seguida, os artigos foram selecionados por título e resumos de acordo com os critérios de elegibilidade. Artigos em texto completo foram obtidos quando o título e o resumo apresentavam informações insuficientes para tomar uma decisão clara. Posteriormente, três revisores (E.M., S.P. e E.A.) classificaram aqueles que atendiam aos critérios de inclusão. Um ID do estudo foi fornecido para cada estudo elegível, combinando o primeiro autor e o ano de publicação.

Informações relevantes sobre o desenho do estudo, participantes, intervenções e resultados foram extraídas usando formulários de extração personalizados por três autores de maneira independente. Com relação à mudança de cor, coletamos dados que representavam o resultado mais imediato (até três meses após o clareamento) e usamos a mesma regra para a sensibilidade dentária (até 1 semana após o clareamento).

3.2.4 Risco de viés dos estudos selecionados

A avaliação do risco de viés dos estudos incluídos foi avaliada usando a ferramenta da *Cochrane Collaboration* para avaliar o risco de viés em estudos randomizados. Os critérios de avaliação continham seis itens: geração de sequência, ocultação de alocação, cegamento dos avaliadores, dados incompletos e relatórios seletivos de resultados.

Para cada domínio da avaliação da qualidade, o risco de viés foi pontuado seguindo as recomendações descritas no Manual Cochrane para revisões sistemáticas das intervenções 5.1.0 (http://handbook.cochrane.org). A análise para cada artigo envolveu julgamentos de baixo risco de viés, alto risco de viés ou risco indefinido, indicando falta de informações ou incerteza sobre o potencial de viés. No nível do estudo, os estudos foram julgados como baixo risco de viés se houvesse

geração de sequência adequada, ocultação de alocação e ocultação do operador (domínios-chave da ferramenta de risco de viés da Cochrane). Se pelo menos um desses domínios fosse considerado indefinido, o estudo receberia o mesmo julgamento. Por outro lado, se pelo menos um dos domínios principais apresentasse alto risco de viés, o estudo seria julgado como alto risco de viés.

3.2.5 Síntese dos Resultados

Tabelas e figuras foram criadas para sintetizar os resultados. Foram coletados resultados sobre mudança de cor, risco e intensidade da sensibilidade dentária e irritação gengival. Os autores não foram contatados para obter mais informações devido ao fato de que as evidências empíricas mostram uma baixa taxa de resposta em artigos publicados há mais de uma década.

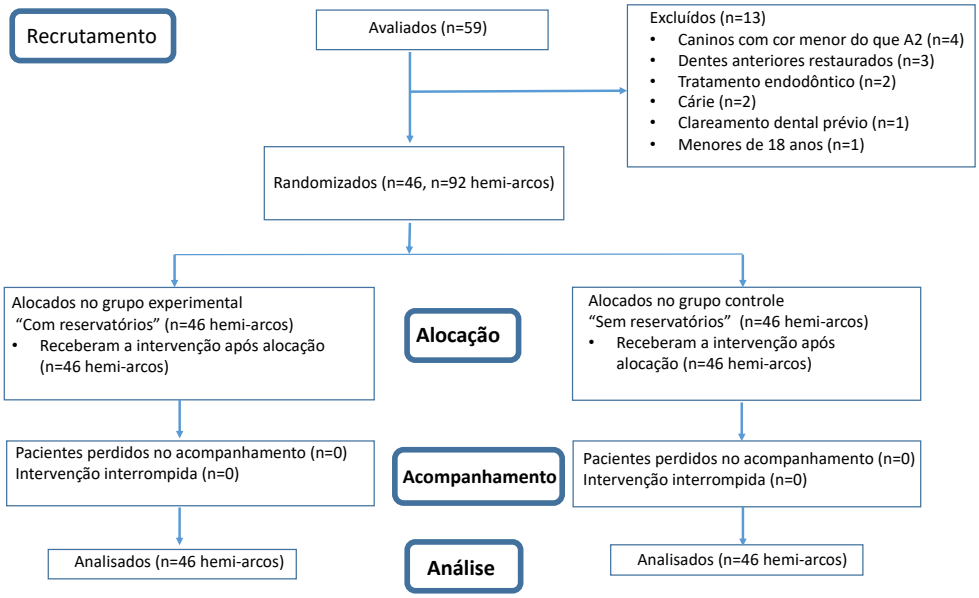
3.3 ESTUDO 3

Este ensaio clínico randomizado cego foi aprovado pelo comitê de revisão científica e pelo Comitê de Proteção de Participantes Humanos da Universidade Estadual de Ponta Grossa (protocolo número 2.124.508 – Anexo C). O protocolo também foi registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC) sob o número de identificação RBR-4w9ht3 e redigido de acordo com as recomendações do *Consolidated Standards of Reporting Trials* (CONSORT), com extensão para ensaios de não-inferioridade e equivalência.

3.3.1 Seleção dos pacientes

Quarenta e seis pacientes foram selecionados para este estudo, com idade entre 18 e 40 anos. Os participantes deveriam ter boa saúde geral (auto-referida pelo paciente como não estando sob tratamento médico) e boa saúde bucal (sem necessidade de tratamento cirúrgico, endodôntico, periodontal e restaurador) (Figura 7). Os participantes deveriam ter os caninos com cor A2 ou mais escuro, avaliada através de escala visual (VITA Classical, Vita Zahnfabrik, Bad Säckingen, Alemanha).

Figura 7 - Fluxograma das fases do ensaio clínico, incluindo o recrutamento, critérios de inclusão e alocação.

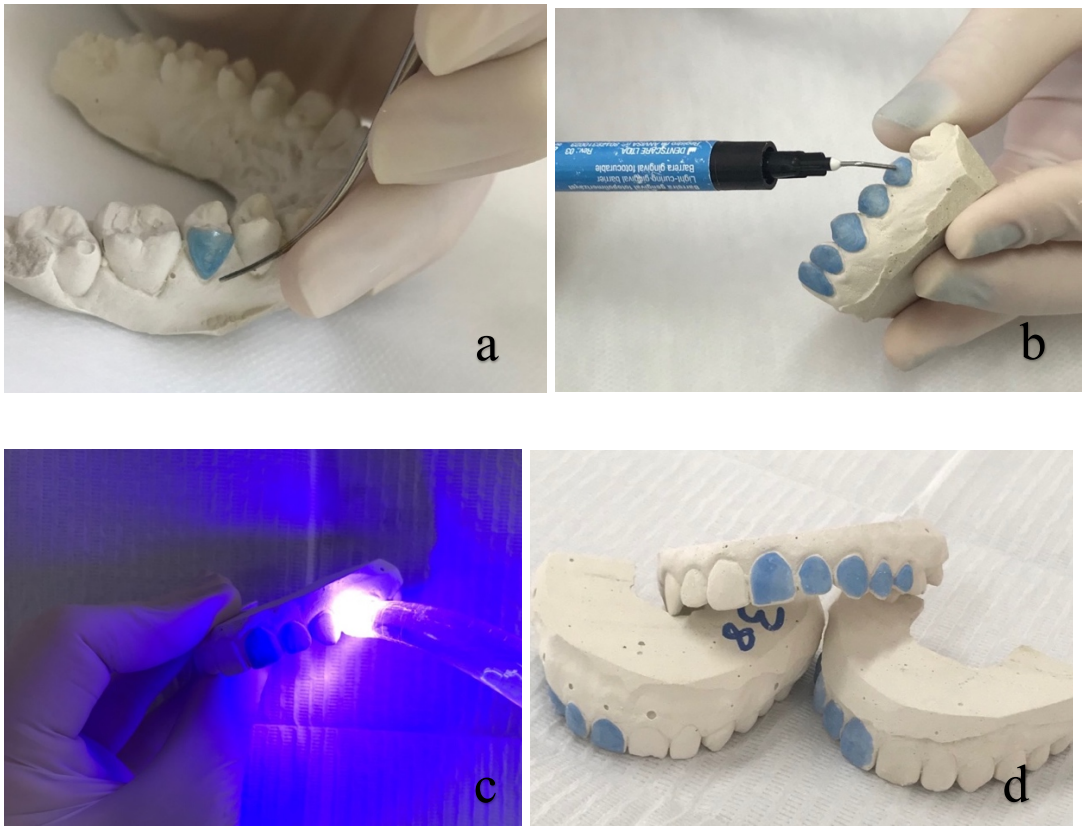


3.3.2 PROTOCOLO EXPERIMENTAL/INTERVENÇÃO

Primeiramente foi realizada a moldagem nas arcadas superior e inferior de cada participante e, após a desinfecção, feito vazamento do gesso. Os modelos do arco superior foram utilizados no estudo. Para tanto, em um dos lados, de acordo com a randomização, uma camada de barreira gengival fotopolimerizável (Top Dam, FGM, Joinville, Brasil) foi aplicada nas superfícies vestibulares do incisivo central, incisivo lateral, canino e pré-molar do lado selecionado da boca do paciente, com objetivo de criar reservatórios nesses dentes.

O material foi aplicado numa espessura de 1 mm, cobrindo a superfície vestibular, exceto 1 mm mesial, distal e cervical (Figura 8) no lado selecionado após randomização, enquanto a outra metade do arco não tinha reservatórios, nem a arcada inferior (após o tratamento clareador, as moldeiras inferiores foram entregues aos pacientes, já que essas não tinham reservatórios, para não interferir no estudo). Uma placa de silicone de 1 mm de espessura (Ultradent, South Jordan, EUA) foi utilizada para fabricar as moldeiras personalizadas na plastificadora Plastivac P7 (BioArt, São Carlos, Brasil). O excesso de material foi cortado a 1 mm da margem gengival.

Figura 8 - a) Confecção dos reservatórios com Top Dam (FGM), deixando um espaçamento de 1 mm livre de material nas margens. b) Inserção do Top Dam até o dente segundo pré-molar no lado escolhido através da randomização. c) Fotopolimerização do Top Dam. d) Reservatórios confeccionados apenas em um lado do modelo de gesso, respeitando o lado verificado após randomização.



Instruímos todos os participantes a usarem a moldeira com o agente clareador (peróxido de carbamida 10%, Opalescence PF, Ultradent, South Jordan, EUA) durante 3 horas diárias, por 21 dias. Eles foram instruídos a preencher com gel clareador até cobrir a superfície vestibular de todos os dentes (essa quantidade é ligeiramente maior no lado com reservatórios da moldeira) e remover a moldeira após cada período de clareamento.

Como medida de adesão ao estudo, os participantes receberam um diário no qual foi solicitado que anotassem o número de horas por dia em que usavam a moldeira durante o tratamento. Eles foram lembrados desse procedimento diariamente, através de mensagens.

3.3.3 Avaliação da cor e sensibilidade

A avaliação de cor foi realizada com a escala VITA Classical e VITA Bleachedguide 3D-MASTER (Vita Zahnfabrik). Também realizamos uma avaliação

objetiva da cor com o espectrofotômetro VITA Easyshade (VITA Zahnfabrik). As avaliações foram realizadas no início do estudo, após cada semana de clareamento e 1 mês após o tratamento.

A área de avaliação de cor no dente era o terço médio da superfície vestibular dos caninos superiores. Para o espectrofotômetro, foi realizado um molde do arco superior com silicona densa (Coltoflax e Perfil Cub Kit, Vigodent, Rio de Janeiro, Brasil). A impressão foi estendida aos caninos superiores e serviu como um guia de medição de cor para o espectrofotômetro. Para cada canino, foi criado uma janela na superfície vestibular da guia de silicone usando um dispositivo de metal (Bisturi circular Punch, Kolplast, São Paulo, Brasil) com um raio de 6 mm, que é precisamente o diâmetro da ponta do espectrofotômetro, o mesmo seguiu o modelo previamente demonstrado na Figura 6.

Instruímos os pacientes a preencher um formulário para registrar a SD diária após o clareamento, eles receberam instruções detalhadas sobre como realizar esse procedimento. Esses formulários retornavam ao investigador em todas as consultas clínicas.

Para a escala de classificação numérica de 0-4 pontos (NRS), solicitamos ao paciente que indicasse o valor numérico do grau de sensibilidade para cada um dos períodos. Além disso, os participantes também foram instruídos a registrar a intensidade da dor usando a escala visual analógica (VAS) de 0-10.

Os participantes também foram instruídos a preencher um formulário para registrar a irritação gengival (IG) diária após o clareamento. Esses formulários retornavam ao pesquisador na próxima consulta, durante as três semanas de tratamento. Para esse questionário, solicitou-se ao participante que indicasse se sentiu algum desconforto na gengiva e se houve desconforto, deveria indicar em qual dos lados.

3.3.4 Análise estatística

Dois testes t unilaterais para amostras pareadas (TOST-P) foram utilizados para testar a equivalência dos grupos de estudo nos diferentes tempos de avaliação (inicial *vs* 1 semana; inicial *vs* 2 semanas; inicial *vs* 3 semanas e inicial *vs* 1 mês após o clareamento), sendo um teste do lado direito para a margem inferior do limite de equivalência e um teste do lado esquerdo para a margem superior do limite de equivalência usando níveis de significância de 0,025 unilaterais. O valor p-*value* é

considerado o maior dos dois valores de p-*value* obtidos nos dois testes inferior e superior. A diferença média e o intervalo de confiança (IC) de 95% foram calculados entre os grupos em cada avaliação de tempo.

Para o ΔE, se os dois tratamentos diferirem em mais de 3,0 unidades em qualquer direção, a equivalência não se aplica. Embora não tenha sido planejado *a priori*, avaliamos a equivalência para a mudança de cor nas unidades de cores das escalas visuais. Nesse caso, considerou-se equivalente os grupos quanto eles não difereriam em 1,0 unidade de cor de cada escala. Uma análise de variância de medidas repetidas de mão única tradicional foi empregada para cada instrumento de mudança de cor para detectar mudanças de cor ao longo do tempo.

Os riscos de SD e IG de ambos os grupos foram comparados usando o teste exato de McNemar, que é usado para comparar a proporção de dados emparelhados (α = 0,05) em estudos de superioridade. O *odds ratio*, bem como o intervalo de confiança (IC) foram calculados. O teste *Wilcoxon Signed Rank* comparou a intensidade de SD obtido com a escala NRS, enquanto o teste t de *Student* pareado comparou a intensidade de SD da escala VAS (α = 0,05).

Calculamos o coeficiente de correlação phi para pares de dados binários do risco de SD e IG entre os dois grupos. O coeficiente de correlação de Spearman e Pearson foi calculado, respectivamente, para a escala NRS e a escala VAS. Utilizamos o coeficiente de correlação de Pearson para calcular o coeficiente de correlação para os pares de mudança de cor de cada instrumento inicialmente *vs* 1 mês após o clareamento.

3.3.5 SÍNTESE DOS RESULTADOS

Após um mês, foi observado um efeito clareador de cerca de oito unidades através da escala Vita Classical, 11 unidades pela escala Vita Bleachedguide e 13 unidades pelo espectrofotômetro, sem diferença significativa entre os grupos com e sem reservatórios. O risco de sensibilidade dental (SD) foi semelhante entre os grupos com e sem reservatórios, sendo que o *odds ratio* para dor não atingiu significância estatística. Também não foi observada diferença significativa na intensidade da SD e na IG entre os grupos.

4 ARTIGOS

4.1 Bleaching-induced tooth sensitivity with application of a desensitizing gel before and after in-office bleaching: a triple-blind randomized clinical trial.

4.2 Does the Use of Reservoirs Have Any Impact on the Efficacy of At-Home Bleaching? A Systematic Review.

4.3 Evaluation of reservoirs in bleaching trays for at-home bleaching: a split-mouth single-blind randomized controlled equivalence trial.

4.1 ARTIGO 1

TÍTULO: Bleaching-induced tooth sensitivity with application of a desensitizing gel before and after in-office bleaching: a triple-blind randomized clinical trial.

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Bleaching-induced tooth sensitivity with application of a desensitizing gel before and after in-office bleaching: a triple-blind randomized clinical trial.

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Abstract

Objectives. This randomized triple-blind clinical trial, split-mouth design, evaluated the application effect of the desensitizing gel before and after in-office bleaching on tooth sensitivity.

Materials and methods. In one group, the desensitizing gel was applied for 10 min before the bleaching with 35% hydrogen peroxide, and then application of placebo gel after (n = 90). In the other group, the desensitizing gel was applied before and after the bleaching procedure for 10 min (n = 90). The primary outcome was pain intensity assessed with a numeric rating scale and a visual analog scale. Color was evaluated by means of a digital spectrophotometer and shade guides.

Results. The proportion of patients that experienced pain in the side of before application was 90% (95% CI 82 to 94.6%), while the side of before and after was 93% (95% CI 86.2 to 96.9%), without significant difference between groups (OR = 0.25; 95% CI 0.005 to 2.52; p = 0.37). Pain was correlated in both groups, for the NRS scale ($p < 0.0001$) and the VAS scale ($p < 0.0001$) in all assessment periods. Significant whitening was detected, and no significant difference of color change was observed between groups ($p > 0.45$).

Conclusions. The application of the desensitizing agent did not influence the effectiveness of bleaching, but it was not efficient in reducing the sensitivity, when applied before the procedure, or before and after.

Clinical relevance. The use of a desensitizing gel before or after in-office bleaching does not reduce incidence or intensity of tooth sensitivity.

Keywords. Tooth bleaching, Dentin sensitivity, Randomized controlled clinical trial, Hydrogen peroxide, Potassium nitrate.

Introduction

Among the esthetic procedures most sought by patients, dental bleaching stands out as a conservative procedure that achieves satisfactory results [1]. Dental whitening arises from the oxidation of organic components of the dental structure produced by the hydrogen peroxide and other reactive forms of oxygen [2], giving teeth a lighter appearance [3]. Among the dentist-supervised bleaching techniques, the in-office protocol of using highly concentrated hydrogen peroxide products has become an excellent alternative for both professionals and patients [4], as it allows faster results without the need to wear bleaching trays for long periods [5, 6]. However, the main drawback of this protocol is the higher intensity of tooth sensitivity (TS) reported by patients in comparison with at-home bleaching [7].

Clinical trials found in the literature reported that the risk of bleaching-induced TS after in-office protocol is variable but affects more than half of the patients that undergo this cosmetic procedure [7–10]. Some studies have reported that TS affects more than 85% of the patients [11]. Upon penetrating the dental tissues to oxidize the organic components of dental structure, hydrogen peroxide and its reactive forms of oxygen diffuse quickly, reaching the pulp chamber and causing the release of inflammatory media- tors [12]. At pulp, it was hypothesized that hydrogen per- oxide reaches chemosensitive ion channels (TRPA1) and activates the intradental nerve [13, 14]. Altogether, these factors may be responsible for the high risk of TS experienced by patients who undergo bleaching procedures.

To minimize bleaching-induced TS, analgesics [15], anti-inflammatory drugs [16–20], antioxidants [9], corticoid [21, 22], and opioid drugs [15] have been evaluated as alternatives. However, clinical studies indicate that the use of oral drugs does not reduce the risk of TS or its intensity, as also reported in a systematic review [23]. Instead, a promising approach to minimize bleaching- induced TS was observed with topical application of desensitizers before in-office bleaching procedures [11, 24, 25] such as 5% potassium nitrate and sodium fluoride gel (0.7–2%) [26].

The mechanism of potassium nitrate that reduces TS seems to be related to the increase in the concentration of potassium ions around the nerve fibers, which

prevents repolarization of the sensory nerve [27, 28]. This was the reason of why the product was mainly evaluated before bleaching, being kept in contact with the dental structure before the application of the whitening gel [11, 24–26]. However, some studies have evaluated the application of desensitizer agent after bleaching procedure [25]. To the author's knowledge, no study was found investigating the application of the product before and after bleaching in an aim to maximize its analgesic effect.

Thus, the objective of this randomized, split-mouth, triple-blind clinical study was to compare the risk and intensity of tooth sensitivity of patients undergoing in-office bleaching with 35% hydrogen peroxide and receiving applications of a potassium-based desensitizing agent before or before and after bleaching.

Methods

Ethics approval and protocol registration

The clinical investigation was approved (protocol number 2.455.095) by the scientific review committee and by the committee for the protection of human participants of the local university. It was registered in the clinical trials registry. We prepared this article using the protocol established by the Consolidated Standards of Reporting Trials statement with extension for within-person designs [29].

Trial design, settings, and locations of data collection

This study was a randomized, split-mouth triple-blind clinical trial, in which the patient, operator, and evaluator were masked to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the randomization process. All participants were informed about the nature and objectives of the study. The study was performed from May 15, 2017 to January 20, 2018, in the Clinics of the School of Dentistry from the local university.

Recruitment

Recruitment of patients was carried out through social media advertising. All volunteer participants signed an informed consent form before being enrolled in the study.

Eligibility criteria

Based on pre-established criteria, we selected 90 subjects volunteered for this study. Participants included in the present randomized clinical trial should be good general and oral health and at least 18–50 years old. The participants were required to have at least six maxillary anterior teeth free of caries, restorations, or endodontic treatment, with canine shade A2 or darker, as judged by comparison with a value-oriented shade guide (VITA Classical Shade, VITA Zahnfabrik, Bad Säckingen, Germany) (Fig. 1).

Participants with orthodontic apparatus, dental prosthesis, and severe internal tooth discoloration (tetracycline stains, fluorosis, or pulpless teeth) were not included in the study. In addition, pregnant and lactating women, participants with bruxism or any pathology that could cause sensitivity (such as recession, dentinal exposure, visible cracks in teeth), anti-inflammatory or analgesic drug users, or participants who had undergone tooth-whitening procedures were also excluded.

Sample size calculation

The primary outcome of this study was the absolute risk of tooth sensitivity (that is, the number of patients [percent] who reported pain at some point during dental bleaching) and was reported to be 85% in an earlier study [11] for in-office bleaching with 35% hydrogen peroxide gel, as used in this study. Using an alpha of 0.05, 90% power, and a two-sided test, the minimum sample size in this equivalence trial was 90 patients (considering 20% loss) in order to detect a 30% difference in the risk of tooth sensitivity between groups.

The sample size calculation was performed without accounting for the potential correlation between the paired treat- ment outcomes. This approach resulted in a larger sample size than if the correlation coefficient between treatment outcomes is not zero. We performed this approach because published within-person trials do not report this correlation coefficient, and thus, we opted for being conservative.

Random sequence generation and allocation concealment

A simple randomization process was performed in the website (www.sealedenvelope.com) by a third person, not involved in the steps of

implementation and evaluation. The distribution of the group to be first assigned were recorded on sequentially numbered cards and placed in opaque and sealed envelopes. The information contained in the envelope determined the treatment to be assigned in the upper right maxillary arch, while the other arch received the alternate treatment. Once the participant was eligible for the procedure and all initial evaluations were completed, the allocation assignment was revealed by opening the envelope immediately after implementation.

Blinding

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

Both the desensitizing and the placebo gels were delivered to operators in identical syringes coded as BA^ (red syringe) and BB^ (green syringe), which would be applied after application of the gel bleaching agent. Both gels had a similar consistency and color. Only the research coordinator knew the coding system.

Study intervention

The bleaching procedure was done by three operators with more than 4 years of clinical experience. After placement of a lip retractor (Arcflex, FGM Dental Products, Joinville, Brazil), a light-cured gingival barrier (Top Dam, FGM Dental Products, Joinville, Brazil) was placed on the gingival tissue of the teeth to be bleached (from second left premolar to second right premolar of the upper and lower arch). The gingival barrier was then light-cured according to the manufacturer's recommendations (Radii-Cal, SDI, Bayswater, Australia).

Then, the desensitizing agent (Desensibilize KF 2%, FGM Dental Products, Joinville, Brazil) was applied to the labial surfaces of both dental hemi-arches in a 2-mm layer. The gel was maintained for 10 min without stirring. Then, the desensitizing gel was removed with a saliva ejector aspirator, and both arches were bleached with a 35% hydrogen peroxide gel containing the commercial product Whiteness HP AutoMixx (FGM, Joinville, Brazil). The bleaching gel was kept for 50 min and removed with saliva ejector, gauze, and water rinsing (Table 1).

At this moment, the right and left sides of the dental arch were separated with a thin Mylar matrix. In one dental hemi-arch, the same desensitizing gel was applied (determined by the randomization process), and the other side received a pla- cebo gel (with the same color, viscosity, etc.) that was applied in the same way reported before the bleaching protocol. This resulted in a before and after group vs. a before group. Two bleaching sessions were performed with a 1-week interval in the same way described for the first bleaching session.

Outcomes

Tooth sensitivity evaluation

The patients were instructed to fill out a form to record the tooth sensitivity immediately after bleaching, up to 1 h, 24 h, and 48 h post-bleaching in both bleaching sessions. Patients were instructed in detail how to perform the procedure. These forms were returned to the researcher on the next appointment (1-week later).

For the five-point numeric rating scale (NRS), the patient was asked to indicate the numeric value of the degree of sen- sitivity for each of the periods above in which 0 means no sensitivity, 1 mild, 2 moderate, 3 considerable, and 4 severe tooth sensitivity. In addition, the participants were also instructed to record the pain intensity using the visual analog scale (VAS). This scale is a 10-cm horizontal line with scores of 0 and 10 at their ends, in which 0 means no sensitivity and 10 means severe tooth sensitivity. The patient should mark with a vertical line across the horizontal line of the scale in the intensity of the tooth sensitivity. Then, the distance in millimeters from the zero end was measured with the aid of a millimeter ruler.

The data from both bleaching sessions were merged for statistical purposes as they were not statistically different one another (data not shown). For this purpose, the worst score (NRS scale) and the highest numerical value (VAS) from the two bleaching sessions at each assessment period were taken for data analysis. If the participant scored 0 (no sensitivity) in all time assessments from both bleaching sessions, this participant was considered to be insensitive to the bleaching protocol. In all other circumstances, the participants were considered to have bleaching-induced tooth sensitivity.

Color evaluation

Three experienced and calibrated dentists (kappa statistics higher than 80% after previous calibration), who were not involved in the randomization procedures, performed clinical assessments at baseline, 1 week after the first bleaching ses- sion, 1 week after the second bleaching, and 1 month after the bleaching treatment. We never performed color evaluation immediately after each bleaching session to avoid the effect of dehydration and demineralization on color measures. We performed the color evaluation using the shade guides VITA Classical and the VITA Bleachedguide 3D-MASTER. In addition, we performed an objective color evaluation with the spectrophotometer VITA Easyshade (VITA Zahnfabrik, Bad Säckingen, Germany).

The VITA Classical scale was arranged in 16 tabs from highest (B1) to lowest (C4) value: B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4, and C4. Although this scale is not linear in the truest sense, color changes were con- sidered as continuous and linear changes as in several clinical studies of tooth whitening [8, 9, 11, 30, 31]. The VITA Bleachedguide 3D-MASTER contains lighter shade tabs, and it is already organized from highest (0M1) to lowest (5M3) value.

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

For color measurement with the spectrophotometer, the examiner took an impression of the maxillary arch with dense silicone paste (Coltoflax and Perfil Cub Kit, Vigodent, Rio de Janeiro, Rio de Janeiro, Brazil). The impression was extended to the maxillary canines and served as a standard color measurement guide for the spectrophotometer. For each canine to be evaluated, we created a window on the buccal surface of the silicone guide using a metal device with a radius of 6 mm, which is exactly the diameter of the tip of the spectrophotometer. The tip of the device was then inserted into the silicone guide, and we obtained the L*, a*, and b* parameters of color from the spectrophotometer. The L* value represents the luminosity (value from 0 [black] to 100 [white]), a* value represents the measurement along the red-green axis, and b* value represents the measurement along the yellow-blue axis. The color

change (ΔE) before (baseline) and after each treatment (in each assessment period) is given by differences between the two colors measured with the spectrophotometer—which is calculated using the formula: ΔE = [(ΔL*)2 + (Δa*)2 + (Δb*)2]1 / 2.

Statistical analysis

The analysis followed the intent-to-treat protocol and involved all participants who were randomly divided (Fig. 1). The statistician was also blinded to the groups. The risks of tooth sensitivity of both groups were compared by means of the McNemar's exact test, used to compare proportion of dependent data (α = 0.05) test. The odds ratio as well as the confidence interval (CI) for the effect size also was calculated.

The tooth sensitivity intensity data set for both the VAS and NRS scales was plotted in histograms and inspected for nor- mal distributions. As data did not have normal distribution, the groups were compared using the Wilcoxon signed rank test and Student-Newman-Keuls method (α = 0.05). We calculated the phi correlation coefficient for pairs of binary data of the risk of pain between the two groups and the Spearman correlation coefficient for the pairs of data for the intensity of tooth sensitivity.

The means and standard deviations of color change in ΔSGU and ΔE between baseline vs. 30 days after bleaching were calculated. In order to assess whether the bleaching therapies were effective, data from both groups were compared using the Mann-Whitney test for the ΔSGU data and the paired t test for ΔE. The level of significance of all tests was set at 5%.

Results

Characteristics of included participants

A total of 122 participants were examined according to the inclusion and exclusion criteria (Fig. 1), but only 90 participants remained for the clinical trial. The baseline tooth color of the participants, mean age, and the distribution of gender is described in Table 2.

Adherence to the protocol

All participants except 1 attended the recall visits during the bleaching protocol. Figure 1 depicts the participant flow diagram in the different phases of the study design. For this participant, we have attributed the last measurable data in the missing cells.

Risk of tooth sensitivity

The phi correlation coefficient for pairs of binary data was moderate and significant ($r = 0.65$; $p < 0.001$). A total of 81 patients presented pain in the before application group, and of these, only 1 patient reported pain exclusively in the before application group. Eighty-four patients reported pain in the before and after application group, and of these, only four experienced pain exclusively in this group. No significant dif- ference between groups was observed (OR = 0.25; 95% CI 0.005 to 2.52; Table 3; McNemar's test $p = 0.37$).

The estimated proportion of patients who experienced pain in the before application side was 90% (95% CI 82 to 94.6%), and 93% reported pain in the before and after side (95% CI 86.2 to 96.9%).

Intensity of tooth sensitivity

Pain was positively correlated in both groups, the correlation being strong, positive, and significant for the NRS scales in all assessment periods (Spearman correlation; $r > 0.77$, $p < 0.0001$; Table 4). A strong, positive, and significant correlation was also observed for the VAS scale in all assessment periods (Pearson correlation; $r > 0.83$, $p < 0.0001$; Table 5). No significant differences between groups at the different time assessments were detected in the NRS scale (Table 4; $p > 0.38$) or the VAS scale (Tables 5 and 6; $p > 0.42$). The difference of means was not relevant for the VAS scale (Table 6).

Color evaluation

Significant bleaching was detected by the three different color evaluation tools (Table 7). A bleaching of approximately 7 units of color in the VITA Classical scale, 9

units in the VITA Bleachedguide, and 14 units in the ΔE was observed (Table 7). No significant difference of color change was observed between groups (Table 7; $p > 0.45$).

Discussion

Studies have reported that tooth sensitivity affects 60 to 100% patients who receive bleaching treatment, especially when in-office bleaching is the selected protocol [7, 25, 30]. Tooth sensitivity caused by hydrogen peroxide or carbamide peroxide bleaching gels is frequent, may have multiple causes, and is not completely avoidable [31]. This is why this randomized clinical trial was designed to investigate this clinical problem.

For this purpose, we opted of a within-paired design (split-mouth). This type of study removes the inter-individual variability from the estimates of the treatment effect [32] and also increases study power without the need of a high sample size. To the extent of the author's knowledge, no study has so far used the advantage of the paired design for reduction of the sample size. This is probably due to a lack of information about the correlation coefficient of the paired data for both risk and intensity of bleaching-induced TS. Had we known this information beforehand (which was described in the results section of the present study), the sample size could have been reduced to 21 patients instead of the 90 patients included, keeping constant all other parameters used for sample size calculation. These figures can serve as a guide for future within-paired RCTs during the sample size calculation.

Bleaching-induced tooth sensitivity is a very common side effect of bleaching. It is known that hydrogen peroxide has a very low molecular weight and thus can easily penetrate enamel and dentin and reach the dental pulp within few minutes [33]. In the pulp tissue, hydrogen peroxide causes an inflammation reaction [34, 35], oxidative stress, and cell damage, leading to the release of adenosine triphosphate, prostaglandins, and other inflammatory mediators that stimulate nociceptors to transmit sensitivity [26, 36].

Potassium nitrate has been described as a good alternative to minimize this side effect. One study has detected its presence in the pulp chamber of bleached teeth 30 min after application [37]. In the pulp tissue, potassium nitrate is believed to reduce

dentinal sensory nerve activity due to the lack of repolarization induced by the presence of K+ outside the nerve membrane [28, 38, 39].

However, contrary to our expectations, the use of a desensitizing bleaching gel either before or before and after bleaching did not reduce the bleaching-induced tooth sensitivity. Although this seems to be contradictory to the results of a systematic review of the literature [26], there are many flaws in the published systematic review, which reduces the reliability of the findings. Although only 6 eligible studies reported data about the risk of bleaching-induced TS [11, 24, 40–43], the authors included 11 studies in the meta-analysis by replicating individual patient data four times in one study [24] and three times in another study [43].

Another concern regarding the meta-analysis of the published systematic review [26] was the statistical model selected. The authors used a fixed-effect model. This model esti- mates a single effect that is assumed common to every study; this model only makes sense when we believe that all the studies included in the analysis are functionally identical. When the researcher is accumulating data from a series of studies that were performed by researchers operating indepen- dently, this assumption is unlikely to be true, and a random-effect meta-analysis should be performed, as it estimates the mean of a distribution of effect sizes [44].

The chances of finding significant differences between groups is higher when using a fixed-effect model, as the confidence intervals for the summary effect are wider under the random-effect model than under the fixed-effect model [44]. Based on the aforementioned discussion, unfortunately, the results of the meta- analysis of the Wang et al. [26] are overpowered, biased, and cannot be considered a reliable source of information.

Indeed, the use of desensitizing agents prior to in-office bleaching seems to be a controversial issue in the literature yet. To the extent of the author’s knowledge, the use of potassium nitrate–desensitizing agents prior to in-office bleaching was effective in three studies [11, 45, 46] and similar to the placebo in three other studies [24, 42, 47] as well as the current one. The study [25] concluded that desensitizing agents can lower tooth sensitivity risk, but they failed in the data analysis. A new statistical analysis of the data run by the authors of the present study revealed that groups were statistically similar to the control (data not shown).

However, we cannot deny that controversy still exists. A closer inspection of all

studies that investigated the use of desensitizing agents showed that the bleaching protocol was not that different. All these studies used high-concentrate hydrogen peroxide, mostly 35% [11, 24, 42, 48], except from one that used 28% [46]. They all applied the bleaching gel three times for 15 min each, and two clinical sessions were employed. The components of the desensitizing gel varied slightly among studies, but all of them contained 5% potassium nitrate.

Perhaps variations in the conclusions of these studies are based on the low sample sizes employed, which reduces the precision of the estimates. In the best scenario, 42 patients were employed in a split-mouth design [45]. In all other studies, sample size varied from 15 to 23 participants per group in a parallel design [11, 24, 42, 46]. The present study was very efficient at detecting significant differences. A total of 90 participants per group were used in a split-mouth trial. Proper control of randomization, allocation concealment, and blinding put the study at a low risk of bias, factors not observed in some of the earlier studies that investigated this issue. Altogether, these factors increase the reliability of the current study findings; but they do not exclude the need for further well-designed randomized clinical trial on this issue.

An additional comment about tooth sensitivity deserves mentioning. Pain is part of an alarming system to protect the pulp from damage, and the intensity of pain is directly correlated with the extent of the damage. Although such damage is reversible in nature, clinicians can think of using low-concentrate at-home products to reach the same bleaching efficacy with reduced side effects [7].

We should mention that the application of a desensitizing gel in the before and before and after bleaching groups did not jeopardize the color change resulting from the oxidization of the organic substrate [49], which is in line with the great majority of the earlier studies on the same topic [24, 25, 45]. Potassium nitrate does not react with hydrogen peroxide or compete with the same sites for binding in the dental structure. The present study also demonstrated that the application of a potassium nitrate–based desensitizing agent before and after bleaching was not effective to reduce bleaching-induced tooth sensitivity, meaning that saturation of the product does not seem to be the limiting factor for the desensitizing efficacy.

In summary, we can conclude that potassium nitrate applied before and before and after bleaching gel was not effective to reduce bleaching-induced TS. However, like any other medication to relieve pain, it is important to determine the onset, duration,

and proper dosage of potassium nitrate for maximum efficacy, and these considerations should be further investigated in future studies.

Conclusion

The additional application of a desensitizing gel based on 5% potassium nitrate was not effective to reduce bleaching-induced tooth sensitivity regardless of a single (before bleaching) or double application (before and after bleaching).

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The clinical investigation was approved (2.455.095) by the scientific review committee and by the committee for the protec- tion of human participants of the State University of Ponta Grossa. It was registered in the Brazilian Clinical Trials Registry (REBEC) under the identification number RBR-5v6g7f. All persons gave their informed con- sent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study were omitted.

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

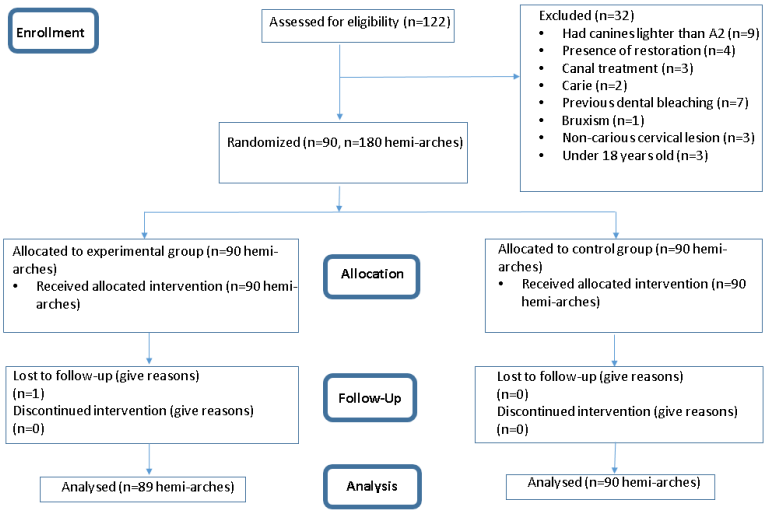

Table 1. Manufacturer, composition, and Application Method of the products employed in this randomized clinical trial

Manufacturer	Composition	Application Method
Whiteness HP AutoMixx (FGM, Joinville, SC Brazil)	Hydrogen peroxide 35%, thickening, neutralizing, consisting of calcium, glycol, dye, inorganic filler and deionized water	A single 50-minute application on dental surfaces
Desensibilize KF 2% (FGM, Joinville, SC Brazil)	Active ingredients: Potassium Nitrate at 5% and Sodium Fluoride at 2%. Inactive ingredients: Deionized Water, Glyceine, neutralizing agent and thickener.	A single 10-minute application on dental surfaces before the bleaching gel.

Table 2. Baseline Characteristics of the Participants.

Baseline color (SGU; mean ± SD)*	9.4 ± 2.3
Age (years; mean ± SD)	22.6 ± 5.5
Gender (female; %)	58.3

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

Table 3. Matched tabulation of outcomes with the two treatments along with the odds ratio.

		Before&after application			**Odds ratio(95% CI interval)***
		Positive	**Negative**	**Total**	
Before-application	Positive	80	1	81	0.25 (0.005 to 2.52)
	Negative	4	5	9	
	Total	84	6	90	

*McNemar's test (p = 0.37). Correlation coefficient between paired data = 0.64; p < 0.001.

Table 4. Medians and interquartile ranges of the tooth sensitivity intensity at different assessment points using the NRS scale and the Spearman correlation coefficient of the paired data with their respective p-values.

Assessment times	Medians and interquartile range		p-value**	Spearman correlation coefficient (p-value)
	Before-application	Before&after application		
During bleaching	1 (0 - 2) A	1 (0 - 2) A	0.97	0.77 (< 0.0001)
Up to 1 h	2 (1 – 3) B	2 (1 – 3) B	0.38	0.80 (< 0.0001)
Up to 24 h	0 (0 – 2) C	0 (0 – 2) C	0.47	0.91 (< 0.0001)
Up to 48 h	0 (0 – 0) D	0 (0 – 0) D	0.81	0.89 (< 0.0001)

**Within each column, significant differences are represented distinct uppercase letters (Friedman test and Student-Newman-Keuls Method) ; ** Wilcoxon Signed Rank test for comparison of groups within each assessment time.*

Table 5. Medians and interquartile range of the tooth sensitivity intensity at different assessment points using the VAS scale, the statistical significance and the and the Pearson correlation coefficient of the paired data with their respective p-values.

Assessment times	Medians and interquartile range*		p-value**	Pearson correlation coefficient (p-value)
	Before-application	Before&after application		
During bleaching	1.8 (0 – 4.5) A	2.1 (0 to 4.8) A	0.81	0.83 (< 0.0001)
Up to 1 h	4.8 (1.7 to 6.8) B	4.9 (1.7 to 6.9) B	0.52	0.89 (< 0.0001)
Up to 24 h	0.2 (0 to 3.5) C	0.1 (0 to 3.3) C	0.47	0.98 (< 0.0001)
Up to 48 h	0 (0 to 0) D	0 (0 to 0) D	0.42	0.92 (< 0.0001)

**Within each column, significant differences (p < 0.05) are represented distinct uppercase letters (Friedman test and Student Newman-Keuls method). ; **Comparisons between groups at each assessment point was performed with the Wilcoxon Signed Rank test.*

Table 6. Means and standard deviations of tooth sensitivity intensity at different assessment points using the VAS scale along with the difference in means (95% confidence interval).

Assessment times	Means and standard deviations		Difference in means (95% CI)
	Before-application	Before&after application	
During bleaching	2.7 ± 2.9	-0.2 (-1.07 to 0.67)	2.9 ± 3.0
Up to 1 h	4.4 ± 2.9	-0.1 (-0.97 to 0.77)	4.5 ± 3.0
Up to 24 h	2.1 ± 2.9	0.1 (-0.78 to 0.98)	2.0 ± 3.0
Up to 48 h	0.3 ± 0.9	0.0 (-0.25 to 0.25)	0.3 ± 0.8

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

Color evaluation tool	Groups		Mean difference (95% CI)	p-value*
	Before-application	Before&after application		
Vita Classical	7.2 ± 2.2	7.2 ± 2.3	0.0 (-0.09 to 0.09)	1.0
Vita Bleached	9.4 ± 2.9	9.4 ± 2.7	-0.0 (-0.30 to 0.21)	0.73
ΔE	13.9 ± 8.3	14.5 ± 10.5	-0.6 (-2.38 to 1.08)	0.45

** Paired t-test*

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4.2 ARTIGO 2

TÍTULO: Does the Use of Reservoirs Have Any Impact on the Efficacy of At-Home Bleaching? A Systematic Review.

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Does the Use of Reservoirs Have Any Impact on the Efficacy of At-Home Bleaching? A Systematic Review

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Abstract

To answer the following focused question through a systematic review: “Is the risk and intensity of tooth sensitivity (TS) and bleaching efficacy, different between adult patients who undergo at-home bleaching using trays with reservoirs and those who use trays without reservoirs?”. A comprehensive search was performed in the MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database, Brazilian Library in Dentistry, Cochrane Library, and grey literature without restrictions. Abstracts from conferences; unpublished and ongoing trial registries, dissertations and theses (ProQuest Dissertations and Periódicos Capes Theses databases) were searched. Only randomized clinical trials (RCTs) were included. We used the Risk of Bias tool (RoB) from the Cochrane Collaboration for quality assessment. After the removal of duplicates, title and abstract screening and full-text examination, nine RCTs remained for qualitative analyses. The great majority of the studies did not report the method of randomization, allocation concealment, and examiner blinding during color assessment. From the nine studies, eight were at unclear risk of bias. In regard to color change, four studies reported no change and two reported improved color change with reservoirs. Only four studies recorded tooth sensitivity and they reported no significant differences. Only one study reported greater gingival irritation with reservoirs. Lack of data reporting prevented us from running a meta-analysis. Further well-designed RCT should be conducted to answer this research question. So far there is not evidence to support that reservoirs in bleaching trays improve color change. PROSPERO - CRD42016037628.

Key Words: systematic review, reservoirs, at-home bleaching, dental sensitivity.

Introduction

Since its introduction by Haywood and Heymann (1), at-home dental bleaching has been the most commonly used method for tooth whitening. This technique is effective and simple for whitening extrinsically stained or discolored teeth (2-4). At-home bleaching has some advantages, such as ease of application, reduced chair time and costs, high success rates (5-8), and safety of materials used (8-12).

This technique requires the use of low hydrogen peroxide or carbamide peroxide concentrations placed into a custom-fabricated tray. The tray is worn from 30 min to 8 h per day or overnight for approximately 3 to 6 weeks. Some variations in the bleaching tray can be found in the literature, such as the type of thermoplastic material used for its fabrication and the presence or absence of reservoirs. The use of tray reservoirs was first introduced by Fischer (13). For such purpose, light-cured block-out resin spacers or even light-curing composite resins are applied on the buccal surface of teeth from the cast models to create an additional space between the tray and the teeth.

Some authors (14,15) report that bleaching trays with reservoirs increase the amount of available product for bleaching and allow for a complete seating of the bleaching tray, mainly when used with more viscous whitening materials (14). However, the benefits of adding a reservoir in bleaching trays are still unclear, and different results have been reported. For example, while researchers in one study observed a significantly higher degree of whitening for bleaching trays with reservoirs (16), others did not observe any benefit (15,17-21), still finding trays with reservoirs were found to be considered harmful for soft tissues due to the observed higher risk of gingival irritation (22).

We cannot rule out the fact that the lack of differences between groups with and without reservoirs could be due to the low power of these studies. Negative findings of underpowered studies do not allow one to conclude that groups are not different from one another, but rather, these results may simply be due to chance. By combining the results of small clinical trials with low risk of bias, we can have a more precise estimate of any difference between at-home bleaching procedures with and without reservoirs.

Therefore, the aim of this study was to determine whether there are evidence-based differences in tooth sensitivity and degree of color change of at-home bleaching performed with bleaching trays with and without reservoirs. For this purpose, we aimed

to answer the following PICO question (population, intervention, comparison, and outcome): “Is the risk and intensity of tooth sensitivity, as well as bleaching efficacy, different between adult patients who undergo at-home bleaching using trays with reservoirs and those who use trays without reservoirs?”

Material and Methods

Protocol and Registration

This study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO-CRD42016037628) and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for report.

Eligibility Criteria

Parallel and split-mouth randomized clinical trials (RCT) that compared at-home bleaching in adult patients of any age with and without reservoirs were included. RCTs that evaluated only one of the techniques was excluded.

Search Strategy and Information Sources

The controlled vocabulary (MeSH terms) and free keyword were used in the search strategy based on the elements of the PICO question addressed in the objectives of the study. The primary outcomes were the risk and intensity of tooth sensitivity during dental bleaching and color change measured in shade guide units (ΔS GU) or with a spectrophotometer (DE*). We also collected the data about the risk of gingival inflammation (secondary outcome).

We searched in electronic databases (MEDLINE via PubMed, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO), and Cochrane Library) and citation databases (Scopus, Web of Science) (Table 1). The reference lists of all primary studies were hand searched for additional relevant publications. No restrictions to publication date or languages were imposed. The date of the update search is described in Table 1.

Gray literature was also searched. The abstracts of the annual conference of the International Association for Dental Research (IADR) and their regional divisions (1990-2018), the database System for Information on Grey Literature in Europe (OpenSigle), dissertations and theses (ProQuest Dissertations and Periódicos Capes Theses database), were also examined. Whenever an abstract in conference meeting was found, we tried to find the full-text by searching or by contacting the study authors.

Unpublished and ongoing trials were searched in the clinical trials registries: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials. gov (www.clinicaltrials.gov), Rebec (www.ensaiosclinicos.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Study Selection and Data Collection Process

After database collection, data from each database were exported to the EndNote reference manager software (X6, Thomson Reuters, USA). Duplicates were then removed in a two-step procedure. In the first step, a specific tool from the EndNote to remove duplicates were used. However, this tool cannot remove all duplicates due to differences in the indexation process used in the different databases. In the second step, articles were alphabetically organized by title and duplicates could be identified and removed manually.

Then, articles were screened by title and abstracts according to the eligibility criteria. Full-text articles were obtained when the title and abstract presented insufficient information to make a clear decision. Subsequently three reviewers (E.M., S.P. and E.A.) classified those that met the inclusion criteria. A study ID was given for each eligible study, combining first author and year of publication.

Relevant information about the study design, participants, interventions, and outcomes were extracted using customized extraction forms by three authors in an independent manner. When data from multiple bleaching sessions were provided, we averaged the data of the same group. When more than one bleaching agent from the same bleaching protocol was included in the study, their values were merged to make a single entry. Concerning color change, we collected data that represented the most immediate result (up to three months after bleaching) and we used the same rule for tooth sensitivity (up to 1 week after bleaching).

Risk of Bias in Individual Studies

As well as data extraction, assessment of the risk of bias of the included trials were evaluated by three independent reviewers, using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (23). The assessment criteria contained six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. This latter one was not assessed in the present study. During data extraction and assessment of the risk of bias, any disagreements between the reviewers were resolved through discussion, and if needed, by consulting a third reviewer.

For each domain of the quality assessment, the risk of bias was scored following recommendations as described in the Cochrane Handbook for Systematic reviews of Interventions 5.1.0 (http://handbook.cochrane.org). The judgment for each entry involved judgements of low risk of bias, high risk of bias or "unclear" risk, indicating either lack of information or uncertainty over the potential for bias.

At the study level, studies were judged at "low" risk of bias if there was adequate sequence generation, allocation concealment and operator blinding (key domains of the Cochrane risk of bias tool). If at least one of these domains were considered "unclear", the study received the same judgment. On the other hand, if at least one key domain was at high risk of bias, the study was judged as "high" risk.

Summary Measures and Synthesis of the Results

Tables and figures were created to synthesize the results. We attempted to collect results about color change, risk and intensity of tooth sensitivity and gingival irritation. Authors were not contacted for further information due to the fact that empirical evidence shows a low response rate in articles published more than a decade ago.

Results

Study Selection

After the database screening and removal of duplicates, 2523 studies were identified. After title screening, 189 studies remained, and this number was reduced to nine after a careful examination of their abstracts. Of these nine, two were abstracts published by the International Association for Dental Research (IADR) (16,17) and one was registered in REBEC (Brazilian Registry of Clinical Trials) (24) (Fig. 1).

Characteristics of Included Articles

The characteristics of the studies selected are listed in Table 2. A split-mouth study design was used in eight studies, and a parallel design was used in only one study (16). For color evaluation, three studies involved the use of shade guides, although data were not reported or were poorly reported in the results section (15,17,19). Subjective description of the findings, based on photographs or clinical observations, was used in three studies (18,20,25). Three other studies used an objective instrument (spectrophotometer or colorimeter) for color assessment (15,16,24), and one did not evaluate color changes (22).

The number of patients included in these studies was small and ranged from 5 to 36 participants. There was a high variability in the participants' age. While some studies predominantly included young adult patients (18 to 40 years old) (16,18,22,25) others included elderly patients as well (19 to 68 years old) (15,16,19,20). This information was not reported in the study of Bosma et al. (17). In one study, males were the majority of the participants (22); in 4 other articles, females predominated (15,19,20,25), and in the remaining 3, this information was not reported (16-18).

The bleaching protocol was different among the studies. Four studies used 10% carbamide peroxide for at-home bleaching (19,20,24,25), and four studies used carbamide peroxide with higher concentrations, such as 15% (15,20), 16% (20,22) and 20% (20). Only two studies used hydrogen peroxide for at-home bleaching (18,20). The type of bleaching agent and concentration was not reported in two studies (16,17). The daily duration of use of the at-home bleaching gel varied from 2 to 8 h per day. In one study, the gel was used twice a day (19). The number of treatment days varied from 10 to 30 days.

Four studies did not evaluate the risk of tooth sensitivity (16,17,20,22). As for gingival irritation, we could not find this information in seven out of nine primary studies (15-18,20,22,25). Kirsten et al (22) classified the inflammation of the gingival tissue via histological evaluation. Only one study evaluated the risk and intensity of tooth sensitivity and gingival irritation (24).

Main Findings

The main findings of the eligible studies are described in Table 3. One may observe a lack of data reporting and the use of adequate instruments for evaluation of color change and the risk and intensity of tooth sensitivity. Description of summary measures and variance of the data was rarely reported. The study of Martini et al (24) was found in a clinical trial registry as protocol and the data were not collected yet.

Regarding color evaluation, only three studies reported color changes using statistical evaluation (15,16). The other studies performed a qualitative description of color changes. Two studies did not evaluate color change (22,25); four reported that changes were not observed (17,18,19,20), two reported that reservoirs improved color change (15,16) and one study have not collected data yet (24).

In regard to tooth sensitivity, four studies did not evaluate this outcome (16-18,22), one did not collected this data yet (24) and the remaining reported similar tooth sensitivity between the groups (15,19,20,25) and were similar in both groups (25). For gingival irritation, four studies did not evaluate this outcome (16,18,20,25), three studies did not observe any difference between groups (15,17,19) and only 1 reported greater inflammation in the group with reservoirs (22).

Assessment of the Risk of Bias

The risk of bias of the selected studies is presented in Figure 2. Except for the study of Bosma (17) and Martini (24), which reported the method of randomization, the other studies did not report the method of randomization or did not perform it correctly (15,16,18-20,22,25). Allocation concealment and examiner blinding during color assessment were also missing in the studies. Another important issue is the selective reporting observed in some studies that did not report color change and/or tooth sensitivity (17,20,22,25). In summary, of the 9 studies, 8 were at unclear risk of bias.

Discussion

Meta-analysis is usually performed in systematic reviews to obtain a statistical summary and an estimate of the effect size for the study problem. However, the meta-analysis will never be better than the primary studies included. Surprisingly, the great majority of the studies from the present review were at unclear risk of bias, which reduced the reliability of the study findings reported by authors and described in Table 3.

Some important aspects of well-designed clinical studies were missing in the eligible studies of the present study, such as randomization, allocation concealment, and blinding. Randomization, when correctly performed, allows a patient or a patient's side mouth to be allocated in either the test or control group, controlling for both known and unknown prognostic factors (23). Among the primary studies of this systematic review, we observed that adequate sequence generation was not performed in most of them (18,20,25). Only one study (17) reported that a random sequence was generated by computer, however without further details. In other two studies (15,24), the authors reported that the study was randomized, but the method of randomization was not clear.

As important as randomization, allocation concealment is necessary to protect the randomization process since the treatment to be allocated is not known before the patient is enrolled into the study (23). The description of the allocation concealment was unclear in eight primary studies, perhaps because the authors did not know its importance at the time the studies were conducted. Both randomization and allocation concealment are essential to minimize selection bias. To clarify whether allocation concealment was done, contact with authors can be established. However, we did not contact them as authors tend to produce only positive answers in regard to the risk of bias, which may not represent the truth (23,26).

Another important issue in clinical trials that prevents another type of bias - performance bias - is blinding of examiner and patient (23). For the focused PICO question evaluated in this study, participant blinding was not possible, as differences between bleaching trays could be easily identified by the participants. However, blinding of the examiner could have been performed.

From the nine studies, only one reported that the evaluator was blinded (24), but this study was a protocol registered in a clinical trial in which results were not

available yet. As for the other eight studies already published, this was a serious limitation of the methodology of these studies that further reduces the reliability of the findings.

Apart from the above limitations, which are not much different from what has already been observed in bleaching studies in general (27), the most shocking finding was the lack of standardized methods for reporting important outcomes in bleaching studies, such as color change, risk of tooth sensitivity, and gingival irritation. This fact along with lack of examiner blinding reduces consistently the reliability of the study findings of the eligible studies. Color change is usually evaluated by using either subjective methods (matching with different shade guide units) or objective methods (spectrophotometer or colorimeters). It is reported that measurement with a spectrophotometer provides more accurate results than visual shade matching with shade guides (28,29) as it is less prone to subjective judgments. Only three out of nine primary studies reported the use of objective tools for measurement of primary outcomes (15,16,24). Future clinical trials on bleaching should use a validated instrument to measure color changes, to improve confidence in the results.

Color evaluation by matching with shade guide units was another way to allow for comparison between groups and this procedure was done in three studies (15,17,19). Two out of these three reported changes in shade guide units, but they failed to report measures of data spread (standard deviation or standard error) (15,17). In the third study (19), color change was not reported at all. All other studies, except for the study of Kirsten (22), which did not evaluate color change, only included a narrative description of what was observed in both groups without any further elaboration (16,18-20,25). This poor description of color change does not allow one to conclude via meta-analysis if bleaching trays with reservoirs are more effective or produce faster color change than bleaching trays without reservoirs. The same concern was observed for the outcomes were “risk of tooth sensitivity” and “risk of gingivalirritation”. These outcomes were not evaluated or were reported inadequately in the great majority of the studies (15-18, 20, 22, 25), which prevents us from making any conclusion about the likely side effects of bleaching trays with reservoirs.

Unfortunately, there are several other variables among the primary studies, apart from the presence or absence of reservoirs in the bleaching trays. The low number of studies included in this systematic review prevented us from evaluating the impact of these differences on the results (different protocols, type and concentration

of bleaching agents, brand and composition of the product, etc.). The comparison of some of these variables was evaluated in other systematic reviews of the literature. For instance, when carbamide peroxide gels were compared with hydrogen peroxide for at-home bleaching, the former showed better color change (30). Although there are other RCTs that addressed the aforementioned variables, they are still in low number, and their qualities were not addressed yet by systematic reviews of the literature (12,31,32), which may be the subject of future studies.

Although most of the manufacturers do not recommend the creation of reservoirs in bleaching trays, at least one important company that produces bleaching products (Ultradent Products, Inc., Salt Lake, UT, USA) still recommends the fabrication of such reservoirs in bleaching trays for at-home bleaching. Considering that at-home bleaching with reservoirs is more expensive, as it employs more material and requires more time for fabrication of the bleaching trays, it is essential, from a clinical standpoint, to gather information about how worthwhile this method is.

From the findings of the present study, we concluded that there is no reliable evidence to make any conclusion about the efficacy and side effects of bleaching trays with reservoirs compared to bleaching trays without reservoirs, due to the lack of well-designed clinical studies on this subject. Further well-designed randomized clinical trials with good reporting should be performed by carefully following the Consolidate Standards of Reporting Trials (CONSORT) (27,33).

Table 1: Electronic Database and Search Strategy

Pubmed (8thOctober 2018)		
#1 tooth discoloration [MeSH Terms] OR color [title/abstract] OR “tooth discoloration" [title/abstract] OR “tooth staining” [title/abstract] OR “stained tooth" [title/abstract] OR “stained teeth" [title/abstract] OR “tooth discolouration" [title/abstract] OR “teeth discolouration" [title/abstract] OR “discolored tooth” [title/abstract] OR “discolored teeth” [title/abstract] OR “discoloured tooth” [title/abstract] OR “discoloured teeth” [title/abstract] OR “dental discoloration” [title/abstract]OR “dental discolouration” [title/abstract]	#2 Peroxides [MeSH Terms] OR tooth bleaching [MeSH Terms] OR tooth bleaching agents [MeSH Terms] OR hydrogen peroxide [MeSH Terms] OR carbamide peroxide [Supplementary Concept]) OR peroxides [title/abstract] OR “hydrogen peroxide” [title/abstract] OR “carbamide peroxide” [title/abstract] OR tray [title/abstract] OR trays [title/abstract] OR reservoir [title/abstract] OR reservoirs [title/abstract] OR whitening [title/abstract] OR bleaching [title/abstract] OR “home-use" [title/abstract] OR nightguard [title/abstract] OR “at-home” [title/abstract]	#3 randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies as topic [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh]))
#1 AND #2		
Scopus (8thOctober 2018)		
#1 TITLE-ABS-KEY (‘‘tooth discoloration’’) OR TITLE-ABS-KEY (‘‘tooth staining’’) OR TITLE-ABS-KEY (“stained tooth") OR TITLE-	#2 TITLE-ABS-KEY (“peroxide”) OR TITLE-ABS-KEY (‘‘hydrogen peroxide’’) OR TITLE-ABS-KEY (‘‘carbamide peroxide’’) OR TITLE-ABS-KEY (“tray”) OR TITLE-ABS-KEY (“reservoir”)	

ABS-KEY (‘‘discolored tooth’’) OR TITLE-ABS-KEY (“dental discoloration”)	OR TITLE-ABS-KEY (“whitening”) OR TITLE-ABS-KEY (“bleaching”) OR TITLE-ABS-KEY (‘‘home-use’’) OR TITLE-ABS-KEY (“nightguard”) OR TITLE-ABS-KEY (‘‘at-home’’)
#1 AND #2	
Web of Science (8thOctober 2018)	
#1TS=("t??thdiscolo$ration") OR TS=("tooth staining") OR TS=("stained t??th") OR TS=("discolo$red t??th") OR TS=("dental discolo$ration")	#2TS=(peroxides) OR TS=("hydrogen peroxide") OR TS=("carbamide peroxide") OR TS=(tray*) OR TS=(reservoir*) OR TS=(whitening) OR TS=(bleaching) OR TS=("home-use") OR TS=(nightguard) OR TS=("at-home")
#1 AND #2	
LILACS and BBO (8thOctober 2018)	
#1(tw:((MH: "tooth discoloration" OR MH: "descoloração de dente" OR MH: "descoloración de dientes" OR "tooth discoloration" OR "descoloração de dente" OR "descoloración de dientes" OR "tooth staining" OR "stained tooth" OR "stained teeth" OR "tooth discolouration" OR "teeth discolouration" OR "discolored tooth" OR "discolored teeth" OR "discoloured tooth" OR "discoloured teeth" OR "dental discoloration" OR "dental discolouration" OR "descoloração dental" OR "manchamento dental" OR "dentesescuros" OR "escurecimento dental" OR "dientes oscuros" OR "manchas en los dientes" OR "oscurecimiento dental" OR "pigmentación dental" OR "dientes pigmentados")))	#2(tw:((MH: "peroxides" OR MH: "tooth bleaching" OR MH: "tooth bleaching agents" OR MH: "hydrogen peroxide" OR "peroxides" OR "tooth bleaching" OR "clareamento dental" OR "blanqueamiento de dientes" OR "tooth bleaching agents" OR "clareadores dentários" OR "blanqueadores dentales" OR "blanqueamiento dental" OR "hydrogen peroxide" OR "peróxido de hidrogênio" OR "peróxido de hidrógeno" OR "carbamide peroxide" OR "peróxido de carbamida" OR "clareamento caseiro" OR "blanqueamiento en casa" OR "trays" OR "moldeira de clareamento" OR "cubeta de blanqueamiento" OR "reservoirs" OR "reservatórios" OR "reservorios" OR "whitening" OR "bleaching" OR "home-use" OR "nightguard" OR "at-home")))
#1 AND #2	

Cochrane Library (8th October 2018)	
#1 MeSH descriptor: [Tooth Discoloration] explode all trees #2 “tooth staining”: ti,ab,kw (Word variations have been searched) #3 stained near t??th :ti,ab,kw (Word variations have been searched) #4 discol*red near t??th:ti,ab,kw (Word variations have been searched) #5 dental near discol*ration:ti,ab,kw (Word variations have been searched) #6 - #1 or #2 or #3 or #4 or #5 #7MeSH descriptor: [Peroxides] explode all trees #8MeSH descriptor: [Tooth Bleaching] explode all trees #9MeSH descriptor: [Tooth Bleaching Agents] explode all trees #10MeSH descriptor: [Hydrogen Peroxide] explode all trees #11 “carbamide peroxide”: ti,ab,kw (Word variations have been searched) #12 tray?:ti,ab,kw (Word variations have been searched) #13 reservoir?:ti,ab,kw (Word variations have been searched)	#14 “whitening”: ti,ab,kw (Word variations have been searched) #15 “bleaching”: ti,ab,kw (Word variations have been searched) #16 “home use”: ti,ab,kw (Word variations have been searched) #17 “nightguard”: ti,ab,kw (Word variations have been searched) #18 “at home”: ti,ab,kw (Word variations have been searched) #19 - #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 #20 - #6 AND #19

Figure 1. Flow diagram of study identification

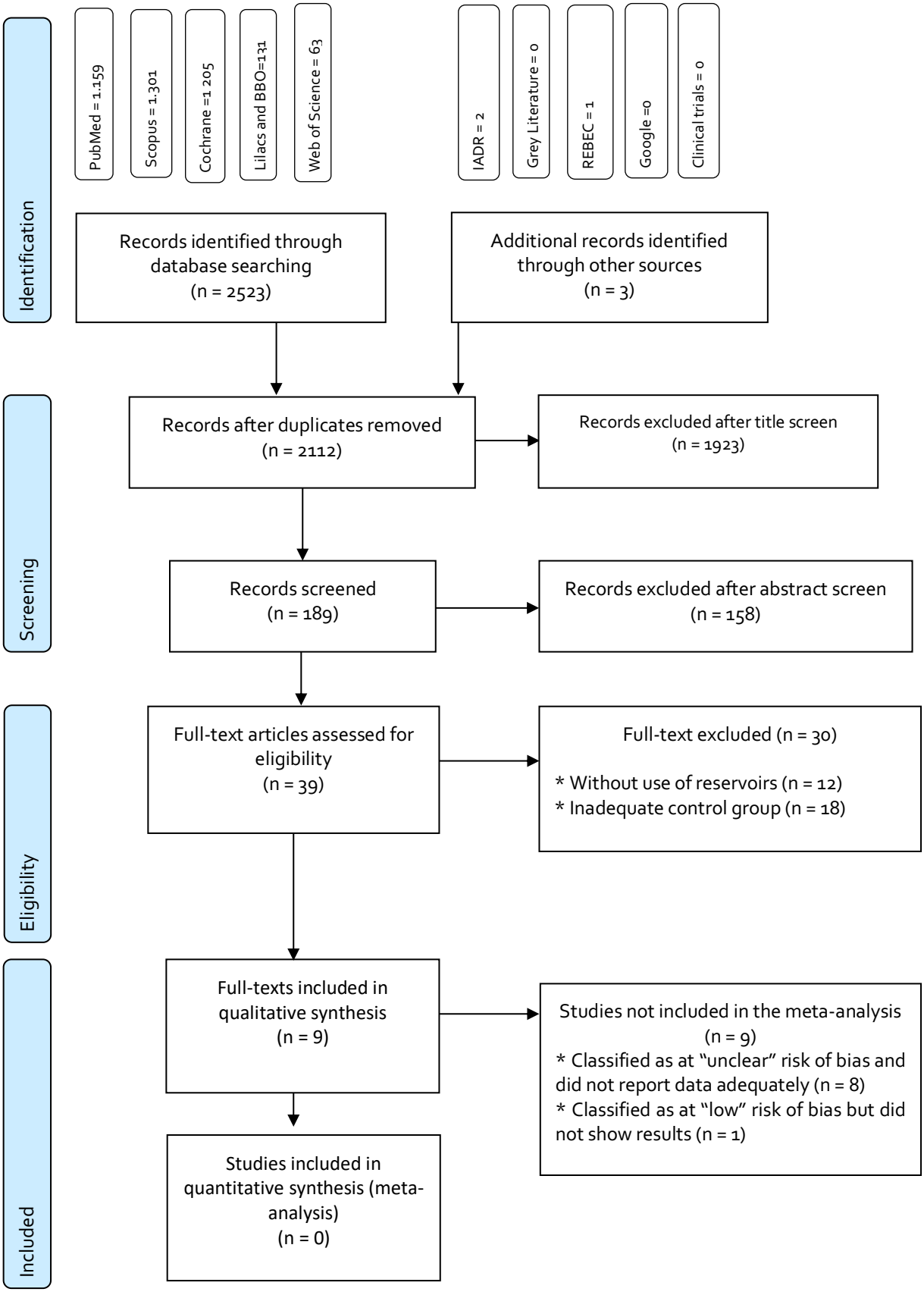

Table 2: Summary of the studies selected for qualitative analysis this systematic review.

Study ID	Study design [setting]	Method of color assessment	Subject's age in mean ± SD [range] (yrs)	No. of subjects (male [%])	No. patients [drop-outs]	Groups/ materials	Bleaching protocol	Outcomes evaluated		
								Color change	Tooth sensitivity	Gingival Inflammation
Bosma 2000[1]	Split mouth [n.r.]	Vita shade guide and narrative description based on photographies	n.r. ± n.r. [n.r.]	n.r.[n.r.]	34 [0]	n.r. 16% CP[c]	4 h daily (2 weeks)	ΔSGU, but SD was not reported	Not evaluated	n.r.
Delgado 2000 [2]	Split mouth [University]	Narrative description based on photographies	n.r. ± n.r. [19-23]	n.r.	12 [0]	15% CP[d]	8 h daily (15 days)	n.r. Only subjective description	Absolute risk, but data was partially reported	Not evaluated.
Ishikawa 2011[3]	Parallel [n.r.]	Colorimeter[a]	n.r. ±n.r. [20-40]	n.r.[n.r.]	5 [0]	n.r. 10% CP[e]	2 h daily (14 days)	ΔL, Δa, Δb, but SD was not reported.	Not evaluated	Not evaluated
Javaheri 2000 [4]	Split mouth [n.r.]	Shade guide unit[b]	n.r. ± n.r. [19-64]	8 [26]	30 [0]	10% CP[f]	2 hours/twice a day (10 days)	ΔSGU but data was not reported.	Absolute risk	Absolute risk
Kirsten 2009 [5]	Split mouth [University]	n.r.	n.r. ± n.r. [18-25]	19 [100]	19 [0]	16% CP[g]	2 hours daily (21 days)	Not evaluated.	Not evaluated.	Not evaluated. Only histological

										evaluation of the gingival tissue.
Matis 2002 [6]	Split mouth [n.r.]	Photos, Shade Guide and Colorimeter readings	48.3 ± n.r. [23-68]	12 [44]	27 [0]	15% CP[h]	2 hours daily (14 days)	ΔE and ΔSGU but SD was not reported in both measures	Absolute risk but SD was not reported	Intensity of pain, but SD was not reported
Miller 2000 [7]	Split mouth [n.r.]	Narrative description based on photographies	n.r. ± n.r. [20-50]	4 [19]	21 [0]	HP (5,5[i] and 7,5%[i]); Nonperoxide[j]; CP (10[l], 10[f], 10[m]; 16[c], 16[l], 16[n], 16[m]; 15[b], 20[o])	Not mentioned (followed manufacturer's directions).	n.r. Only subjective description.	Not evaluated	Not evaluated
Morais e Moura 2007 [8]	Split mouth [n.r.]	Narrative description based on photographies	n.r. ± n.r. [15-40]	8 [22]	36 [0]	10% CP[p]	4 h daily (14-30 days)	n.r. Only subjective description	Absolute risk, data was partially reported	Not evaluated
Martini 2018 [9]	Split mouth [University]	Shade Guide and Colorimeter readings	n.r. [18-50]	n.r.	n.r.	10% CP[q]	3 h daily (21 days)	ΔE and ΔSGU	Risk and intensity (VAS and NRS scales)	Absolute risk

Abbreviations: CP, carbamide peroxide; HP, hydrogen peroxide; n.r., not reported; SD, standard deviation; ΔSGU, shade guide units; ΔE (color difference measured with a spectrophotometer). Absolute risk of TS is the percentage of patients that presented TS during bleaching, while intensity of TS is the pain intensity measured in a pain scale.*

[a] Shofu Shade Eye NCC, Shofu, Kyoto, JP

[b] VITAPAN classical, VITA Zahnfabrik, Bad Säckingen, GE

[c] Nite White Classic 16%, Discus Dental, Culver City, CA, USA

[d] Opalescence 15%, Ultradent, South Jordan, UT, USA

[e] HiLite Shade Up, Shofu Dental Products, Tonbridge, Kent, UK

[f] Nupro White Gold 10%, Dentsply, York, PA, USA

[g] Whiteness Perfect 16%, FGM, Joinville, SC, BR

[h] Rembrandt Xtra-Comfort Non- Sensitizing Bleaching Gel Regular Strength , Den-Mat Corporation, Santa Maria, CA, USA

[i] Day White 2, Discus Dental, Culver City, CA, USA

[j] Hi Lite 2, Shofu Dental Products, Tonbridge, Kent, UK

[l] Nite White Excel 2Z, Discus Dental, Culver City, CA, USA

[m] Zaris 3M dental, Zaris White & Brite; 3M ESPE, St. Paul, USA

[n] Nite White Excel 2NSF, Discus Dental, Culver City, CA, USA

[o] Opalescence 20%, Ultradent, South Jordan, UT, USA

[p] Whiteness Perfect 10%, FGM, Joinville, SC, BR

[q] Opalescence 10%, Ultradent, South Jordan, UT, USA

Table 3: Summaries of the main findings of the articles included in the qualitative analysis.

Study ID	**Description of the results**		
	Color change	**Tooth sensitivity**	**Gingival Inflammation**
Bosma 2000[1]	Subjective description through photos with a reduction of 5.6 color units in the 2 groups, without significant differences (p> 0.05).	Not evaluated	Not observed in any group.
Delgado 2000 [2]	Subjective description through photos. The authors concluded that the groups were not different.	Only one patient reported tooth sensitivity and was treated with 1.1% NaF. No measurement in pain scale was reported by the authors.	Not evaluated
Ishikawa 2011[3]	5 patients were evaluated through objective color measurement. 8 units of color on the side with reservoirs and 6.8 on the side without reservoirs (p < 0.05).	Not evaluated	Not evaluated
Javaheri 2000 [4]	30 patients evaluated with subjective color measurement, no difference between sides was noted and no statistical analysis was performed.	None of the patients reported tooth sensitivity.	None of the patients reported irritation in the mucosa..

Kirsten 2009 [5]	Not evaluated.	Not evaluated.	19 patients evaluated, sides with reservoir increase of inflammation only immediately after bleaching ($p = .0075$). Differences were found in the inflammation intensity between groups immediately after and 45 days after bleaching ($p < 0.01$). Mild inflammation in the group without reservoir and moderate inflammation with a reservoir.
Matis 2002 [6]	Group with reservoirs had significantly higher ΔE than group without reservoirs in all time assessments ($p < 0.01$), except week 6 ($p = 0.11$).	No significant difference ($p = 0.90$).	No significant difference ($p = 0.46$).
Miller 2000 [7]	Subjective description through photos and without differences between groups.	No significant difference.	Not evaluated.
Morais e Moura 2007 [8]	Not evaluated.	18^{th} day only – same tooth sensitivity in both groups.	Not evaluated.
Martini 2018 [9]	Results not collected yet (study found in a clinical trial registry)	Results not collected yet	Results not collected yet

Figure 2: Summary of the risk of bias assessment according to the Cochrane Collaboration tool.

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4.3 ARTIGO 3

TÍTULO: Evaluation of reservoirs in bleaching trays for at-home bleaching: a split-mouth single-blind randomized controlled equivalence trial.

STATUS: Submetido e aguardando revisão.

REVISTA: Clinical Oral Investigations.

Evaluation of reservoirs in bleaching trays for at-home bleaching: a split-mouth single-blind randomized controlled equivalence trial.

Abstract

Background. This randomized, split-mouth, single-blinded trial assessed whether the use of reservoirs in at-home bleaching trays is equivalent to non-reservoir trays in color change. Our choice for equivalence trial was based on the expectation that a non-reservoir tray is sufficient to produce a color change. Secondary outcomes such, tooth sensitivity (TS) and gingival irritation (GI) were also assessed.

Methods. Forty-six patients were selected for this trial. Participants had canines shade A2 or darker. In half of the patient's arch, bleaching trays were made with reservoirs and the other half, without reservoirs. At-home bleaching was performed (carbamide peroxide 10%; 3 h daily; 21 days). Color change (CC) was evaluated with a digital spectrophotometer and shade guide units at baseline, during and one-month post-bleaching. TS and GI were assessed with a numeric rating scale (NRS) and a visual analog scale (VAS).

Results. After one month, the equivalence of reservoir and non-reservoir groups were observed in all color instruments, with an average CC of eight units in Vita Classical, 11 units in Vita Bleachedguide and 13 unis in ΔE. Fifteen and sixteen patients presented pain (absolute risk: 33% and 35%, 95%CI 21-46% and 23-49%) in the reservoir and no reservoir side, respectively. The odds ratio for pain was 0.8 (95%CI 0.2-3.0) and not significance ($p = 1.0$). TS intensity was similar between both groups in any of the pain scales ($p > 0.05$). No difference in the GI was observed ($p > 0.05$).

Conclusions. It is concluded that the protocol with reservoirs is equivalent in color change to the non reservoir, although no superiority of the latter was observed in terms of reduced TS and GI with at-home 10% carbamide peroxide bleaching.

Practical Implications. The presence of reservoirs in a bleaching tray did not improve color change or affect tooth sensitivity and gingival irritation.

Key words. Tooth bleaching; dentin sensitivity; randomized controlled clinical trial; reservoirs; carbamide peroxide.

Introduction

Dental bleaching is widely used to make teeth whiter and brighter, which is a desire of most patients.[1-3] The dentist-supervised dental bleaching technique can be professionally performed using high-concentrate materials (in-office protocol) or by dispensing low concentrate-material in a custom bleaching tray (at-home use).

Among these available protocols, clinicians consider at-home bleaching safer as it employs low concentrate products[2] and therefore reduces the risk and intensity of tooth sensitivity.[4, 5] Additionally, it is an easy protocol, requires reduced chair-time, and it is less costly than the in-office protocol.

Since the introduction of at-home bleaching, several modifications of the protocol and materials occurred in the past years. Carbamide peroxide or hydrogen peroxide with varied concentrations can be employed.[6] The daily usage time of the bleaching tray was reduced[7, 8] and modifications in the manufacture of the bleaching trays[9] were proposed with the presence of reservoirs.[2, 10, 11]

Reservoirs are modifications in the tray molds to increase the amount of bleaching material carried by the bleaching tray, thus seeking greater bleaching efficacy. Fisher first introduced the use of tray reservoirs in 1992.[12] For such purpose, light-cured block-out resin or light-curing composites are applied on the buccal surface of teeth from the cast models to create an additional space between the tray and the teeth. The first report on the efficacy of reservoirs in bleaching trays come from the end of the 1990s.[11] This as well as other clinical studies[11, 13, 14] contested the efficacy of tray reservoirs in bleaching trays.

In a recent systematic review, the authors concluded that the majority of the studies that compared no-reservoir and reservoirs were at unclear risk of bias, indicating the need for well-designed clinical trials.[15] Some important aspects of well-designed clinical studies such as randomization, allocation concealment, and blinding were missing in the eligible studies[10, 11, 13, 14, 16-18] and the studies lacked standardized methods for reporting important outcomes, such as color change, tooth sensitivity, and gingival irritation. This prevented the authors from

this systematic review[15] to conclude on the study's findings but to ask for the conduction of additional well-designed clinical trials that answer the same research question.

Therefore, the objective of this study was to conduct a randomized controlled equivalence trial with a split-mouth design to test that non reservoir trays are 'as effective as' reservoir trays in terms of color change. The secondary outcomes risk of tooth sensitivity, intensity of tooth sensitivity, and gingival irritation were compared in a traditional superiority hypothesis testing.

Methods

Ethics approval and protocol registration

The clinical investigation was approved (protocol number 2.124.508) by the scientific review committee and by the Committee for the Protection of Human Participants of the State University of Ponta Grossa. We registered the protocol in the Brazilian Clinical Trials Registry (REBEC) under the identification number RBR-4w9ht3. We prepared this study using the protocol established by the Consolidated Standards of Reporting Trials statement with extension for noninferiority and equivalence trials and within-person designs.[19, 20] Readers can found the explanatory document about these CONSORT extensions in the website: www.consort.org.

Trial design, settings and locations of data collection

This equivalence trial was a randomized, split-mouth, and single-blind controlled equivalence trial. The study was performed from April 5, 2018, to October 15, 2018, in the Clinics of the School of Dentistry from the local university. Participants, reference treatment, main and secondary outcomes are identical to those used in other trials that establish efficacy of the reference treatment.

Recruitment

Recruitment of patients was carried out through social media advertising. To facilitate communication between the research staff and the volunteers, we

set up a social network group. All volunteer participants signed an informed consent form before being enrolled in the study.

Eligibility criteria

Based on pre-established criteria, we selected 46 subjects volunteered for this study. Participants should be in good general health (self-reported by the patient as not being under medical treatment) and good oral health (not in need of surgical, endodontic, periodontal and restorative treatment). They should be at least 18 to 40 years old. The participants were required to have the six maxillary anterior teeth free of caries, restorations or endodontic treatment, with canine shade A2 or darker, as judged by comparison with a value-oriented shade guide (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Germany).

Participants with orthodontics apparatus, dental prosthesis, severe internal tooth discoloration (tetracycline stains, fluorosis or pulpless teeth) were not included in the study. Besides, pregnant and lactating women, participants with bruxism or any pathology that could cause sensitivity (such as recession, dentinal exposure, visible cracks in teeth), taking anti-inflammatory or analgesic drugs or participants who had already undergone tooth-whitening procedures were also excluded.

Sample size calculation

We designed this study to demonstrate equivalence in color change between at-home bleaching with reservoirs and without reservoirs. The sample size calculation showed that a minimal of 30 participants (alpha of 5%; power 90%) would be necessary to demonstrate an equivalence of 3 units of ΔE. The standard deviation of the ΔE after 3-week bleaching with a 10% carbamide peroxide was reported to be around 3.5 units, 21 and this value was used for sample size calculation. Due to the high number of volunteers for bleaching, a total of 46 participants took part in this controlled trial. The equivalence margin was specified a priori based on earlier studies that report that only ΔE higher than 3.3 is clinically perceptible.[22]

The sample size calculation was performed without accounting for the potential correlation between the paired treatment outcomes, as done for parallel designs. This approach resulted in a larger sample size than if the correlation coefficient between treatment outcomes is not zero. We performed this approach because published within-person trials do not report this correlation coefficient, and thus, we opted for being conservative.

Randomization and allocation concealment

A simple randomization process was performed on the website www.sealedenvelope.com by a third person, not involved in the steps of implementation and evaluation. The distribution of the group to be first assigned was recorded on sequentially numbered cards, and placed in opaque and sealed envelopes. The information contained in the envelope determined the treatment to be assigned in the upper right maxillary arch, while the other arch received the alternate treatment. Once the participant was eligible for the procedure and all initial evaluations were completed, the allocation assignment was revealed by opening the envelope immediately after implementation.

Blinding

This study was a randomized, single-blind controlled trial, in which the evaluator was masked to the group assignment. A researcher, not involved in the implementation and evaluation process, was responsible for the randomization process, and another operator was responsible for the delivery and guidance on the administration of the bleaching trays.

Study Intervention

Two dentists, with more than 5 years of clinical experience (E.M. and F.M.C.) performed the bleaching procedure. They made alginate impressions of each participant's jaw, and after disinfection, filled them with dental stone. The upper arch models were used in the study. In one of the sides, a photopolymerized blocking material (Top Dam, FGM, Joinville, SC, Brazil) was applied in the buccal surfaces of the central, lateral, canine and premolar teeth in one side of the patient’s mouth to create reservoirs on these teeth.

The blocking resin was applied so that the labial surface was covered except for 1 mm mesial, distal and cervical. The other half arch had no reservoirs. The randomization processed defined the side that would receive the reservoirs. A 1.0 mm soft vinyl material (Ultradent Products, South Jordan, UT, USA) was used to fabricate the custom-fitted trays that would hold the whitening gel in the Plastivac P7 (BioArt, São Carlos, Brazil). The excess material from the labial and lingual surfaces was trimmed to 1 mm away from the gingival margin.

We instructed all participants to use the bleaching tray with the bleaching agent (10% carbamide peroxide with potassium nitrate and fluoride, Opalescence PF, Ultradent Products) for 3 hours once a day for 21 days. They were instructed to place an amount of gel to cover the buccal surface of all teeth (this amount being slightly higher in the reservoir-side of the bleaching tray). Participants were instructed to remove the tray after each bleaching period, rinse teeth with water and brush their teeth as usual.

As a measure of adherence to the experimental protocol study, participants received a diary in which they were asked to take note of the number of hours a day they used the tray during treatment. They were reminded of this procedure daily using the social media network group set up at the beginning of the study protocol.

Outcomes

Color evaluation

For the evaluation of this primary outcome, two experienced and calibrated dentists (kappa statistics higher than 80% after previous calibration), who were not involved in the randomization procedures, performed clinical assessments at baseline, after each week of bleaching and 1 month after the bleaching treatment.

We performed the calibration procedure using twenty volunteers. The operators checked the color of canines independently, using shade guides, and when differences were noted, they had to reach an agreement. This procedure was repeated until they get a kappa equal to or higher than 80% in two consecutive measurements.

We performed the color evaluation using the shade guide VITA Classical and the VITA Bleachedguide 3D-MASTER. Also, we performed an objective color evaluation with the spectrophotometer VITA Easyshade (VITA Zahnfabrik, Bad Säckingen, Germany).

We arranged the Vita Classical scale in 16 tabs from highest (B1) to lowest (C4) value: B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4, C4. The VITA Bleachedguide 3D-MASTER contains lighter shade tabs, and it is already organized from highest (0M1) to lowest (5M3) value. The tooth matching area was the middle third of the buccal surface of the upper canines. Color changes were calculated from the beginning of the active phase up to the specific recall times by calculating the change in the number of shade guide units (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs. In case of disagreement between operators, they should reach a consensus.

For color measurement with the spectrophotometer, the examiner took an impression of the maxillary arch with dense silicone paste (Coltoflax and Perfil Cub Kit, Vigodent, Rio de Janeiro, Rio de Janeiro, Brazil). The impression was extended to the maxillary canines and served as a standard color measurement guide for the spectrophotometer. For each canine, we created a window on the buccal surface of the silicone guide using a metal device with a radius of 6 mm, which is precisely the diameter of the tip of the spectrophotometer. The tip of the device was then inserted into the silicone guide and we obtained the L*, a*, and b* parameters of color from the spectrophotometer. The L* value represents the luminosity (value from 0 [black] to 100 [white]), a* value represents the measurement along the red-green axis, and b* value represents the measurement along the yellow-blue axis. The color change (ΔE) before (baseline) and after each treatment (in each assessment period) is given by differences between the two colors measured with the spectrophotometer — which is calculated using the formula: $\Delta E = [(\Delta L^*)2 + (\Delta a^*)2 + (\Delta b^*)2]1/2$.

Tooth sensitivity evaluation

We instructed patients to complete a form to record daily dental sensitivity after bleaching. Patients were instructed in detail on how to perform this procedure. These forms returned to the investigator at every clinical appointment.

For the 5-point numeric rating scale (NRS), we asked the patient to indicate the numeric value of the degree of sensitivity for each of the periods above in which zero means no sensitivity, one mild, two moderate, three considerable, and four severe tooth sensitivity. In addition, the participants were also instructed to record the pain intensity using the visual analog scale (VAS). This scale is a 10-centimeter horizontal line with scores of zero and ten at their ends, in which zero means no sensitivity, and ten means severe tooth sensitivity. The patient should mark with a vertical line across the horizontal line of the scale the intensity of the tooth sensitivity. Then, the distance in millimeters from the zero end was measured with the aid of a millimeter ruler.

We merged the daily data from the three weeks of bleaching for statistical purposes. For this purpose, the worst score (NRS scale) and the highest numerical value (VAS scale) from the total period were taken to represent the patient's sensitivity level throughout the study. If the participant scored zero (no sensitivity) in all time-assessments, this participant was considered to be insensitive to the bleaching protocol. In all other circumstances, the participants were believed to have bleaching-induced tooth sensitivity.

Gingival irritation evaluation

Participants were instructed to fill out a form to record the daily GI after bleaching. These forms returned to the researcher at the next appointment (1 week after), during the three weeks of treatment. For the GI questionnaire, the participant was asked to indicate if they felt any discomfort in the gingiva and if there was discomfort should indicate side.

As with tooth sensitivity assessments, when the participants reported no gingival irritation at all three-week bleaching time evaluations, they were considered insensitive to the bleaching protocol. In all other circumstances, participants were considered to have GI induced by bleaching.

Statistical methods

All participants received the intended protocol and had their outcomes measured, meaning that the intention-to-treat protocol and per-protocol analysis results in the same findings (Figure 1). The statistician was blinded to the groups.

Two one-sided t-tests for paired samples (TOST-P) approach was used to test the equivalence of the study groups at the different assessment points (baseline vs. 1-week; baseline vs. 2-week and baseline vs. 3-week and baseline vs. 1-month post-bleaching). Such an approach includes a right-sided test for the lower margin of the equivalence limit and a left-sided test for the upper margin using one-sided 0.025 significance levels. The overall p-value is taken to be the larger of the two p-values from the lower and upper tests. Mean difference, and 95% confidence interval (CI) were calculated between groups at each time assessment. For ΔE, if both treatments differ by more than 3.0 units in either direction, then equivalence does not hold. Although not powered for, we similarly evaluated equivalence for color change in shade guide units (defined as a change in 1.0 shade guide unit for both shade guide scales). A traditional one-way repeated-measures ANOVA was employed for each color change instrument to detect color changes over time.

The risks of TS and GI of both groups were compared using the McNemar's exact test, which is used to compare the proportion of paired data (α = 0.05) in superiority trials. The odds ratio, as well as the confidence interval (CI) for the effect size also was calculated. The Wilcoxon Signed Rank test compared the dataset of TS intensity obtained with the NRS scale while the paired Student t-test compared the TS intensity from VAS scale (α = 0.05).

Correlation coefficients in paired designs are essential to allow more precise sample size calculation for future randomized clinical trials. We calculated the phi correlation coefficient for pairs of binary data of the risk of TS and GI between the two groups. The Spearman and Pearson correlation coefficient was calculated respectively for the NRS scale and VAS scale. We used the Pearson correlation coefficient to calculate the correlation coefficient for the pairs of color change for each instrument for the baseline vs. 1-month post bleaching time.

Results

Characteristics of included participants

We examined a total of 59 participants according to the inclusion and exclusion criteria (Figure 1), but only 46 participants remained for the clinical trial. The baseline color of the participants was 9.8 ± 2.3 in shade guide units

measured with the Vita Classical guide. The mean age was 24.2 ± 5.1 years and approximately 60% of them were females.

All participants attended the recall visits during the bleaching protocol, and none quit the treatment. Figure 1 depicts the participant flow diagram in the different phases of the study design.

Primary outcome color change

Table 1 presents the mean differences in color changes for both treatment groups and this can be visualized in Figure 2. The TOST test demonstrated the equivalence of color change for ΔE, ΔSGU from Vita Classical scale and ΔSGU from Vita Bleached guide. The two-sided 90% CI of the difference of the means are within the predetermined equivalence margins of -3 and +3 for ΔE and -1 and +1 for ΔSGU.

The traditional one-way repeated measures ANOVA detected significant whitening over time (Table 1; $p > 0.05$). After one month, a whitening effect of near eight units in the Vita Classical scale, 11 units in the Vita Bleachedguide, and 13 units in the ΔE was observed (Table 1).

The Pearson correlation for the baseline vs. 1-month post bleaching in the ΔSGU from Vita Classical was 0.80 ($p < 0.01$); from Vita Bleachedguide was 0.74 ($p < 0.01$) and for ΔE was 0.55 ($p < 0.01$).

Secondary outcomes

Risk of tooth sensitivity

A total of 15 patients presented risk of pain in the experimental arch side (absolute risk: 33%, 95% CI 21 to 46%), and from these, five patients did not report risk of pain in the control side. Sixteen patients (absolute risk: 35%, 95% CI 23 to 49%) reported pain in the control group, and from these, six did not experience pain in the experimental side. In relative terms, the odds ratio for pain was 0.8 (0.2 to 3.0; Table 2), and it did not reach statistical significance ($p = 1.0$, McNemar's test). The Spearman correlation coefficient for pairs of binary data was moderate and significant ($r = 0.47$; $p < 0.01$).

Risk of gingival irritation

A total of 16 patients presented pain in the experimental arch side (absolute risk: 35%, 95% CI 23 to 49%), and from these, four patients did not report pain in the control side. Seventeen patients reported pain in the control group (absolute risk: 37%, 95% CI 25 to 51%), and from these, five did not experience pain in the experimental side. In relative terms, the odds ratio for pain was 0.8 (0.16 to 3.7; Table 3), and it did not reach statistical significance ($p = 1.0$, McNemar's test). The Spearman correlation coefficient for pairs of binary data was moderate and significant ($r = 0.57$; $p < 0.01$).

Intensity of tooth sensitivity

The statistical analysis did not show any significant difference in the TS intensity between groups in any of the pain scales ($p = 0.64$ for NRS scale, and $p = 0.23$; for VAS scale; Table 6). The mean difference of pain intensity in VAS scale was on average - 0.2 units, a difference far from being clinically important. Pain was positively correlated in both groups (Table 4). Correlation was moderate and significant for both pain scales. For NRS scale, the Spearman correlation was 0.52 ($p < 0.01$) and for VAS scale, the Pearson correlation was 0.69 ($p < 0.01$).

Discussion

The use of reservoirs in the bleaching trays was initially seen as positive, since higher accumulation of material could provide the patient with greater treatment efficacy.[11] After the emergence of this new technique, some clinical trials[11, 13, 14] observed that the efficacy of this treatment was not dependent on reservoirs but the exposure area and gel application time.[10] However, although these studies reported these findings, they were considered at unclear risk of bias in a recent systematic review.[15] Additionally, these earlier studies were low powered. Negative results of low-powered studies may not indicate that one group is different from another, but rather that these results may be due to chance alone.

These earlier studies[10, 11, 13, 14, 16-18] also lacked the use of standardized outcomes to report their findings of color change, tooth sensitivity and gingival irritation, which reduced the reliability of the study's findings. The limitations above of the previous studies on this issue motivated us to conduct this randomized clinical trial.

In the present study, we measured color change by using either subjective methods (matching with different shade guide units) along with objective methods (spectrophotometer). It is reported that measurement with a spectrophotometer provides more accurate results than visual shade matching with shade guides[23, 24] as it is less prone to subjective judgments; however, results published in ΔE is less clinically tangible. This explains why we have reported color change using different tools. Few published studies that evaluated color change using bleaching trays with and without reservoirs included objective tools for color change in their analysis.[10, 25]

A significant whitening of approximate eight units in the Vita Classical scale and 13 units for ΔE were observed in the sides with and without reservoirs. Equivalence was demonstrated in all time-assessments, irrespective of the tool used for color change. The results of this study suggest that the efficacy of at-home bleaching is not related to the amount of bleaching material presented at the buccal surface of teeth to be bleached. A similar finding was reported by a randomized controlled trial that showed no difference in efficacy when 10% hydrogen peroxide was delivered in a bleaching strip or customized/prefilled bleaching trays. In the latter, the amount of bleaching product is significantly higher [26] than in the bleaching strip.

Other factors such as concentration[7, 27] daily usage time,[28] total treatment time[29] and degradation kinetics of the product[30] may be more important than the amount of bleaching gel on the bleaching tray.

Bleaching-induced TS is directly related to the passage of hydrogen peroxide to the pulp chamber.[31] As the presence of reservoirs offers a higher amount of bleaching gel, it is believed that the tooth sensitivity could be aggravated, as well as gingival irritation.[13] However, the present study showed that there is no significant difference between groups lightened with and without reservoirs for gingival irritation or tooth sensitivity. Approximately 30% of the

patients reported tooth sensitivity with a very low intensity (about 1.6 unit in the VAS scale), and no type of additional desensitization was required.

The similar risk of TS between both groups reinforces the fact that the amount of material placed on the enamel surface does not affect the bleaching outcome. The penetration of the bleaching agent is not driven by the mass (amount) of product placed on the surface but by the diffusion coefficient of the bleaching product itself on the dental substrate. This diffusion coefficient is dependent on the nature of the substance under diffusion and on the area of application. Factors such as viscosity and solution properties (concentration, pH and, temperature) which were not altered between groups can affect diffusion, but not the product mass. Therefore, one can expect that the amount of hydrogen peroxide that achieved the pulp chamber was similar in both sides of the patient's arches, leading to a similar risk of bleaching-induced TS.

For calculation of risk and intensity of TS, we summarized the tooth sensitivity data based on the worst episode of pain in the bleaching period. To the author's opinion, the experience of considerable pain makes the experience negative for patients, even if it is a single episode or multiple episodes. However, this provides us with the worst scenario. Other ways to report the adverse effect of tooth sensitivity exists. For instance, in an exploratory analysis we calculated the mean number of days patients experienced tooth sensitivity (reservoir side: 3.9 ± 5.0; no-reservoir side; 4.6 ± 5.9), and also the intensity of TS (VAS scale) by taking the mean of the daily TS during the bleaching period (reservoir: 0.8 ± 1.0; no-reservoir: 0.9 ± 1.0). By using appropriate statistics, we reached up with the conclusion of no significant difference between groups which makes the results of the present investigation robust and not affected by these prior decisions.

Apart from not bringing benefits to the at-home bleaching, designing bleaching trays with reservoirs will require a more significant amount of bleaching material used to whiten teeth, and it requires more time for tray fabrication, increasing the costs associated with this procedure. Some companies, such as Ultradent Products still recommend the manufacturing of bleaching trays with reservoirs. This recommendation is not based on the findings of controlled trials but probably on the fact that more material is required to fill in the bleaching tray with reservoirs. While this may be an advantage for the company, it is not for

clinicians and patients, who will spend more in bleaching material than one would if the bleaching were performed with trays without reservoirs. Unfortunately, clinicians have much more access to the manufacturer's instruction of bleaching products than access to findings of randomized clinical trials.

Finally, we should mention the limitations of the present study. We have just evaluated one material brand in this clinical trial. Although this may be seen as a limitation, bleaching agents have very similar composition which contrasts with the majority of the dental materials used in the daily practice. Researchers should conduct further clinical trials using different brand of materials. As the vast majority of the participants were young in this clinical trial, results should not be generalizable to older adult populations without care.

Conclusion

The presence of reservoirs in a bleaching tray did not affect color change, tooth sensitivity, or gingival irritation of a dentist-supervised, at-home bleaching performed with 10% carbamide peroxide gel.

Conflict of Interest

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

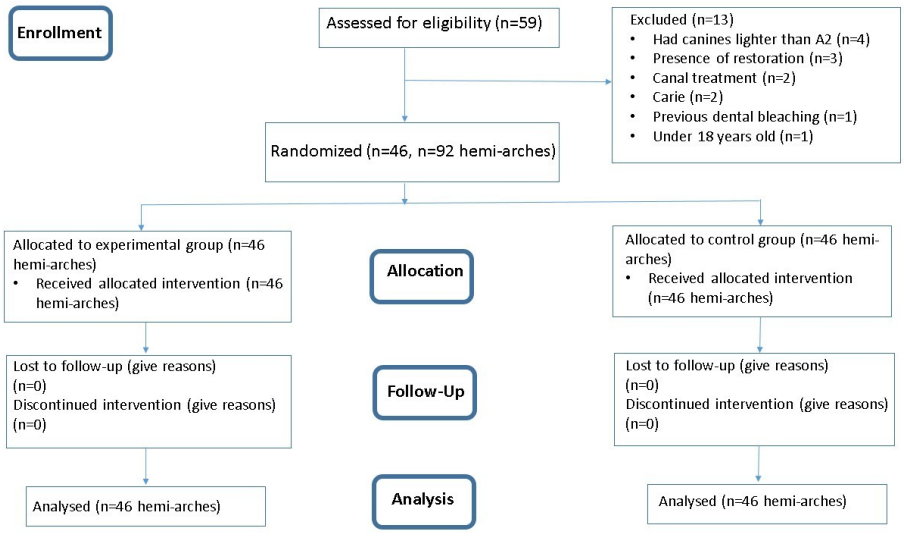

Figure 1. Flow diagram of study design phases including enrollment and allocation criteria.

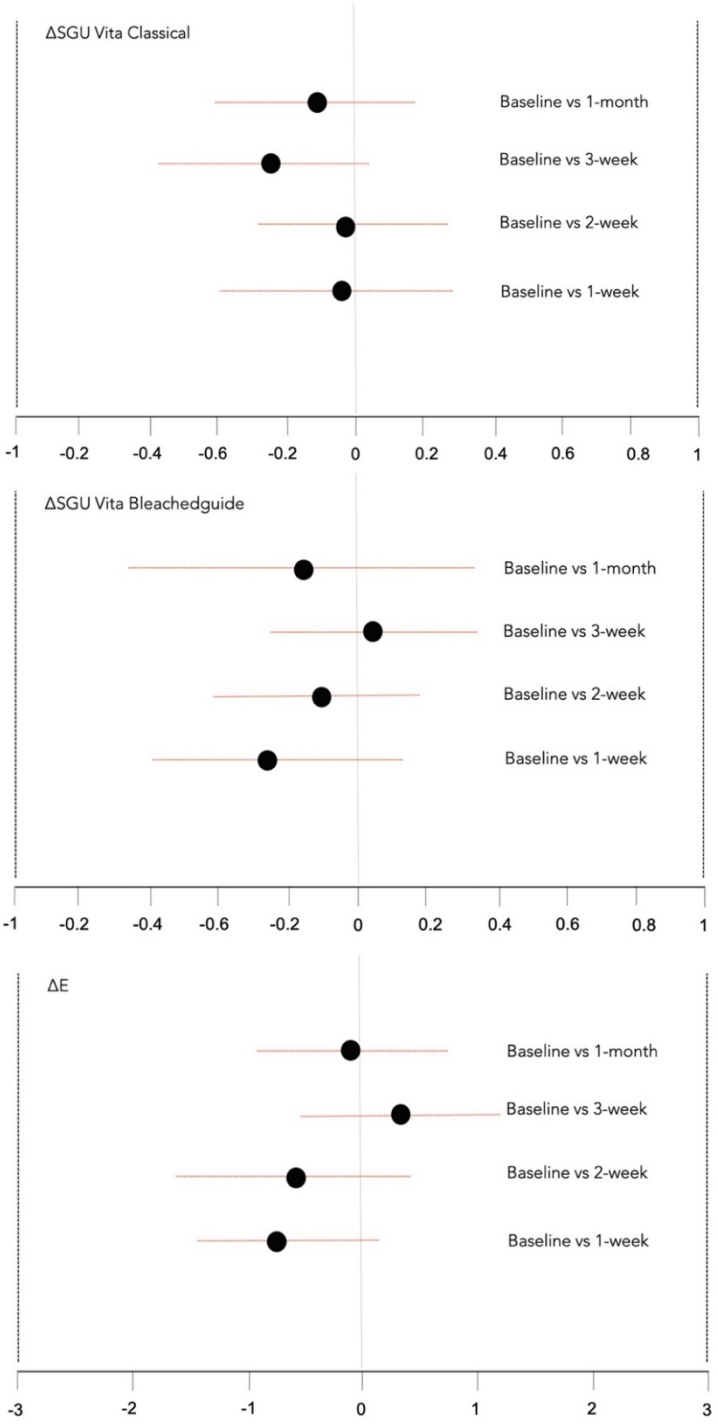

Figure 2 – Mean differences of color change measured with different instruments between non-reservoir and reservoir groups at the different assessment times. Horizontal bars indicate two-sided 90% confidence interval (CI) of the mean difference between treatment groups. The zone between the dashed lines indicates the equivalence margin.

Table 1. Means ± standard deviations of ΔSGU and ΔE obtained the color change instruments at different time assessments and the mean difference (90% confidence interval [CI]) for the pairwise comparison.

Color evaluation tool	Time assessments	Groups		Mean difference (90% CI)	Equivalence (p-value*)	Main factor time**
		With reservoirs	Without reservoirs			
Vita Classical	Baseline vs. 1-week	4.7 ± 2.0	4.8 ± 1.8	-0.1 (-0.4 to -0.2)	Yes, p < 0.01	4.8 ± 2.6 A
	Baseline vs. 2-week	7.3 ± 2.0	7.5 ± 1.9	-0.2 (-0.5 to 0.1)	Yes, p < 0.01	7.4 ± 2.3 B
	Baseline vs. 3-week	8.3 ± 2.1	8.3 ± 2.0	-0.0 (-0.3 to 0.3)	Yes, p < 0.01	8.3 ± 2.0 C
	Baseline vs. 1-month	7.9 ± 2.2	7.9 ± 2.0	-0.0 (-0.4 to 0.3)	Yes, p < 0.01	7.9 ± 2.0 B,C
Vita Bleached	Baseline vs. 1-week	5.2 ± 2.3	5.6 ± 2.3	-0.3 (-0.6 to 0.1)	Yes, p < 0.01	5.5 ± 3.7 A
	Baseline vs. 2-week	9.3 ± 2.6	9.6 ± 2.4	-0.1 (-0.4 to 0.2)	Yes, p < 0.01	9.4 ± 3.1 B
	Baseline vs. 3-week	11.6 ± 2.5	11.6 ± 2.3	0.0 (-0.3 to 0.3)	Yes, p < 0.01	11.6 ± 2.4 C
	Baseline vs. 1-month	10.5 ± 2.9	10.7 ± 2.6	-0.2 (-0.7 to 0.3)	Yes, p < 0.01	10.6 ± 2.7 D
ΔE	Baseline vs. 1-week	9.3 ± 4.6	10.1 ± 4.6	-0.8 (-1.5 to 0.1)	Yes, p < 0.01	9.5 ± 4.5 A
	Baseline vs. 2-week	11.8 ± 3.7	12.5 ± 4.1	-0.6 (1.64 to 0.4)	Yes, p < 0.01	12.0 ± 4.3 B
	Baseline vs. 3-week	14.2 ± 3.4	13.9 ± 3.5	0.29 (0.54 to 1.12)	Yes, p < 0.01	14.1 ± 3.4 C
	Baseline vs. 1-month	13.4 ± 3.4	13.5 ± 3.5	-0.12 (-0.93 to 0.69)	Yes, p < 0.01	13.5 ± 3.8 C

** The p-value reported is the larger of the two p-values from the upper and lower one-sided tests (TOST test); ** One-way repeated measures ANOVA (p < 0.05).*

Table 2. Matched tabulation of the absolute risk of tooth sensitivity for both groups along with the odds ratio and 95% confidence interval.

		Without reservoirs			Odds ratio(95% CI interval)
		Positive	Negative	Total	
With reservoirs	Positive	10	5	15	0.8 (0.2 to 3.2)
	Negative	6	25	31	
	Total	16	30	46	

McNemar's test (p = 1.0); Spearman correlation between paired data = 0.47; p-value = 0.0001.

Table 3. Matched tabulation* of the absolute risk of gingival irritation for both groups along with the odds ratio and 95% confidence interval.

		Without reservoirs			Odds ratio (95% CI)
		Positive	Negative	Total	
With reservoirs	Positive	12	4	16	0.8 (0.16 to 3.7)
	Negative	5	30	30	
	Total	17	29	46	

** McNemar's test (p = 1.0). Spearman phi correlation between paired data = 0.57; p = 0.0001.*

Table 4. Intensity of tooth sensitivity for both groups, mean difference of the paired VAS means and mean difference along with 95% confidence interval [CI].

Pain scales	With reservoirs	Without reservoirs	Mean difference (95% CI)	p-value
NRS 0-4	1 (0 – 1.25)	1 (0 – 1)	--	0.64*
VAS 0-10	1.5 ± 1.7	1.7 ± 2.0	- 0.2 (-1.0 to 0.6)	0.23**

*For NRS scale, the values reported are medians and the interquartile range. For VAS scale, the values are reported in means and standard deviations. * Wilcoxon Signed Rank test; ** Paired t-test*

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5 DISCUSSÃO

A SD induzida pelo clareamento infelizmente é um efeito colateral comum (Dourado Pinto et al.[3] 2019). Devido ao baixo peso molecular do peróxido de hidrogênio (Hanks et al.[34] 1993), ele penetra no tecido pulpar e causa uma reação inflamatória (Soares et al.[35] 2014; Costa et al.[36] 2010), estresse oxidativo e dano celular, levando à liberação de mediadores inflamatórios e sensibilidade dolorosa (Wang et al.[14] 2015; Cook et al.[37] 2002), que pode ser de leve a exacerbada, mesmo quando submetidos a mesma técnica de clareamento (Rezende et al.[6] 2016; Cardenas et al.[38] 2019).

Essa mesma SD causada pela penetração do gel de peróxido de hidrogênio ou peróxido de carbamida é frequente, pode ter múltiplas causas e não pode ser completamente prevenida (Tam[39] 2001). Estudos relatam que 60 a 100% dos pacientes que recebem o tratamento clareador, principalmente o realizado em consultório, sentem dor em algum momento do tratamento (Nanjundasetty et al.[40] 2016; Mehta et al.[41] 2013). É por isso que estudos laboratoriais investigam a taxa de permeabilidade dos tecidos dentais aos protocolos clareadores e também ensaios clínicos randomizados são realizados para testar o efeito de agentes dessensibilizantes que possam ser capazes de reduzir esse efeito colateral, que foi objetivo do Artigo 1.

Contrariamente às nossas expectativas, o uso de um gel dessensibilizante aplicado somente antes ou antes e depois do clareamento não reduziu a SD induzida pelo tratamento clareador, mesmo não interferindo na eficácia do tratamento clareador, já que o agente dessensibilizante e o gel clareador não reagem pelos mesmos sítios de ligação na estrutura dentária (Rezende et al.[6] 2016). Embora isso seja contraditório com os resultados de uma revisão sistemática (Wang et al.[14] 2015), existem algumas falhas metodológicas neste trabalho, que reduz a confiabilidade de seus achados.

Com base na revisão citada (Wang et al.[14] 2015), o uso de agentes dessensibilizantes a base de nitrato de potássio antes do clareamento em consultório foi eficaz em três estudos (Tay et al.[22] 2009; Parreiras et al.[42] 2018; Pale et al.[43] 2014) e semelhante ao placebo em outros três estudos (Bonafe et al.[23] 2014; Reis et al.[44] 2011; Loguercio et al.[45] 2015). Atualmente estamos conduzindo outra revisão sistemática (Prospero ID: CRD42016037628) bem

delineada e atualizada sobre essa mesma pergunta de estudo para se chegar realmente a resposta da eficácia desses agentes.

O clareamento caseiro, considerado durante muitos anos o “padrão-ouro” para clareamento dental desde seu primeiro relato em 1989 por Haywood,[46] sofreu alterações em seu protocolo original, com objetivo de melhorar a eficácia, aumentar o conforto e reduzir a sensibilidade. Dentre as modificações, diferentes concentrações e tempos de uso do gel (de Geus et al.[47] 2018; Llena et al.[48] 2020), peróxido de hidrogênio *vs* peróxido de carbamida (Luque-Martinez et al.[49] 2016), alterações nas moldeiras, como a presença de reservatórios. A eficácia do uso de reservatórios em moldeiras foi tema dos Artigos 2 e 3 da presente tese.

O uso de reservatórios foi recomendado por acreditar que maior acúmulo de material poderia proporcionar ao paciente maior eficácia do tratamento (Javaheri et al.[50] 2000). Após o surgimento dessa nova técnica, alguns ensaios clínicos realizados (Kirsten et al.[33] 2009; Javaheri et al.[50] 2000; Miller et al.[51] 2000) observaram que a eficácia do tratamento não dependia da presença ou não de reservatórios, mas sim da área de exposição e do tempo de aplicação do gel clareador (Matis et al.[29] 2002). No entanto, embora esses estudos tenham relatado esses achados, eles foram considerados de alto risco de viés e eram estudos com pequeno tamanho amostral como detalhado no Artigo 2 desde trabalho. Resultados negativos em estudos com baixo tamanho amostral podem ser devido ao acaso e não a similaridade dos grupos investigados.

Além disso, os estudos primários incluídos na revisão sistemática do Artigo 2 mostraram falta de randomização adequada, ocultação da alocação e cegamento. Essas limitações estão em acordo com as limitações gerais apresentadas em estudos de clareamento dental (Loguercio et al.[53] 2017). Outro problema desses estudos primários avaliados (Matis et al.[29] 2002; Ishikawa[30] 2011; Delgado et al.[32] 2000; Kirsten et al.[33] 2009; Javaheri et al.[50] 2000; Miller et al.[51] 2000; Morais e Moura et al.[52] 2007) foi a falta de padronização na apresentação dos resultados para a alteração de cor, sensibilidade dentária e irritação gengival. Ao término deste estudo ficou claro a necessidade da condução de um ensaio clínico randomizado bem delineado que investigasse o tema em questão, que foi então objetivo do artigo 3 desta tese.

A mudança de cor é geralmente avaliada usando métodos subjetivos (combinando com diferentes unidades de escalas de cor) ou métodos objetivos (espectrofotômetro). Apenas três dos nove estudos primários encontrados na revisão sistemática relataram o uso de ferramentas objetivas para mensuração dos resultados relacionados a cor (Matis et al.[29] 2002; Ishikawa [30] 2011; Martini[55] 2018).

Existem ainda outras variáveis relevantes entre os estudos primários (diferentes protocolos, tipo e concentração de agentes clareadores, marca e composição do produto, etc.), além da presença ou ausência de reservatórios nas moldeiras de clareamento. O baixo número de estudos incluídos na revisão sistemática nos impediu de avaliar o impacto dessas diferenças nos resultados. Mesmo com falta de evidência científica sólida, muitos autores utilizam a confecção de reservatórios como protocolo padrão em seus estudos, como observado em outra revisão sistemática (de Geus et al.[47] 2018) e esse protocolo é recomendado por uma empresa de produtos odontológicos (Ultradent Products, Inc., Salt Lake, UT, USA).

Ao término da revisão sistemática da literatura (Artigo 2) ficou claro a necessidade da condução de um ensaio clínico randomizado bem delineado que investigasse o tema em questão o que nos motivaram a realizar o ensaio clínico randomizado relatado no Artigo 3 deste trabalho. Após a condução do ensaio cínico do tipo boca-dividida, não observamos diferença na eficácia clareadora e no risco de SD e de IG entre os grupos com e sem reservatórios nas moldeiras.

Os resultados encontrados após o ensaio clínico reforçam o fato de que a quantidade de material colocado na superfície do esmalte devido a presença dos reservatórios nas moldeiras, não afeta o resultado do clareamento. A penetração do agente clareador não é impulsionada pela massa (quantidade) de produto colocado na superfície, mas pelo coeficiente de difusão do próprio produto no substrato dental. Este coeficiente de difusão depende da natureza da substância sob difusão e da área de aplicação. Fatores como viscosidade e propriedades da solução (concentração, pH e temperatura) que não foram alterados entre os grupos podem afetar a difusão, mas não a massa do produto (Matis et al.[29] 2002; Matis et al.[54] 2002). Portanto, pode-se esperar que a quantidade de peróxido de hidrogênio que atingiu a câmara pulpar seja semelhante em ambos os lados dos

arcos do paciente, o que gerou resultados semelhantes de risco de SD (Matis et al.[54] 2002).

Além de não trazer benefícios para o clareamento caseiro, a presença de reservatórios com moldeiras exige um passo laboratorial adicional, que pode trazer aumento no custo do tratamento, além do emprego de uma quantidade mais significativa de material clareador a ser usado, que somente é vantajoso para as empresas, não para pacientes e nem aos profissionais.

6 CONCLUSÃO

Com base nos resultados encontrados, podemos concluir que um dessensibilizante a base de nitrato de potássio 5% e fluoreto de sódio 2% aplicado somente antes ou antes e depois do gel clareador não foi eficaz para reduzir a SD induzida pelo clareamento.

Os resultadas da revisão sistemática da literatura apontaram para falta de evidências sobre os possíveis benefícios do uso de reservatórios em moldeiras de clareamento caseiro e o ensaio clínico randomizado sobre o mesmo tema mostrou que o uso de reservatórios não produziu diferenças entre eficácia clareadora, risco de SD e risco de IG.

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*De acordo com as normas do PPGO-UEPG.

ANEXO A - APROVAÇAO DO ESTUDO CLÍNICO PELA COMISSAO DE ETICA EM PESQUISA DA UNIVERSIDADE ESTADUAL DE PONTA GROSSA

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Comparação entre a aplicação de um gel para reduzir a dor dental decorrente do clareamento, antes do gel e antes/após o gel. Um estudo clínico em pacientes.

Pesquisador: Alessandra Reis
Área Temática:
Versão: 1
CAAE: 80704817.1.0000.0105
Instituição Proponente: Universidade Estadual de Ponta Grossa
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.455.095

Apresentação do Projeto:
O objetivo desse estudo clínico será avaliar se a aplicação de gel dessensibilizante somente antes do ge clareador, como é recomendado pelos fabricantes, comparado à aplicação antes e depois do gel clareador é eficaz na redução da taxa de sensibilidade dental. O estudo será do tipo boca dividida e antes do clareamento, ambos os lados de todos os pacientes receberão dessensibilizante e gel clareador conforme recomenda o fabricante, após a remoção do clareador e conforme randomização, um dos lados receberá novamente dessensibilizante, enquanto outro lado receberá apenas um placebo, que será confeccionado com gel de viscosidade e cor igual ao grupo experimental, sendo que as seringas serão identificadas apenas com A/B, por uma pessoa não envolvida na parte experimental, isso fará com que o estudo seja considerado triplo-cego, uma vez que o paciente, o operador nem o avaliador saberão qual dos dois géis será aplicado após o gel clareador.

Objetivo da Pesquisa:
Objetivo primário é reduzir a sensibilidade dentária decorrente do clareamento feito em consultório.
Objetivo secundário é avaliação de cor, ou seja, se o clareamento foi eficiente.

Avaliação dos Riscos e Benefícios:
Riscos:

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748. UEPG, Campus Uvararanas, Bloco M, Sala 100.
Bairro: Uvaranas **CEP:** 84.030-900
UF: PR **Município:** PONTA GROSSA
Telefone: (42)3220-3108 **E-mail:** coep@uepg.br

ANEXO B - REGISTRO DA REVISÃO SISTEMÁTICA NO PROSPERO

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Does the use of reservoirs in bleaching trays have any impact on the efficacy of at-home bleaching? A systematic review and meta-analysis

Eveline Martini, Sibelli Parreiras, Viviane Hass, Eric Acuna, Eloisa de Paula, Alessandro Loguercio, Alessandra Reis

Citation

Eveline Martini, Sibelli Parreiras, Viviane Hass, Eric Acuna, Eloisa de Paula, Alessandro Loguercio, Alessandra Reis. Does the use of reservoirs in bleaching trays have any impact on the efficacy of at-home bleaching? A systematic review and meta-analysis. PROSPERO 2016 CRD42016037628 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016037628

Review question

During at-home bleaching of adult patients, does the use of bleaching trays with reservoirs produce a higher degree of color change than bleaching trays without?

Searches

To identify trials to be included in this review, we will search on MEDLINE database via PubMeb, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO) and Cochrane Library. An expert librarian (D.M.) will guide the whole search strategy.
We will hand-search the reference lists of all primary studies for additional relevant publications and the related articles link of each primary study in the PubMed database.
No restrictions will be placed on the publication date or languages.
We will search the abstracts of the annual conference of the International Association for Dental Research (IADR) and their regional divisions (1990 2016) and will get in touch with authors of relevant abstracts for further information.
We will explore the grey literature using the database System for Information on Grey literature in Europe (SIGLE), and dissertations and the using the Pro Quest Dissertations and Theses Full text database, as well as the Periódicos Capes Theses database.
To locate unpublished and ongoing trials related to the review question, we will search the following clinical trials registry: Current Controlled Trials (www.controlledtrials.com), International Clinical trials registry plataforma (http://apps.who.int/trialsearch/), the Clinical Trials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).
The search strategy will be appropriately modified for each database and performed by two reviewers to identify eligible studies. Full text versions of the papers that appeared to meet the inclusion criteria will be retrieved for further assessment and data extraction.

Types of study to be included

We will include randomized clinical trials (RCTs) that compare the effectiveness of at-home bleaching with or without reservoirs in the mouth impression of the patients. Details of the effectiveness of bleaching, tooth sensitivity and gum irritation will be assessed. The primary outcome of the study will be the effectiveness of both interventions.Non-controlled clinical trials, editorial letters, pilot studies, historical reviews, in vitro studies, cohort, observational and descriptive studies such as case reports and case series will be excluded.

Condition or domain being studied

Patients with dental discoloration, darkened teeth.

Participants/population

Inclusion criteria: Adult patients with discolored teeth and patients that want to whiten their teeth.
Exclusion criteria: Patients not eligible for cosmetic treatments due to the presence of other important

ANEXO C - APROVAÇAO DO ESTUDO CLINICO PELA COMISSAO DE ETICA 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: Avaliação da presença e ausência de reservatórios em moldeiras para clareamento caseiro: ensaio clínico randomizado, multicêntrico e cego.

Pesquisador: Alessandra Reis

Área Temática:

Versão: 2

CAAE: 62060716.8.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.124.508

Apresentação do Projeto:

Avaliação da presença e ausência de reservatórios em moldeiras para clareamento caseiro: ensaio clínico randomizado,
multicêntrico e cego.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar a efetividade do clareamento dental caseiro, em pacientes adultos, com peróxido de carbamida a 16%, na presença de reservatórios nas
moldeiras, se comparado a ausência destes.

Objetivo Secundário:

Avaliar a sensibilidade pós-operatória e inflamação gengival nos pacientes submetidos ao clareamento dental caseiro.

Metodologia Proposta:

O delineamento experimental seguirá o CONSORT. Será um estudo multicêntrico, randomizado e cego

Avaliação dos Riscos e Benefícios:

Riscos:

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748, UEPG, Campus Uvaranas, Bloco M, Sala 103.
Bairro: Uvaranas **CEP:** 84.030-900
UF: PR **Município:** PONTA GROSSA
Telefone: (42)3220-3108 **E-mail:** coep@uepg.br

ANEXO D - FICHA CLÍNICA PARA ANAMNESE DOS PACIENTES UTILIZADA NOS ESTUDOS

Nome:			Idade:	Gênero:
Endereço:				Email:
Cidade :	UF:	CEP:		Fone:
Profissão :		RG:		CPF:
Endereço Comercial:				Fone comercial:
Fone Familiar:		Endereço:		

História médica

Está ou esteve em tratamento médico nos últimos 6 meses?
Faz ou fez uso contínuo de algum medicamento nos últimos 6 meses?
Quais?Anti-inflamatórios ( ) Corticóides ( ) Antibiótico ( ) Depr do SNC ( )
Imunossupressores ( ) Anti-hipertensão ( ) Outros ( )
ALERGIA: Anestésico: Sim( ) Não( ) Antibiótico: Sim ( ) Não( ) Antiinflamatórios: Sim ( ) Não( ) Alérgico a lactose: Sim( ) Não( ) Outros:
Doenças cardíacas: Hipertensão: PA:
Diabetes( ) Doenças hepáticas( ) Doenças renais ( ) Doenças no estômago(Como úlcera e gastrite) ( )
Doença no intestino( ) Doenças Reumáticas ( ) DST( )
Grávida: Sim( ) Não( ) Amamentando: Sim( ) Não( )
Fumante: Sim( ) Não( )

Hábitos de higiene bucal
Números de vezes que escova os dentes por dia:
Tipo de escova: macia ( ) média ( ) dura ( )
Uso do fio dental: S ( ) N( )

HIPERSENSIBILIDADE PRÉVIA: ( ) Sim ( ) Não
( ) Nenhuma( ) Leve ( ) Moderada ( ) Considerável ( ) Severa

AR: ( ) Sim ( ) Não
FRIO: ( ) Sim ( ) Não
PERCUSSÃO HORIZONTAL/VERTICAL: ( ) Sim ( ) Não / ( ) Sim ( ) Não
PALPAÇÃO: ( ) Sim ( ) Não

PRESENÇA DE LCNC: ( ) Sim ( ) Não **QUAIS DENTES?**
PRESENÇA DE TRINCAS NO ESMALTE: ( ) Sim ( ) Não **QUAIS DENTES?**

HÁBITO PARAFUNCIONAL: ( ) Sim ( ) Não **QUAL?**

*considerar Bleachedguide Europa (valor intermediário)

Período	VITA: 13	3	3	HED: 23	
Inicial					
1 Sem					QUAL DENTE DOEU?
2 Sem					QUAL DENTE DOEU?
3 Sem					QUAL DENTE DOEU?
1 mês					QUAL DENTE DOEU?

Dente 13	Cor	Variação	Master	L	C	H	a	b

Inicial								
1 Sem								
2 Sem								
3 Sem								
1 mês								
Dente 23	Cor	Variação	Master	L	C	H	a	b
Inicial								
1 Sem								
2 Sem								
3 Sem								
1 mês								

ANEXO E - TCLE ARTIGO 1

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

A pesquisa intitulada "Avaliação da aplicação de um gel dessensibilizante antes *vs*

antes e depois do clareamento em consultório: ensaio clínico randomizado e triplo-cego" tem como objetivo avaliar o grau de clareamento dos dentes, bem como a intensidade da sensibilidade dental quando um gel dessensibilizante é aplicado apenas antes do procedimento e antes+depois dele. A resposta da pesquisa pode trazer benefício clínico aos pacientes que desejarem clarear os seus dentes, pois espera-se que os efeitos adversos como sensibilidade dental seja menor. Esta pesquisa será realizada nas clínicas odontológicas da Universidade Estadual de Ponta Grossa, pela alunas de doutorado Eveline Claudia Martini, Fabiana Coppla e Sibelli Parreiras, pelo aluno de graduação Michael Favoreto e pela Profa Dra Alessandra Reis. Para execução da pesquisa serão necessários 90 voluntários que atendam aos critérios de seleção e concordem em participar do estudo. O cirurgião-dentista irá realizar uma limpeza prévia dos dentes, depois inserido um afastador labial, aplicação de uma barreira para proteção da gengiva e o procedimento clareador, sendo realizadas duas sessões de clareamento com uma semana de intervalo entre cada uma. Os voluntários serão instruídos como devem preencher as fichas de sensibilidade dental. Todo o material empregado no tratamento será fornecido pelos pesquisadores sem nenhum custo para os voluntários. Durante todo o período da pesquisa os voluntários serão acompanhados pelos pesquisadores para verificação de qualquer efeito adverso como sensibilidade dental e irritação na gengiva. Caso ocorra os voluntários serão imediatamente tratados e acompanhados. Se ocorrer sensibilidade dental muito forte, poderá ser aplicado gel dessensibilizante e se necessário o paciente será medicado com medicações. A utilização de qualquer agente químico para o clareamento dental pode ocasionar efeitos adversos como sensibilidade dental, ardência, descamação e ulceração das mucosas bucais, dependendo de cada voluntário. Para o tratamento de reações adversas, os custos estão previstos no orçamento do projeto.

Os indivíduos terão a garantia de que receberão 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 vontade do indivíduo em continuar participando dele. Os voluntários 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,_____, certifico que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Eveline Martini e Alessandra Reis. Estou de acordo com a realização do experimento. Assim, concordo em participar como voluntário do trabalho de pesquisa, exposto acima. Certifico também ter recebido uma cópia deste Termo de Consentimento Livre e Esclarecido.

Ponta Grossa, _____ de _____ de 201__.

Nome:_____

Assinatura:_____

Pesquisador Responsável:_____

Eveline Martini (42) 99829-2999

ATENÇÃO: A sua participação em qualquer tipo de pesquisa é voluntária. Em caso de dúvida quanto aos seus direitos, entre em contato com a Comissão de Ética em Pesquisa da UEPG. Endereço – Av. Carlos Cavalcanti, n.4748, Bloco M, Sala 100, CEP- 84030-900 – Ponta Grossa – PR. Fone: (42) 3220-3108. e-mail: coep@uepg.br.

ANEXO F - TCLE ARTIGO 3

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

A pesquisa intitulada "Avaliação da presença e ausência de reservatórios em moldeiras para clareamento caseiro: ensaio clínico randomizado e cego" tem como objetivo avaliar o grau de clareamento dos dentes obtido com ou sem a presença de reservatórios nas moldeiras de clareamento, bem como a intensidade da sensibilidade dental e possíveis efeitos colaterais como irritação gengival. A resposta da pesquisa pode trazer benefício clínico aos pacientes que desejarem clarear os seus dentes, pois espera-se que os efeitos adversos como sensibilidade dental e irritação gengival sejam menores. Esta pesquisa será realizada nas clínicas odontológicas da Universidade Estadual de Ponta Grossa, pela aluna de doutorado Eveline Claudia Martini, aluno de graduação Michael Favoreto e pela Profa Dra Alessandra Reis. Para execução da pesquisa serão necessários 45 voluntários que atendam aos critérios de seleção e concordem em participar do estudo. O cirurgião-dentista irá realizar uma limpeza prévia dos dentes, depois será feita uma moldagem da arcada superior e inferior para confecção das moldeiras individuais que acomodará o gel clareador. Os voluntários serão instruídos como devem preencher a moldeira com o gel clareador e deverão utilizar durante 3 horas diárias. Todo o material empregado no tratamento será fornecido pelos pesquisadores sem nenhum custo para os voluntários. Durante todo o período da pesquisa os voluntários serão acompanhados pelos pesquisadores para verificação de qualquer efeito adverso como sensibilidade dental e irritação na gengiva. Caso ocorra os voluntários serão imediatamente tratados e acompanhados. Alguns pacientes podem apresentar sensibilidade nos dentes, que é ocasionada pela ação do produto. Se ocorrer sensibilidade dental muito forte, poderá ser aplicado gel dessensibilizante e se necessário o paciente será medicado com medicações. A utilização de qualquer agente químico para o clareamento dental pode ocasionar efeitos adversos como sensibilidade dental, ardência, descamação e ulceração das mucosas bucais, dependendo de cada voluntário. Para o tratamento de reações adversas, os custos estão previstos no orçamento do projeto.

Os indivíduos terão a garantia de que receberão 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 vontade do indivíduo em continuar participando dele. Os voluntários 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,_____, certifico que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Eveline Martini e Alessandra Reis. Estou de acordo com a realização do experimento. Assim, concordo em participar como voluntário do trabalho de pesquisa, exposto acima. Certifico também ter recebido uma cópia deste Termo de Consentimento Livre e Esclarecido.

Ponta Grossa, _____ de _____ de 201__.

Nome:_____

Assinatura:_____

Pesquisador Responsável:_____

Eveline Martini (42) 99829-2999

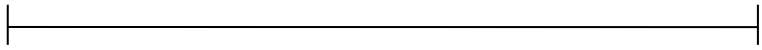
ATENÇÃO: A sua participação em qualquer tipo de pesquisa é voluntária. Em caso de dúvida quanto aos seus direitos, entre em contato com a Comissão de Ética em Pesquisa da UEPG. Endereço – Av. Carlos Cavalcanti, n.4748, Bloco M, Sala 100, CEP- 84030-900 – Ponta Grossa – PR. Fone: (42) 3220-3108. e-mail: coep@uepg.br.

ANEXO G - ESCALA DE DOR (NRS)

Data	0= nenhuma Direi / Esque		1=leve Direi/Esque		2=moderada Direi / Esque		3=considerável Direi / Esque		4=severa Direi /Esque	
Dia 1:										
Dia 2:										
Dia 3:										
Dia 4:										
Dia 5:										
Dia 6:										

ANEXO H – ESCALA DE DOR (VAS)

Marque o lugar que você considera o nível de sensibilidade e em qual lado (se houver diferença):
____° Dia



0 = Sem Dor 10 = Dor insuportável

Apresentou dor/sensibilidade na gengiva? SIM ( ) NÃO ( ) SE SIM, LADO DIREITO ( ) ESQUERDO ( )

ANEXO I - TABELA DE ADESÃO CLAREAMENTO CASEIRO (ARTIGO 3)

_____° Dia : realizou o tratamento DURANTE 3 HORAS?
( )Sim ( )Não. Quantas horas usou?_____
_____

ANEXO J - ARTIGO 1 PUBLICADO

Clinical Oral Investigations
https://doi.org/10.1007/s00784-019-02942-9

ORIGINAL ARTICLE

Bleaching-induced tooth sensitivity with application of a desensitizing gel before and after in-office bleaching: a triple-blind randomized clinical trial

E. C. Martini[1] · S. O. Parreiras[2] · A. L. Szesz[3] · F. M. Coppla[4] · A. D. Loguercio[1,5] · Alessandra Reis[1,5]

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Abstract

Objectives This randomized triple-blind clinical trial, split-mouth design, evaluated the application effect of the desensitizing gel before and after in-office bleaching on tooth sensitivity.

Materials and methods In one group, the desensitizing gel was applied for 10 min before the bleaching with 35% hydrogen peroxide, and then application of placebo gel after ($n = 90$). In the other group, the desensitizing gel was applied before and after the bleaching procedure for 10 min ($n = 90$). The primary outcome was pain intensity assessed with a numeric rating scale and a visual analog scale. Color was evaluated by means of a digital spectrophotometer and a shade guides.

Results The proportion of patients that experienced pain in the side of before application was 90% (95% CI 82 to 94.6%), while the side of before and after was 93% (95% CI 86.2 to 96.9%), without significant difference between groups (OR = 0.25; 95% CI 0.005 to 2.52; $p = 0.37$). Pain was correlated in both groups, for the NRS scale ($p < 0.0001$) and the VAS scale ($p < 0.0001$) in all assessment periods. Significant whitening was detected, and no significant difference of color change was observed between groups ($p > 0.45$).

Conclusions The application of the desensitizing agent did not influence the effectiveness of bleaching, but it was not efficient in reducing the sensitivity, when applied before the procedure, or before and after.

Clinical relevance The use of a desensitizing gel before or after in-office bleaching does not reduce incidence or intensity of tooth sensitivity.

Keywords Tooth bleaching · Dentin sensitivity · Randomized controlled clinical trial · Hydrogen peroxide · Potassium nitrate

Introduction

Among the esthetic procedures most sought by patients, dental bleaching stands out as a conservative procedure that achieves satisfactory results [1]. Dental whitening arises from the oxidation of organic components of the dental structure produced by the hydrogen peroxide and other reactive forms of oxygen [2], giving teeth a lighter

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ANEXO K - ARTIGO 2 PUBLICADO

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Does the Use of Reservoirs Have Any Impact on the Efficacy of At-Home Bleaching? A Systematic Review

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To answer the following focused question through a systematic review: "Is the risk and intensity of tooth sensitivity (TS) and bleaching efficacy, different between adult patients who undergo at-home bleaching using trays with reservoirs and those who use trays without reservoirs?". A comprehensive search was performed in the MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database, Brazilian Library in Dentistry, Cochrane Library, and grey literature without restrictions. Abstracts from conferences; unpublished and ongoing trial registries, dissertations and theses (ProQuest Dissertations and Periódicos Capes Theses databases) were searched. Only randomized clinical trials (RCTs) were included. We used the Risk of Bias tool (RoB) from the Cochrane Collaboration for quality assessment. After the removal of duplicates, title and abstract screening and full-text examination, nine RCTs remained for qualitative analyses. The great majority of the studies did not report the method of randomization, allocation concealment, and examiner blinding during color assessment. From the nine studies, eight were at unclear risk of bias. In regard to color change, four studies reported no change and two reported improved color change with reservoirs. Only four studies recorded tooth sensitivity and they reported no significant differences. Only one study reported greater gingival irritation with reservoirs. Lack of data reporting prevented us from running a meta-analysis. Further well-designed RCT should be conducted to answer this research question. So far there is not evidence to support that reservoirs in bleaching trays improve color change. PROSPERO - CRD42016037628

Key Words: systematic review, reservoirs, at-home bleaching, dental sensitivity.