UNIVERSIDADE ESTADUAL DE PONTA GROSSA
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA – MESTRADO
ÁREA DE CONCENTRAÇÃO: DENTÍSTICA RESTAURADORA

MICHAEL WILLIAN FAVORETO

USO DE DESSENSIBILIZANTES BIOATIVOS CONTENDO CÁLCIO NO CLAREAMENTO DENTAL: UMA REVISÃO SISTEMÁTICA E METANÁLISE

PONTA GROSSA
2022

MICHAEL WILLIAN FAVORETO

USO DE DESSENSIBILIZANTES BIOATIVOS CONTENDO CÁLCIO NO CLAREAMENTO DENTAL: UMA REVISÃO SISTEMÁTICA E METANÁLISE

Dissertação apresentada como pré-requisito para obtenção do título de Mestre em Odontologia na Universidade Estadual de Ponta Grossa, no curso de Mestrado em Odontologia – Área de Concentração Dentística Restauradora. Linha de Pesquisa: Pesquisa Clínica em Odontologia.

Orientadora: Profª. Drª. Alessandra Reis.
Coorientadora: Profª. Drª. Fabiana Dias Simas Dreweck.

PONTA GROSSA
2022

Favoreto, Michael Willian

F275 Uso de dessensibilizantes bioativos contendo cálcio no clareamento dental: uma revisão sistemática e metanálise / Michael Willian Favoreto. Ponta Grossa, 2022.

104 f.

Dissertação (Mestrado em Odontologia - Área de Concentração: Dentística Restauradora), Universidade Estadual de Ponta Grossa.

Orientadora: Profa. Dra. Alessandra Reis.

Coorientadora: Profa. Dra. Fabiana Dias Simas Dreweck.

1. Clareamento dental. 2. Peróxido de hidrogênio. 3. Ensaios Clínicos Randomizados. 4. Revisão sistemática. I. Reis, Alessandra. II. Dreweck, Fabiana Dias Simas. III. Universidade Estadual de Ponta Grossa. Dentística Restauradora. IV.T.

CDD: 617.6

Ficha catalográfica elaborada por Maria Luzia Fernandes Bertholino dos Santos- CRB9/986

MICHAEL WILLIAN FAVORETO

USO DE DESSENSIBILIZANTES BIOATIVOS CONTENDO CÁLCIO NO CLAREAMENTO DENTAL: UMA REVISÃO SISTEMÁTICA E METANÁLISE

Dissertação apresentada ao Programa de Pós-graduação Stricto sensu em Odontologia da Universidade Estadual de Ponta Grossa, como requisito parcial à obtenção do título de Mestre em Odontologia, área de concentração em Dentística Restauradora, linha de pesquisa de Pesquisa Clínica em Odontologia.

Ponta Grossa, 18 de fevereiro de 2022.

Profa. Dra. Alessandra Reis
Universidade Estadual de Ponta Grossa

Prof. Dr. Heitor Marques Honório
Universidade de São Paulo - Bauru

Prof. Dr. André Luís Faria e Silva
Universidade Federal do Sergipe

Nem tudo são flores, mas tudo é semente.

AGRADECIMENTOS

***À minha mãe**, Ana.*

***A minha família**, Juliana, Isabelle, Pedro e Manu.*

***Ao meu namorado**, Diego.*

***À minha amada orientadora**, Profª. Drª. Alessandra Reis.*

***Ao meu orientador paralelo**, Prof°. Dr°. Alessandro Loguercio.*

***À minha orientadora de PIBIC-Jr**, Profª. Drª. Christiane Phllippini Ferreira Borges.*

***Aos meus amigos de pesquisas,** Taynara, Laís, Helo, Michel, Elisama, Adri, Gabi, Thiago, João, Léo.*

*À **Coordenação do Programa de Pós-Graduação em Odontologia UEPG**.*

***Ao Departamento de Odontologia Restauradora**.*

A todos que contribuíram de alguma forma seja ela direta ou indireta para realização e desenvolvimento desta dissertação, meus mais sinceros agradecimentos!

“O único passo entre o sonho e a realidade é a atitude.”

(autor desconhecido)

DADOS CURRICULARES

MICHAEL WILLIAN FAVORETO

NASCIMENTO 10.10.1995	Ponta Grossa, Paraná – Brasil.
FILIAÇÃO	Ana Marcia Kwiatkowski Marcos Favoreto
2014 – 2018	Curso de Graduação em Odontologia. Universidade Estadual de Ponta Grossa (UEPG). Ponta Grossa – PR, Brasil.
2019 – 2019	Curso de Aperfeiçoamento em de Estética e Prótese Metal-Free. Associação Brasileira de Odontologia Regional de Ponta Grossa (ABO-PG). Ponta Grossa – PR, Brasil.
2020 – Em andamento	Curso de Pós-Graduação em Odontologia. Área de Concentração em Dentística Restauradora. Nível Mestrado. Universidade Estadual de Ponta Grossa. Ponta Grossa – PR, Brasil.
2021 – Em andamento	Curso de Especialização em Dentística Restauradora. Instituto Odontológico das Américas (IOA Style). Curitiba, PR – Brasil.
2021 – Em andamento	Curso de Especialização em Prótese Dentária. Instituto Odontológico das Américas (IOA Style). Curitiba, PR – Brasil.

RESUMO

A aplicação tópica de dessensibilizantes bioativos contendo cálcio (BC) tem sido usada para minimizar a sensibilidade dental induzida pelo clareamento (SD). Este estudo respondeu à pergunta de pesquisa “O risco de SD é menor quando BC são usados com clareamento dental em adultos em comparação com clareamento sem dessensibilizantes?” Os autores incluíram ensaios clínicos randomizados comparando a aplicação tópica de BC com um placebo ou nenhuma intervenção durante o clareamento. As buscas de artigos elegíveis foram realizadas no MEDLINE via PubMed, Biblioteca Cochrane, Biblioteca Brasileira de Odontologia, Literatura Latino-Americana e do Caribe em Ciências da Saúde, Scopus, Web of Science, Embase e literatura cinzenta sem restrições de idioma e data e atualizada em setembro de 2022. O risco de viés foi avaliado usando o Risk of Bias versão 2.0. Os autores conduziram meta-análises com o modelo de efeitos aleatórios. Os autores avaliaram a heterogeneidade com o teste Cochrane Q, estatísticas I^2 e intervalo de predição. Os autores usaram a abordagem Grading of Recommendations Assessment, Development and Evaluation para avaliar a certeza das evidências. Após a triagem do banco de dados, 22 estudos permaneceram, com a maioria com alto risco de viés. Nenhuma diferença no risco de SD foi detectada (razão de risco, 0,95; IC 95%, 0,90 a 1,01; p = 0,08, baixa certeza). Em uma escala analógica visual, a intensidade de SD foi menor para o grupo BC (diferença média, −0,98; IC 95%, −1,36 a −0,60; p < 0,0001, certeza muito baixa). A mudança de cor não foi afetada (p > 0,08). Embora o clareamento dental tópico CB não tenha reduzido o risco de SD e mudança de cor, esses agentes reduziram levemente a intensidade do SD, mas a certeza da evidência é muito baixa.

Palavras-chave: Clareamento Dental. Peróxido de Hidrogênio. Ensaios Clínicos Randomizados. Revisão Sistemática.

ABSTRACT

Topical application of calcium-containing bioactive desensitizers (CBs) has been used to minimize bleaching-induced tooth sensitivity (TS). This study answered the research question “Is the risk of TS lower when CBs are used with dental bleaching in adults compared with bleaching without desensitizers?” The authors included randomized clinical trials comparing topical CB application with a placebo or no intervention during bleaching. Searches for eligible articles were performed in MEDLINE via PubMed, Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature, Scopus, Web of Science, Embase, and gray literature without language and date restrictions and updated in September 2022. The risk of bias was evaluated using Risk of Bias Version 2.0. The authors conducted meta-analyses with the random-effects model. The authors assessed heterogeneity with the Cochrane Q test, I2 statistics, and prediction interval. The authors used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty of the evidence. After database screening, 22 studies remained, with most at high risk of bias. No difference in the risk of TS was detected (risk ratio, 0.95; 95% CI, 0.90 to 1.01; $p = 0.08$, low certainty). In a visual analog scale, the intensity of TS (mean difference, −0.98; 95% CI, −1.36 to −0.60; $p < 0.0001$, very low certainty) was lower for the CB group. The color change was unaffected ($p > 0.08$). Although topical CB dental bleaching did not reduce the risk of TS and color change, these agents slightly reduced the TS intensity, but the certainty of the evidence is very low.

Keywords: Tooth bleaching. Hydrogen Peroxide. Randomized Clinical Trials. Systematic Review.

LISTA DE FIGURAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

a*	Eixo vermelho-verde
b*	Eixo azul-amarelo
$CH_6N_2O_3$	Peróxido de carbamida
CIE	Comissão Internacional de Iluminação
ΔE_{ab}	Variação de cor
ΔUEV	Variação de Unidades na Escala Vita
cm	Centímetro
h	Hora (s)
H_2O_2	Peróxido de Hidrogênio
L*	Luminosidade
mL	Mililitro (s)
min	Minuto (s)
mm	Milímetro (s)
PC	Peróxido de carbamida
PH	Peróxido de hidrogênio
pH	Potencial hidrogeniônico
s	Segundo (s)
SD	Sensibilidade Dental
UEPG	Universidade Estadual de Ponta Grossa
UEV	Unidades na Escala Vita
VAS	*Visual Analogic Scale* (Escala Visual Analógica)

LISTA DE SÍMBOLOS

Δ	Delta
=	Igual
±	Mais ou menos
<	Menor
>	Maior
%	Porcentagem
p	Valor da significância estatística
®	Marca Registrada

SUMÁRIO

1 INTRODUÇÃO

A valorização da estética ganhou popularidade principalmente devido à significativa influência das mídias sociais (Theobald et al. [1] 2006). Um estudo recente relatou que 45,6% dos indivíduos que usaram as mídias sociais editaram suas fotos para aparecer com dentes mais claros (Martel et al. [2] 2020). Este achado demonstra a importância dos procedimentos clareadores na vida social das pessoas (Bonafé et al. [3] 2021). Essas pessoas podem utilizar esses programas de edição, ao invés de serem submetidas ao clareamento dental, devido aos custos reduzidos ou simplesmente porque não sabem que o clareamento dental é um procedimento seguro que melhora o sorriso dos pacientes (Kwon e Wertz [4] 2015; Reis et al. [5] 2018; Haywood e Sword [6] 2021).

Existem duas técnicas recomendadas supervisionadas por dentistas para o clareamento de dentes vitais: clareamento caseiro e clareamento em consultório. O protocolo caseiro consiste na aplicação de agentes clareadores de baixa concentração utilizando uma moldeira individual (Haywood e Sword [6] 2021), enquanto no consultório, os cirurgiões-dentistas aplicam agentes clareadores com alta concentração no consultório odontológico, após a proteção dos tecidos gengivais com uma barreira gengival fotopolimerizavel (Reis et al. [5] 2018). Independentemente do protocolo de clareamento, o clareamento ocorre pela capacidade do peróxido de hidrogênio (PH) em oxidar o componente orgânico da estrutura dental (Kwon e Wertz [4] 2015). Portanto, o PH é o principal componente ativo de todos os produtos clareadores ou é derivado de outros produtos como o peróxido de carbamida (PC) (Kwon e Wertz [4] 2015).

É inegável que o clareamento dental pode promover uma mudança de cor efetiva, como demonstrado em diversos estudos clínicos randomizados (de Sá et al. [7] 2021; Donassollo et al. [8] 2021; Kothari et al. [9] 2020; Martini et al. [10] 2020; Meireles et al. [11] 2021). Embora vários efeitos adversos tenham sido descritos na literatura, como a penetração do PH na câmara pulpar (Parreiras et al. [12] 2020), redução da resistência de união (Coppla et al. [13] 2019), redução da microdureza do esmalte (Coceska et al. [14] 2016), alterações na morfologia e desmineralização superficial (Acuña et al. [15] 2019; Cavalli et al. [16] 2018), esses efeitos foram essencialmente observados *in vitro*, e foram comprovados como temporários devido ao efeito remineralizante da saliva (Jager et al. [17] 2011; Sa et al. [18] 2012; Sa et al. [19] 2013).

Um dos principais efeitos adversos é a sensibilidade dental (SD) induzida pelo clareamento, que é relatada na literatura em 50 a 90% dos pacientes submetidos ao clareamento dental (de Sá et al. [7] 2021; Donassollo et al. [8] 2021; Kothari et al. [9] 2020; Martini et al. [10] 2020; Meireles et al. [11] 2021). Uma das abordagens utilizadas para reduzir esse efeito colateral é a aplicação tópica de dessensibilizantes à base de nitrato de potássio. Estudos relataram que o nitrato de potássio pode reduzir a SD por atividade neural, ou seja, impedindo a transmissão de impulsos nervosos (Parreiras et al. [12] 2020; Kwon et al. [20] 2016; Martini et al. [21] 2021). Uma revisão sistemática recente sobre este tópico relatou que os dessensibilizantes a base de nitrato de potássio têm um efeito estatisticamente significativo na redução do risco e na intensidade da SD, no entanto, de uma perspectiva clínica, a magnitude dessa redução ainda é modesta. (Martini et al. [21] 2021).

Outro tipo de dessensibilizante a base de agentes bioativos contendo cálcio, parece ser uma alternativa para o manejo da SD (Browning et al. [22] 2012; de Araújo et al. [23] 2021; Mehta et al. [24] 2018; Oldoini et al. [25] 2018; Singh et al. [26] 2017; Tawfik et al. [27] 2019; Yassin e Milly [28] 2019). Esses produtos contendo cálcio interagem notavelmente com os tecidos duros por precipitação no esmalte (Parreiras et al. [12] 2020), assim, minimizando os efeitos nocivos da desmineralização e as alterações na morfologia do esmalte. (Coceska et al. [14] 2016; Gomes et al. [29] 2018; Ubaldini et al. [30] 2020). Estudos também demonstraram que agentes contendo cálcio reduzem consideravelmente a penetração de PH na câmara pulpar. (Parreiras et al. [12] 2020; Barbosa et al. [31] 2020). Isso, por sua vez, pode ser responsável pelos níveis mais baixos de SD relatados em ensaios clínicos randomizados (Browning et al. [22] 2012; de Araújo et al. [23] 2021; Mehta et al. [24] 2018; Oldoini et al. [25] 2018; Singh et al. [26] 2017; Tawfik et al. [27] 2019; Yassin e Milly [28] 2019).

Até o momento, não foram encontradas revisão sistemática da literatura que avaliaram até que ponto os resultados dos atuais ensaios clínicos randomizados (ECRs) sobre o efeito de dessensibilizantes bioativos contendo cálcio no manejo da SD induzida pelo clareamento representam uma estimativa imparcial da verdade. As revisões sistemáticas identificam, avaliam e resumem as descobertas de todos os artigos relevantes sobre uma questão de pesquisa específica, tornando as evidências mais acessíveis aos tomadores de decisão.

2 REVISÃO DE LITERATURA

2.1 HISTÓRICO

Dentes mais claros sempre foram importantes desde tempos remotos quanto a antiguidade, os romanos por exemplo utilizavam uma técnica tanto quanto inusitada com a combinação de pasta de leite de cabra e urina com o objetivo de deixar os dentes mais claros; os egípcios utilizavam uma outra combinação de pedra-pomes e vinagre de vinho; no século XII houve uma recomendação do uso da combinação de sálvia e sal e até mesmo que esfregassem os dentes com flores. Em 1848 foi documentado o primeiro tratamento clareador com o uso de cloreto aplicado sobre um dente não vital (Haywood [32] 1992). Diferentes produtos foram testados até chegar no cenário que se encontra o tratamento clareador de hoje como: cloreto de alumínio, ácido oxálico, pirozona, amônia, cianeto de potássio PH, peróxido de sódio, ácido sulfúrico entre outros (Kwon e Wertz [4] 2015). Devido aos efeitos adversos desses produtos nas estruturas dentais aos poucos essas substâncias foram caindo em desuso.

O PH é o agente clareador mais empregado atualmente, em 1884 foi realizado o primeiro relato, seguido da observação efetiva da técnica no fim dos anos 1960 através da aplicação de gly-oxide, um antisséptico contendo PC 10% no posicionador ortodôntico durante à noite para facilitar a reparação gengival, além dos efeitos benéficos aos tecidos gengivais, foi observado mudança de cor nos dentes (Kwon e Wertz [4] 2015).

Um marco na literatura foi em 1989, onde os autores Haywood e Heymann demonstraram a técnica de clareamento dental caseira através do uso PC 10% (Haywood e Heymann [33] 1989). Desde então, os pesquisadores e empresas investiram em pesquisas em relação aos agentes clareadores e técnicas clareadoras, permitindo o conhecimento atual sobre o tema.

2.2 QUÍMICA DO CLAREAMENTO DENTAL

Todos os produtos para clareamento de dentes vitais são compostos por substâncias ativas, responsáveis pelo ação do clareamento dental. Além dessas substâncias, há outros componentes nos agentes clareadores, cada um exercendo

diferentes funções. Atualmente, existem no mercado duas principais substâncias ativas empregadas em produtos comerciais para clareamento de dentes vitais: PH, PC (Kwon e Wertz [4] 2015; Luque-Martinez et al. [34] 2016).

2.2.1 Peróxido de hidrogênio

O PH, é um líquido claro, de baixa massa molecular (34,0147 g/mol), com fórmula química H_2O_2, sua constante de dissociação (pKa) é em 11,6, possui alto poder desinfetante e oxidante (Torres et al. [35] 2014). Pode ser apresentado em baixas concentrações (de 4 a 10%), sendo indicado para o clareamento caseiro por períodos que variam de 30 minutos até 4 horas diárias (Terra et al. [36] 2021; Chemin et al. [37] 2021; Chemin et al. [38] 2018). Pode também ser apresentado em concentrações mais elevadas (de 20 a 40%), o produto deve ser utilizado em âmbito profissional, por períodos menores, de 30 a 50 minutos (de Sá et al. [7] 2021; Kiyuna et al. [39] 2021; Maran et al. [40] 2020).

Quando entra em contato com o dente, o PH se cliva e produz radicais livres como hidroxila, peridroxil e ânions superóxidos (Torres et al. [35] 2014). Esses radicais livres oxidam as moléculas insaturadas presente na estrutura dental, tornando-as saturadas. Essas moléculas saturadas dispersam mais a luz pela modificação do índice de refração da dentina, que passa a ficar mais branca e opaca. Por muito tempo, acreditou-se que a cor dos elementos dentais fosse afetada pela presença de cromóforos orgânicos (Kwon e Wertz [4] 2015; Watts e Addy [41] 2001; Sulieman [42] 2004). Entretanto, não foi identificado até o momento, por meio de técnicas de análise química (Eimar et al. [43] 2012), a presença de substâncias com características de cromóforos na estrutura dental vital (Eimar et al. [43] 2012; Eimar et al. [44] 2011; Fattibene et al. [45] 2005). Em dentes vitalizados, propôs-se recentemente que o PH clareia os elementos dentais pela simples oxidação do conteúdo orgânico da dentina, que em grande parte se deve ao colágeno. O colágeno é incolor em sua estrutura original, mas oxidado, ele se torna mais branco e mais opaco, resultando em dentes com aparência bem mais clara (Eimar et al. [43] 2012; Kawamoto e Tsujimoto [46] 2004).

2.2.2 Peróxido de carbamida

É um sólido branco e cristalino que se dissolve em água e produz PH e ureia. Em concentrações de 10 a 22% é, geralmente, indicado para o clareamento caseiro e empregado por períodos que variam de 1 a 8 horas diárias (Martini et al. [10] 2020; Cardoso et al. [47] 2010; de Geus et al. [48] 2018). Quando em concentrações acima de

30% sua utilização pode ser feita em consultório sob supervisão do profissional ou de forma caseira com tempo de aplicação reduzido (Sutil et al. [49] 2020; Abrantes et al. [50] 2021).

O PC é comercializado em gel e, em meio úmido, rapidamente se dissocia em PH e ureia nas concentrações de 3,6% e 6,4%, respectivamente. Enquanto o PH atua ativamente sobre os pigmentos, a ureia ainda se dissocia em amônia e gás carbônico. A amônia eleva o pH da solução ou do gel, favorecendo a dissociação do PH em radicais oxidativos.

2.2.3. Outros componentes dos produtos para clareamento

Além dos agentes ativos, os produtos para clareamento dental contêm várias outras substâncias: água deionizada, carbopol, propilenoglicol, glicerina, ácido etilenodiamino tetra-acético dissódico, metilparabeno, hidróxido de sódio, fluoretos, pantenol, nitrato de potássio, fluoretos e agentes remineralizante.

2.3 TÉCNICAS DE CLAREAMENTO DENTAL

Em dentes vitalizados, o clareamento pode ser realizado em vários dentes simultaneamente tanto no arco superior quanto no inferior. As técnicas principais para dentes vitais são classificadas em:

2.3.1. Técnica caseira (*at-home*)

O clareamento é realizado em casa pelo próprio paciente, sob supervisão de um cirurgião-dentista, através de moldeiras para clareamento individualizadas associadas a agentes clareadores em baixas concentrações. Essas moldeiras são confeccionadas com um material termoplastificável, o copolímero de etileno e acetato de vinila, com espessura aproximada de 1 mm.

Tanto o PH em baixas concentrações (4 a 15%), como o PC (10 a 22%) podem ser empregados na técnica caseira. O PH é instável e praticamente sofre dissociação em 30 a 60 minutos após aplicação (Al-Qunaian et al. [51] 2003). O PC libera aproximadamente 50% de seu peróxido nas primeiras 4 horas e o remanescente nas 4 a 6 horas restantes (Matis et al. [52] 1999). O tempo inicialmente proposto de 8 horas à noite foi gradualmente substituído por tempos reduzidos de uso da moldeira, tornando o tratamento mais confortável para o paciente (Cardoso et al. [47] 2010). Atualmente, com mais conhecimento a respeito da cinética de degradação dos géis clareadores, reduziu-se o tempo recomendado de uso, de 30 minutos a 4 horas

diárias, a depender do tipo do agente ativo e de sua concentração (Martini et al. [10] 2020; Terra et al. [36] 2021; Chemin et al. [37] 2021; Chemin et al. [38] 2018; Favoreto et al. [53] 2022 in press). Recomenda-se o tratamento clareador caseiro por aproximadamente 2 semanas, com aplicações diárias e consecutivas por esse período. Esse tempo é suficiente para produzir uma alteração de cor clinicamente significativa. No entanto, usos prolongados de 3 e 4 semanas também podem ser empregados para uma maior satisfação do paciente.

2.3.2. Técnica de consultório (*in-office*)

O clareamento é realizado em consultório pelo cirurgião-dentista, com agentes clareadores em altas concentrações, após proteção dos tecidos moles com barreiras gengivais.

Com essa técnica é possível obter resultados mais rápidos e não tem o inconveniente do uso de uma moldeira carregada com gel. É realizada em consultório odontológico, utilizando PH em altas concentrações (20 a 40%) (Reis et al. [5] 2018). Os tecidos moles da cavidade bucal devem ser protegidos com retratores labiais e com a aplicação de uma barreira gengival fotoativada (de Sá et al. [7] 2021). Após a proteção dos tecidos moles, realiza-se a mistura dos componentes do gel clareador. Conforme já mencionado, os produtos à base de PH idealmente devem ser armazenados em pH ácido, a fim de proporcionar maior longevidade (Torres et al. [35] 2014). Entretanto, o pH mais favorável para sua eficiência é o alcalino (Torres et al. [35] 2014). Por esse motivo, os fabricantes têm apresentado suas formulações em dois frascos ou seringas separadas, sendo que um dos frascos contém PH (concentração aproximada de 50%) em meio ácido, e o segundo contém um espessante em meio alcalino. Ao serem misturados, conferem um produto alcalino com concentração próxima de 35 a 38% e com viscosidade ideal para aplicação. O produto deve ser aplicado nas superfícies dentais dos dentes em espessura suficiente para cobrir a face vestibular. Alguns fabricantes, recomendam a troca do gel da superfície dental de 15 em 15 minutos; porém, para alguns produtos recomendam-se tempos de oito e 20 minutos. Essa troca é realizada de três a quatro vezes dependendo do produto comercial (Kury et al. [54] 2021). Há produtos que por serem mais alcalinos, podem ser aplicados uma única vez por períodos que variam de 40 a 50 minutos, dependendo das instruções dos fabricantes de cada produto clareador. São necessárias pelo menos duas sessões clínicas de consultório para alcançar uma alteração de cor

clinicamente importante. O intervalo entre essas sessões deve ser de 2 a 7 dias (de Paula et al. [55] 2015).

2.3.3. Técnica associada (*jump-start ou power bleaching*).

Associação da técnica de consultório com a caseira. Geralmente, a técnica de consultório é realizada em uma primeira sessão, seguido da técnica caseira (Cardenas et al. [56] 2019).

2.4 EFEITOS ADVERSOS DO CLAREAMENTO DENTAL

2.4.1. Tecidos moles

O contato direto de agentes clareadores com o tecido gengival ou a mucosa bucal pode causar queimaduras que resultam no desenvolvimento de lesões e erosões gengivais. Esses efeitos adversos são proporcionais à concentração do agente ativo e do tempo de contato. Em técnicas de clareamento caseiro, dois fatores podem ocasionar irritação gengival: trauma mecânico devido a uma falta de adaptação da moldeira e efeito agressivo do gel em contato com a mucosa, em especial quando são usados géis em altas concentrações (Haywood e Sword [6] 2021).

Apesar dos agentes clareadores para uso em consultório serem bem mais cáusticos e agressivos para os tecidos moles, o afastamento da mucosa e da língua com retratores de lábio e tecido gengival, além da aplicação de uma barreira gengival fotoativada são suficientes para prevenir a queimadura tecidual que advém do contato do peróxido com o tecido. No caso de contato acidental, a aplicação de um agente neutralizador à base de bicarbonato de sódio e/ou catalase, presente no kit de alguns agentes clareadores, reverte o quadro rapidamente (Guasso et al. [57] 2016), e o aspecto esbranquiçado desaparece em menos de 1 hora após aplicação.

2.4.2. Tecidos duros

As principais alterações observadas nesse tecido são: alterações da morfologia superficial, aumento da porosidade do esmalte, exposição dos prismas do esmalte, redução do conteúdo orgânico e redução da dureza (Kwon e Wertz [4] 2015; Coceska et al. [14] 2016; Acuña et al. [15] 2019; Cavalli et al. [16] 2018). Todas essas alterações dependem do tipo de gel clareador, do pH e do tempo de aplicação. Entre estas variáveis, o pH parece ser a mais significativa, já que a maior porosidade superficial é possivelmente resultado da desmineralização causada pelo pH do produto e a oxidação das proteínas do esmalte. Essas alterações superficiais também são

observadas em clareamento de consultório, principalmente aqueles com pH mais ácidos (Acuña et al. [15] 2019). Embora a maioria dos géis clareadores tenha pH ao redor de 6,5, há no mercado clareadores para consultório com pH entre 3,6 e 5,0; ou seja, pH abaixo do valor crítico de dissolução do esmalte (5,5). Essa dissolução de esmalte deve explicar a redução da dureza do esmalte quando comparada antes e após o tratamento clareador. Produtos mais ácidos tendem a produzir maior desmineralização superficial que agentes com pH próximo ao neutro ou alcalinos (Acuña et al. [15] 2019). No entanto, a dureza superficial tende a retornar aos valores iniciais após algum tempo imerso em saliva artificial. Alguns produtos clareadores associam agentes remineralizantes às suas formulações, com o intuito de recuperar a perda de conteúdo inorgânico causada pela ação ácida e oxidante das substâncias clareadoras, a aplicação tópica de produtos remineralizantes também parece ser uma alternativa.

2.5 SENSIBILIDADE DENTAL

A teoria mais aceita atualmente para a SD é que o agente clareador consegue atravessar os tecidos duros do dente e chegar no tecido pulpar causando uma inflamação do tecido, o que deflagra a dor (Markowitz [58] 2010). Já foi demonstrado que o PH alcança o tecido pulpar em até 15 minutos após a aplicação (Cooper et al. [59] 1992; Favoreto et al. [60] 2021). A SD pode ser resultado de uma pulpite decorrente da agressão sofrida pela polpa devido ao contato com o PH, entretanto, estudos demonstram que ela parece ser reversível.

Vários fatores podem estar associados a presença de SD que estejam relacionados ao paciente, como a presença de hipersensibilidade prévia, pacientes mais jovens, pacientes com dentes mais claros, pacientes com lesões cervicais. O tipo e a condição dental como tamanho e espessura, presença de restaurações ou dentes com trincas. Outros fatores que afetam a SD estão relacionados ao gel como o aumento do tempo de contato do gel com a superfície dental, maior concentração e pH ácido.

Foram conduzidos diversos estudos clínicos para avaliar alternativas preventivas de reduzir o risco e a intensidade da dor. Diversos medicamentos anti-inflamatórios não esteroidais, anti-inflamatórios esteroidais, analgésicos opioides ou antioxidantes usados antes e durante o clareamento não foram eficientes para reduzir

a dor produzida pelo clareamento dental (Carregosa Santana et al. [61] 2019; Almassri et al. [62] 2019; Costa et al. [63] 2020). A aplicação tópica de medicamentos também foi testada, mas não foram eficientes (Favoreto et al. [64] 2021; Vilela et al. [65] 2021; Rezende et al. [66] 2018). Uma técnica que se mostrou eficaz em um estudo foi a aplicação prévia de um dessensibilizante à base de nitrato de potássio pois esses agentes atuam na condução do impulso nervoso [ação neural] (Martini et al. [21] 2021). Os agentes bioativos contendo cálcio também demonstraram alguns efeito benéficos no manejo da SD em diferentes estudos clínicos (Browning et al. [22] 2012; de Araújo et al. [23] 2021; Mehta et al. [24] 2018; Oldoini et al. [25] 2018; Singh et al. [26] 2017; Tawfik et al. [27] 2019; Yassin e Milly [28] 2019).

2.6 AGENTE BIOATIVOS QUE CONTÊM CÁLCIO

Sua ação é diferente da ação neural, esses agentes atuam por saturação do meio com precipitação no esmalte, assim, minimizando os efeitos deletérios da desmineralização e as alterações na morfologia do esmalte. Esse efeito na sensibilidade pode estar diretamente relacionado com a redução da penetração do PH na polpa (Parreiras et al. [12] 2020; Barbosa et al. [31] 2020).

3 PROPOSIÇÃO

3.1 PROPOSIÇÃO GERAL

Esta atual revisão sistemática teve como objetivo responder à seguinte questão de pesquisa: “O uso de dessensibilizantes bioativos contendo cálcio (*intervenção*) antes e/ou após o clareamento dental em adultos (*participante*) pode reduzir o risco e a intensidade de SD (*desfechos*) comparado ao clareamento sem dessensibilização/placebo (*comparador*)?"

3.2 PROPOSIÇÕES ESPECÍFICAS

3.2.1 Avaliar o efeito do uso de dessensibilizantes bioativos contendo cálcio em pacientes adultos durante o clareamento dental, na redução do risco absoluto e intensidade de SD.

3.2.2 Avaliar a efetividade clareadora quando é realizado o uso de dessensibilizantes bioativos contendo cálcio durante o clareamento dental.

4 MATERIAIS E MÉTODO

Nesta sessão será descrita a metodologia de forma resumida, as informações detalhadas dos seguintes itens podem ser encontradas no artigo descrito após a sessão, bem como novos tópicos.

4.1 PROTOCOLO DE REGISTRO

Esta revisão sistemática foi registrada no *International Prospective Register of Systematic Reviews* (PROSPERO; *https://www.crd.york.ac.uk/prospero/*) sob o número de registro CRD42020178042 (ANEXO A) e seguiu as recomendações do *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA).

4.2 CRITÉRIOS DE ELEGIBILIDADE

Foram incluídos ensaios clínicos randomizado paralelos, split-mouth e cross-over que avaliaram a aplicação tópica de dessensibilizantes bioativos contendo cálcio antes e/ou após sobre o risco e a intensidade da SD durante o clareamento dental em consultório e/ou caseiro em pacientes adultos. Foram excluídos se os estudos: 1) incorporaram os dessensibilizantes bioativos contendo cálcio no gel clareador; 2) avaliaram dentifrícios contendo dessensibilizantes bioativos contendo cálcio; 3) avaliaram outros tipos de agentes dessensibilizantes; 4) não tiveram um grupo placebo ou agente não dessensibilizante para comparação; e 5) incluiu ambos os grupos, mas não comparou géis clareadores com concentrações equivalentes.

4.3 FONTES DE INFORMAÇÃO E ESTRATÉGIA DE BUSCA

A estratégia de busca foi inicialmente definida para a base de dados MEDLINE via PubMed usando um vocabulário controlado (*MeSH* termos) e palavras-chave para cada conceito da pergunta de pesquisa descrita no objetivo geral do estudo. Os resultados a serem avaliados foram: 1) o risco de SD, 2) intensidade de SD, 3) mudança de cor nas unidades de guia de cores da escala Clássica e 4) mudança de cor através de espectrofotômetro em unidades de ΔE_{ab}. (de l'Eclairage [67] 1978)Após a estratégia de busca MEDLINE via PubMed foi adaptada para demais bases de dados eletrônicas, a literatura cinzenta também foi consultada.

4.4 SELEÇÃO DE ESTUDOS E PROCESSO DE COLETA DE DADOS

Todos os estudos foram inicialmente selecionados quanto à relevância por título; seguido pelo resumo e, finalmente, pela recuperação do texto completo. Os textos completos foram lidos para verificar se atendiam aos critérios de inclusão. Cada artigo elegível recebeu uma identificação de estudo, combinando o primeiro autor e o ano de publicação e categorizaram independentemente os dados, como desenho do estudo, número de pacientes, intervenções e resultados.

4.5 RISCO DE VIÉS EM ESTUDOS INDIVIDUAIS

O risco de viés (RoB) foi avaliado utilizando a ferramenta da *Cochrane Collaboration* (RoB versão 2) para ensaios clínicos randomizados (Higgins et al. [68] 2019).

4.6 MEDIDAS RESUMIDAS E SÍNTESE DOS RESULTADOS

Os dados foram analisados usando Revman 5.4.1 (*Review Manager Versão 5.4.1*, The Cochrane Collaboration, Copenhagen, Denmark). Metanálises foram realizadas em todos os estudos elegíveis.

4.7 AVALIAÇÃO DA CERTEZA DA EVIDÊNCIA USANDO GRADE

A certeza do corpo de evidências foi avaliada usando o *Grading of Recommendations: Assessment, Development, and Evaluation* (GRADE).

5 ARTIGO

TÍTULO: Use of calcium-containing bioactive desensitizers in dental bleaching: A systematic review and meta-analysis

STATUS: Aceito

REVISTA: The Journal of the American Dental Association

doi: https://doi.org/10.1016/j.adaj.2022.11.012

Use of calcium-containing bioactive desensitizers in dental bleaching: A systematic review and meta-analysis

Michael Willian Favoreto [DDS, MS student][1], Taynara de Souza Carneiro [DDS, MS student][1], Heloisa Forville de Andrande [DDS, MS student][1], Adriely Burey [DDS, MS, Ph.D.][2], Fabiana Dias Simas Dreweck [DDS, MS, Ph.D.][1], Alessandro Dourado Loguercio [DDS, MS, Ph.D.][1], Alessandra Reis [DDS, Ph.D.][1]

[1] Department of Restorative Dentistry, State University of Ponta Grossa, Ponta Grossa, Paraná, Brazil
[2] Department of Restorative Dentistry, Unicesumar, Ponta Grossa, Paraná, Brazil
[3] Department of Restorative Dentistry, Cescage, Ponta Grossa, Paraná, Brazil

Corresponding author: Alessandra Reis. Universidade Estadual de Ponta Grossa. Curso de Odontologia. Avenida Carlos Cavalcanti, 4748. CEP: 84.030-900. Phone: +55 4232203740. Bloco M, Sala 04. e-mail: reis_ale@hotmail.com

Use of calcium-containing bioactive desensitizers in dental bleaching: A systematic review and meta-analysis

Abstract

Background

Topical application of calcium-containing bioactive desensitizers (CBs) has been used to minimize bleaching-induced tooth sensitivity (TS). This study answered the research question “Is the risk of TS lower when CBs are used with dental bleaching in adults compared with bleaching without desensitizers?”

Types of Studies Reviewed

The authors included randomized clinical trials comparing topical CB application with a placebo or no intervention during bleaching. Searches for eligible articles were performed in MEDLINE via PubMed, Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature, Scopus, Web of Science, Embase, and gray literature without language and date restrictions and updated in September 2022. The risk of bias was evaluated using Risk of Bias Version 2.0. The authors conducted meta-analyses with the random-effects model. The authors assessed heterogeneity with the Cochrane Q test, I^2 statistics, and prediction interval. The authors used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty of the evidence.

Results

After database screening, 22 studies remained, with most at high risk of bias. No difference in the risk of TS was detected (risk ratio, 0.95; 95% CI, 0.90 to 1.01; *P* = .08, low certainty). In a visual analog scale, the intensity of TS (mean difference, −0.98; 95% CI, −1.36 to −0.60; *P* < .0001, very low certainty) was lower for the CB group. The color change was unaffected (*P* > .08).

Practical Implications

Although topical CB dental bleaching did not reduce the risk of TS and color change, these agents slightly reduced the TS intensity, but the certainty of the evidence is very low.

Prospero

CRD42020178042

Keywords

Tooth bleaching, hydrogen peroxide, dentin desensitizing agents, randomized clinical trials, systematic review

Abbreviation Key

ΔE_{ab}, Color change; **ΔSGU**, Color change in shade guide units; **CB**, Calcium-containing bioactive desensitizer; **D**, Domain; **GRADE**, Grading of Recommendations Assessment, Development and Evaluation; **RCT**, Randomized controlled trial; **SGU**, Shade guide unit; **TS**, Tooth sensitivity; **VAS**, Visual analog scale.

Introduction

There are 2 recommended dentist-supervised techniques for vital bleaching: at home and in office.[1,2] The at-home protocol consists of applying low-concentrate bleaching agents using a customized bleaching tray,[1] whereas in the in-office protocol, clinicians apply high-concentrate bleaching products after gingival tissue protection with a light-cured gingival barrier.[2] Regardless of the bleaching protocol, whitening occurs through hydrogen peroxide's ability to oxidize the dental structure's organic component.[3] Therefore, hydrogen peroxide is the main active component of all bleaching products, or it is derived from other products such as carbamide peroxide.[3]

It is undeniable that dental bleaching can promote an effective color change, as shown in several controlled clinical studies.[4, 5, 6, 7, 8, 9, 10, 11] Although several adverse effects have been described in the literature, such as the penetration of hydrogen peroxide into the pulp chamber,[12] decreased bond strength,[13] enamel microhardness reduction,[14] morphology changes,[15] and superficial demineralization,[16] these effects were essentially observed in vitro, and they were proven temporary owing to the remineralizing effect of saliva.[17, 18, 19]

One of the main adverse effects is bleaching-induced tooth sensitivity (TS),[4, 5, 6, 7, 8, 9, 10, 11] which has been reported to affect 50% to 90% of the patients submitted to dental bleaching.[4, 5, 6, 7, 8, 9, 10, 11] One of the approaches to reduce this adverse effect is the topical application of potassium nitrate–based desensitizers. Studies have reported that potassium nitrate can reduce TS through neural activity (that is, via preventing the transmission of nerve impulses).[20,21] A 2021 systematic review on this topic reported that potassium nitrate desensitizers significantly reduced the risk and intensity of TS.[22] However, from a clinical perspective, the magnitude of such reduction is still modest.[22]

Another type is the calcium-containing bioactive desensitizer (CB), which appears to be an alternative for managing TS.[23, 24, 25, 26, 27, 28, 29] These CBs interact with hard tissues by precipitating on enamel,[20] thus minimizing the harmful effects of demineralization and the changes on the enamel morphology.[14,30,31] Studies have also shown that CBs considerably reduced the penetration of hydrogen peroxide in the pulp chamber,[20,32,33] which may, in turn, be responsible for the lower levels of TS reported in randomized controlled trials (RCTs).[23, 24, 25, 26, 27, 28, 29]

To our knowledge, no systematic review of the literature has evaluated the effect of CBs for bleaching-induced TS. Systematic reviews identify, evaluate, and summarize the findings of all relevant articles over a specific research question, making the evidence more accessible to decision makers. Therefore, our systematic review aimed to answer the following focused research question: Is the risk of TS (outcome) lower when CBs (intervention) are used with dental bleaching in adults (participant) compared with bleaching without desensitizers (comparator)?

Methods

Protocol and registration

We registered this systematic review in the International Prospective Register of Systematic Reviews under the registration CRD42020178042, and we followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[34]

Eligibility criteria

On the basis of our population, intervention, control, and outcome question, we include primary parallel, split-mouth, and cross-over RCTs that evaluated adult participants 18 years or older. These participants should have undergone in-office or at-home dental bleaching associated with the topical application of CBs before bleaching, after bleaching, or both. The comparators were no intervention or placebo.

We excluded RCTs that incorporated a CB in the bleaching gel, evaluated dentifrices containing CBs for daily use, evaluated other types of desensitizing agents, did not have a comparator group, or included experimental and comparator groups but did not use bleaching gels with equivalent concentrations of the active agent in both groups.

Information sources and search strategy

We first defined the search strategy (eTable 1, available online at the end of this article) for the MEDLINE database via PubMed using a controlled vocabulary (Medical Subject Headings terms) and free key words for each concept of the population,

intervention, control, and outcome question described above. The outcomes to be evaluated were the risk of TS (primary outcome), the intensity of TS (secondary outcome), visual color assessment in shade guide units (SGU) ([ΔSGU] final SGU measurements) (secondary outcome), and objective color evaluation with spectrophotometer color evaluation in units of color change (ΔE^{ab}) (CIEL∗a∗b∗ system) (secondary outcome).[35]

We adapted the MEDLINE search strategy to other electronic databases (Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature, Embase, and citation databases [Scopus and Web of Science]). In addition, we investigated gray literature by means of searching the abstracts of the annual conferences of the International Association for Dental Research and its regional divisions (2001-2022), the System for Information on Grey Literature in Europe database, and dissertations and theses using the ProQuest Dissertations and Theses full-text database and the Periódicos Capes Theses database. We also consulted the first 10 pages of Google Scholar. We searched ongoing studies in the following clinical trial registries: Current Controlled Trials, International Clinical Trials Registry Platform, ClinicalTrials.gov, Brazilian Registry of Clinical Trials, and European Union Clinical Trials Register.

In addition, we hand-searched the reference lists of our systematic review's primary and eligible studies for additional relevant publications. We also reviewed the first 2 pages of the related articles linked to each primary study in the PubMed database to search for eligible studies. We did not restrict studies on the basis of publication date and language in the search process.

Selection process and data collection process

After running the search strategy, we used a reference management program (EndNote X9, Clarivate Analytics) to store the files of all databases. Then, we removed duplicate articles using a software tool, followed by manual removal after organizing titles in alphabetical order. We initially scanned all studies for relevance by title, abstract, and full text, using an online software program (Rayyan, Qatar Computing Research Institute).[36] If the review authors were unsure about the eligibility of any

study, the study was kept for the next phase. Three independent reviewers (M.W.F., T.d.S.C., H.F.) carried out all phases to check whether they met the inclusion criteria.

Each eligible article received a study identification, combining the first author and year of publication. The same 3 reviewers summarized and categorized data, such as study design, number of patients, interventions, and outcomes. In cases of disagreements, a decision was reached via consulting a fourth reviewer (A.R.). If there were multiple reports of the same study (that is, reports with different follow-ups), data from all reports were extracted directly into a single data-collection form to avoid multiple data entries.

We extracted the worst mean value of spontaneous TS from the first clinical appointment reported between the immediate and 48-hour postbleaching period for in-office bleaching. In contrast to in-office bleaching, the spontaneous TS intensity of the at-home treatment usually was reported daily in the eligible articles. Thus, there was a substantial fluctuation in the daily records of the mean TS of the different groups. For this reason, we averaged these values during data extraction for each study arm. We opted for this post hoc decision before any data extraction to avoid the effects of such fluctuations if we chose a specific period for data extraction. Some studies also reported stimuli-induced TS. The same approaches that we used for spontaneous TS were used to extract this secondary outcome from primary studies.

For the color change, we extracted the data from periods ranging from 7 days through 3 months postbleaching. This variation was due to differences in the assessment periods reported in the primary studies. We recorded results as close to 30 days postbleaching for all analyses. If the information at 30 days was unavailable, we used data ranging between the end of the bleaching treatment and 90 days postbleaching (we preferred the time point closer to 30 days postbleaching).

Data extraction and conversion to the desired format

Whenever necessary and possible, we imputed missing SDs on the basis of the average variance coefficient of the eligible articles.[37] If a study reported interquartile ranges instead of SDs, we calculated the SD as approximately 1.35 times the size of the interquartile range.[37] If a study with a low sample size reported a CI instead of SD,

then we calculated the SD using a value from a t distribution.[38] If a study had 2 or more experimental or control groups, we merged them using appropriate formulas described in the Cochrane Handbook for Systematic Reviews of Interventions.[37] If a study contributed information for both study subgroups of the meta-analysis, we divided data from the comparator group into subgroups to avoid double counting.[37] When the primary articles presented graphical results, we performed approximate data extraction through a specific software (GetData Graph Digitizer Version 2.24). When data were missing, we attempted to contact the authors.

Risk of bias in individual studies

The Cochrane Collaboration's recommended tool for assessing the risk of bias (RoB Version 2.0) is neither a scale nor a checklist. It is a domain-based evaluation in which critical assessments are made separately for different domains. The risk of bias between studies for each outcome assessed was verified by 3 independent researchers (M.W.F., A.B., F.D.S.D.), using RoB 2.0 to analyze the risk of bias of RCTs.[39] This tool evaluated bias arising from the randomization process (domain [D] 1), bias due to deviations from intended interventions (D2), bias due to missing outcome data (D3), bias in the measurement of the outcome (D4), bias in the selection of the reported result (D5), and overall bias (overall). In each domain, the risk of bias was judged as low risk of bias, some concerns, or high risk of bias via answering signaling questions.

For the overall risk of bias judgment, we considered a study to be at low risk of bias if all domains were judged as at low risk. We considered the study to have some concerns if at least 1 domain was judged to have some concerns. Finally, we considered the study to be at high risk of bias if at least 1 domain was deemed at high risk. When 3 or more domains were considered to have some concerns, the study also had a high risk of bias. During data selection and quality assessment, disagreements between the reviewers were solved through discussion and, if needed, via consulting a third reviewer (A.R.). Each outcome was evaluated individually, and some studies can be considered to have different risks of bias within the same study.

Summary measures and synthesis of the results

We analyzed data using statistical software (Review Manager, Version 5.4.1, The Cochrane Collaboration). We performed meta-analyses in all eligible studies. We summarized data by means of calculating the risk ratio for the risk of TS, whereas we calculated the mean difference (MD) for the intensity of TS.

The color change was summarized in MD for ΔEab and ΔSGU (change from baseline and postintervention values). In theory, the comparison of the final measurements in RCTs estimates the same quantity as the comparison of changes from baseline does. Because primary studies usually varied the way they reported color change, we combined final SGU and ΔSGU, and as such, MD had to be used as the effect measure. Therefore, we evaluated studies reporting color change using different color instruments separately.

We performed subgroup analyses (mixed effect) to investigate the different bleaching techniques (at home, in office). We used the random-effects model because it is the most appropriate model for studies conducted in different populations. Fixed-effects model is only adequate when studies are conducted in the same study center. We assessed heterogeneity using the Cochran Q test, which tests the null hypothesis that all studies share the same effect size; I^2 statistics, which describe the proportion of the observed heterogeneity that is due to real variation of the true effect sizes; and the prediction interval, which is the dispersion of the observed effect sizes. We performed post hoc sensitivity analyses to investigate the effect of high heterogeneity whenever detected.

Sensitivity analyses

We conducted post hoc sensitivity analyses to investigate whether assumptions made during data collection, such as imputations of SD, would affect the results and explain any heterogeneity detected. When imputations were made, we performed other analyses using extreme imputations and evaluated the conclusions' impact. We also assessed the effect of different variables on the study's findings: the exclusion of studies with a high risk of bias, the type of comparator (placebo vs no desensitization), the moment of desensitization (either before or after bleaching), and the inclusion of split-mouth studies.

Reporting bias assessment

We assessed the impact of small-study effects by generating funnel plots for meta-analyses when we included at least 10 RCTs. If asymmetry in the funnel plot was detected, we planned to assess whether the asymmetry was likely due to publication bias or other factors, such as the trial's methodological or clinical heterogeneity.

Assessment of the certainty of the evidence using Grading of Recommendations Assessment, Development and Evaluation reporting bias assessment

We graded the certainty of the evidence for each outcome across studies (body of evidence) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) reporting bias assessment. This technique determined the overall strength of evidence for each meta-analysis.[40] The GRADE assessment grades the evidence according to 4 levels: very low, low, moderate, and high. The high level suggests high confidence that the true effect lies close to the estimate of the effect. At the other end, a very low grading indicates very low confidence in the effect estimate, meaning that the reported estimate can be substantially different from what was measured. For RCTs, the GRADE approach addresses 5 reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, publication bias) for possibly rating down the quality of the evidence by 1 or 2 levels. Each of these aspects was assessed as having no limitation (no downgrade), serious limitations (downgraded 1 level), and very serious limitations (downgraded 2 levels). We used the GRADEpro Guideline Development Tool, available online (www.gradepro.org), to create a summary of the findings table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.[38]

Results

Study selection

The search strategy was conducted initially on September 17, 2020, updated on October 14, 2021, and updated again on September 19, 2022. After database screening and duplicate removal, we identified 2,852 studies (Figure 1). After title

screening, 59 studies remained, and 30 were kept for full-text inspection after the abstract screening.

From the 30 studies, we excluded 8 studies because they did not have a placebo group,41, 42, 43 did not use a CB,44 used the desensitizer in a way other than topically,45,46 applied 2 different desensitizers on the same patient,47 and incorporated a CB in the bleaching gel.48

Characteristics of the included studies

The characteristics of the 22 selected studies[23, 24, 25, 26, 27, 28, 29,49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63] are listed in eTable 2, available online at the end of this article. The split-mouth design was used in 3 studies.[24,25,61] The cross-over design was used in 1 study.[59] The parallel design was used in 18 studies.[23,26, 27, 28, 29,49, 50, 51, 52, 53, 54, 55, 56, 57, 58,60,62,63]

Visual analog scale (VAS) for pain was the scale most often used[23, 24, 25, 26, 27, 28, 29,49, 50, 51, 52, 53,55, 56, 57, 58, 59,61,62,63]; 15 studies evaluated spontaneous TS,[23, 24, 25, 26, 27, 28, 29,52,53,57, 58, 59,61,62,63] 4 studies evaluated air-stimulated TS,[49, 50, 51, 52] and 3 evaluated both.[56,58,59]

For color measurement, 8 studies used SGUs,[23,25,27,28,52,54,55,63] and 2 studies used shade guides and spectrophotometer or colorimeter.[59,61] In 7 studies, only spectrophotometer was used.[24,29,49,51,53,57,62] In the other 5 studies,[26,50,56,58,60] the authors did not evaluate color change.

The number of patients per group included in these studies ranged from 18 through 55. The mean (SD) age of all participants included in the RCTs was approximately 25.0 (5.3) years, and the minimum age to participate in the study was 18 years. In 9 of 22 studies, most of the participants were female.[25,28,50,54,55,58,59,62,63] Only 7 studies reported that sex distribution was similar,[24,26,51, 52, 53,60,61] and in another 6 studies, this information was not reported.[23,27,29,49,56,57]

Whereas 7 studies performed at-home bleaching,[23,29,51,57,58,59,62] 16 studies performed in-office bleaching.[24,25,26,27,28,49,50,52,53,54,55,56,58,60,61,63] Only 1 study performed combined dental bleaching. We only extracted data from the in-office bleaching technique in this case.[26] This was possible because the authors performed

an in-office bleaching session with the previous application of a CB. The authors assessed postintervention TS, which was within our evaluation period. We did not extract data from the at-home technique because it began the day after the in-office bleaching. Because TS from in-office bleaching can last up to 48 hours, we assumed its effects could affect the at-home TS outcomes.

Regarding the bleaching protocol, hydrogen peroxide gels with concentrations varying from 30% through 40% were used in 16 studies.[24,25,26,27,28,49,50,52,53,54,55,56,58,60,61,63] One study used hydrogen peroxide in low concentration (6%).23 Six RCTs used carbamide peroxide gels with concentrations varying from 15% through 22%.[29,51,57,58,59,62]

The most used protocol with high-concentrate hydrogen peroxide was 3 sessions of 3 15-minute applications each.[28,52,53,54,55,56] However, other protocols also were used, as seen in eTable 2 (available online at the end of this article). Two studies used light-emitting diode activation during hydrogen peroxide bleaching.[52,60] The daily use of at-home bleaching agents ranged from 30 minutes through 8 hours, and the total treatment time took 1 week[29,57,63] through 2 weeks.[23,27,51,55,58,59]

Regarding the desensitization protocol, studies used several CBs, such as casein phosphopeptide–amorphous calcium phosphate,[26,27,28,29,49,52,55,56,59,60] calcium phosphate nanostructured in hydroxyapatite,[24,50,51,53,54,58] nanohydroxyapatite,[23,52,63] tetracalcium phosphate and dicalcium phosphate anhydrate,[25] tricalcium phosphate,[27,57] calcium sodium phosphosilicate,[49,62] bioglass,[58] and calcium gluconate.[61]

Whereas 14 studies applied the products after dental bleaching,[23,24,27,29,49,51,53,55,56,57,58,59,60,62] 7 studies applied them before dental bleaching,[25,26,50,52,54,61,63] and in 1 study, the authors applied the product before bleaching, after, or both.[28] Regarding the comparator group, 14 studies used a placebo group,[24,25,27,28,29,51,52,54,55,56,57,60,61,62] and the other 8 studies did not apply any desensitizer as the comparator.[23,26,49,50,53,58,59,63]

Assessment of the risk of bias

Because the RoB 2.0 tool is outcome-based, it was applied separately for the different outcomes of our systematic review.

Risk of TS

Regarding the overall risk of bias, most studies were at high risk, 1 study was rated as having some concerns, and only 2 were at low risk of bias for this outcome. Bias in the outcome measurement (D4) presented the most concerns because it is directly related to the method used for TS assessment and patient blinding (Figure 2).

Intensity of TS

Most studies were at high risk of bias, 3 were at some concerns, and only 5 were at low risk of bias. Similar to the risk of bias, most concerns were related to the bias in measuring the outcome (D4) (Figure 3).

Visual Color Assessment in ΔSGU and Final SGU Measurements

Of the 11 studies included in the subjective assessment using the Vita Classical scale, 4 were at low risk of bias, 1 was deemed to have some concerns, and 6 were at high risk. Blinding of the evaluators, which was evaluated at D2 (deviation from the intended interventions) and D4 (measurement of the outcome), presented some concerns, which put the studies at a high risk of bias in the overall evaluation (eFigure 1, available online at the end of this article).

Objective Color Evaluation with Spectrophotometer

Of the 8 studies included, 2 studies were at low risk of bias, 3 studies were deemed to have some concerns, and 3 studies were at high risk of bias. Some concerns due to the high number of missing patients detected in the D3 domain (missing outcome data) put most studies at a high risk of bias (eFigure 2, available online at the end of this article).

Meta-analysis

One study could not be added to eligible studies because no data were reported. The study was found in a clinical trial registry; the authors were contacted, but they said the article had not been written yet.[57]

Spontaneous TS

We calculated the risk of spontaneous TS from 11 studies. There was no difference in the risk of TS (P = .08), with a risk ratio of 0.95 (95% CI, 0.90 to 1.01) (Figure 4). The prediction interval varied from 0.89 through 1.01. Heterogeneity was not detected (P = .19; I^2 = 27%).

The data on the intensity of spontaneous TS were pooled in the VAS (Figure 5). Fourteen studies were included, giving a significant average MD of −0.98 units of VAS (95% CI, −1.36 to −0.60; P < .0001) in favor of the CBs. The prediction interval varied from −2.02 through 0.06). Heterogeneity was detected (P < .0001), mainly due to variations in the true effect sizes (I^2 = 48%). We omitted 2 studies[54,60] in the meta-analysis because they only presented data on an ordinal scale.

These 2 studies not included in the meta-analysis presented their values on an ordinal scale from 0 through 4. Adil and colleagues[60] reported the values as the mean (SD) for both groups. The intensity (SD) was 2.74 (1.64) for the experimental group and 1.72 (0.73) for the control. Loguercio and colleagues[54] reported the median (minimum value, maximum value) values. For the control group, the median TS intensity was 2 (0 and 3), and for the experimental group, it was 1.5 (0 and 3).

The evaluation of data from stimuli-induced TS showed a pattern similar to those reported by the spontaneous TS (Appendix, eFigures 3 and 4, available online at the end of this article).

Color Change

The meta-analysis of color change from Vita Classical units was performed with 9 studies; whereas 4 studies only presented the final values of SGU,[25,52,54,63] 5 studies presented the values in ΔSGU.[23,27,28,55,61] We observed no significant difference between groups (MD, 0.28; 95% CI, −0.02 to 0.59; P = .07). The prediction interval varied from −0.09 through 0.65. Heterogeneity was not detected in any meta-analyses (P = .51) (Figure 6).

Two studies were not included in our meta-analysis.[53,59] Lima and colleagues[53] reported Vita Classical units obtained from a spectrophotometer, not shade guides. Rashid and ElSalhy[59] presented only the statistical P value.

The meta-analysis of color change from ΔE_{ab} was performed with 6 studies. We observed no significant difference between groups (MD, −0.92; 95% CI, −2.09 to 0.24; P = .12). The prediction interval varied from −4.30 through 2.46. Heterogeneity was detected in the meta-analysis (P = .02) (Figure 7).

Subgroup analysis

We performed subgroup analysis based on the bleaching protocol used (at home, in office), as seen in the forest plots of outcomes. The bleaching protocol did not affect the overall results observed in the meta-analysis or explain the heterogeneity whenever detected.

Sensitivity analysis

Imputations had to be made in 1 case in which SDs were not reported in the full texts for color-change data in classical scale units.[23] We performed sensitivity analyses using extreme values of imputations, but the overall conclusions were not affected. In addition, other post hoc sensitivity analyses (exclusion of studies with a high risk of bias, studies that reported color change in final SGU values, studies that compared the experimental intervention with no intervention, the moment of desensitization [before, after]) were performed, and they did not affect the overall conclusion we report in this article. Only 3 studies used the split-mouth design. Keeping these studies or excluding them from the meta-analysis did not affect the general conclusions that we present (eFigures 5 and 6, available online at the end of this article).

Reporting bias assessment

The studies with high accuracy (large sample sizes) are plotted close to the point estimate, and studies with low precision (small sample sizes) are distributed on both sides of the point estimate, creating an approximately funnel-shaped distribution.

In the funnel plot analysis of the risk of spontaneous TS (eFigure 7, available online at the end of this article), we observed that the study by Browning and colleagues[23] showed a slight asymmetry, with a positive effect in favor of the CBs. However, this study had a low weight in the meta-analysis (0.5%). No reporting bias was observed in the meta-analysis of the intensity of spontaneous TS (eFigure 8, available online at the end of this article).

Certainty of the evidence

We evaluated 2 outcomes for TS (risk of spontaneous TS, intensity of spontaneous TS in the VAS) and 2 for color change (SGU from Vita Classical and ΔE_{ab}).

The certainty of the evidence for all these outcomes is summarized in the table. For all outcomes, the body of evidence was downgraded by 3 levels owing to the high risk of bias, inconsistency, and imprecision in most studies.

Discussion

CBs are obliterating products that act more frequently in remineralizing dental tissue through surface saturation. Thus, when these agents are applied, they interact with the dental surface and can be retained, providing large amounts of calcium and phosphates for interaction with the tissues.[20] These products started being used before and after bleaching because of the enamel morphology alterations bleaching causes.[15] Even though this morphology change is transient and reversible via the effect of saliva,[17,18,19] several researchers and manufacturers aimed to reduce even further such potential problems. Another approach evaluated in RCTs was the effect of calcium-containing bioactive products in reducing bleaching-induced TS, which is the most undesirable adverse effect of dental bleaching.

Although not fully elucidated yet, it seems that bleaching-induced TS results from the damage caused by hydrogen peroxide in the connective living tissues of the dental structure. Because of its low molecular weight, strong oxidative potential,[3] and rapid diffusion rate, hydrogen peroxide can cross the dental hard tissues, reaching the pulp chamber[3] and causing an acute inflammatory reaction that may eventually cause pain.

Although no precise correlation exists between hydrogen peroxide diffusion and clinical symptoms, the rationale of evaluating obliterating materials to reduce bleaching-induced TS relies on the fact that such problems could reduce the fast hydrogen peroxide passage to the pulp. This way, they can slow the inflammatory response and allow more time for the pulp to deal with the oxidizing molecules. Our study did not show any reduction in the risk of spontaneous TS, meaning these

products did not prevent patients from experiencing TS. Indeed, this is in line with an earlier laboratory finding that none of the desensitizers tested so far could completely avoid the diffusion of hydrogen peroxide to the pulp tissue.[20,32,33]

However, we detected a slight decrease in the intensity of TS when CBs were used. Other mechanisms of action, besides obliteration, have been reported for CBs. Some in vitro studies have found that divalent calcium ion agents can reduce nerve impulse transmission,[64,65] acting as a neural desensitizing product. However, its role in lowering bleaching-induced TS still needs further investigation. In addition, hydrogen peroxide can react with these CBs, forming other by-products such as calcium hydroxide, further reducing the excess of peroxide that diffuses into the pulp chamber.[66]

The formation of alkaline products in the tooth structure can change the pH of bleaching agents to make them more alkaline and consequently break more hydrogen peroxide molecules, owing to the acid dissociation constant of hydrogen peroxide being more alkaline around a pH of 11.[5,67] affecting not only the degradation kinetics but also the by-products formed in the decoupling reaction.[67] All these reactions can decrease the concentration in the pulp and consequently the TS.[15,68,69]

Although the MD in the TS intensity was statistically significant, the relevance of this finding is questionable from a clinical perspective. For instance, a change in the TS intensity from 3 VAS units to 2 VAS units may not be of great value clinically, considering that bleaching-induced TS is transient and does not last longer than 48 hours. Taking TS findings altogether, we may say that most patients will experience some discomfort during the treatment but with a subtly lower TS intensity. This finding, although positive in favor of the CBs, should be interpreted with caution owing to the low certainty of the body of evidence collected.

To assess the risk of bias, we used the RoB 2.0 tool,[39] which allowed us to search in depth all sources of information in the published study that may lead to biases. Most eligible studies were at high risk of bias due to concerns about the randomization process.

Most studies did not correctly report the randomization process. Most of them mentioned that the study was randomized but gave no further information.

Randomization needs to be planned a priori, safely concealed until implementation, and well described in the final article. Failures in the random implementation may result in groups with unknown prognostic features, so the cause-effect conclusion that RCTs can provide cannot be established. Deviations from the intended interventions presented another problematic issue in the primary studies. The participants or caregivers can give different levels of attention to the implemented protocol if they know the group assignment.

Other issues in the methodology of the eligible studies deserve attention. Instead of measuring spontaneous TS, some authors measured stimuli-induced TS during or after bleaching.[49,51,52,58,59] In our opinion, stimuli-induced TS is not a relevant patient-centered outcome because neither patients nor operators induce TS on purpose in real life. Perhaps the authors used this approach to increase the number of events in their RCT so that study power can be obtained even with low sample size. We discourage the use of stimuli-induced TS in future RCTs, or at least authors should report spontaneous TS data in the study findings.

The bleaching efficacy is usually evaluated via comparing baseline and after-treatment color changes. The Vita Classical scale, arranged in 16 tabs from the highest (B1) to the lowest value (C4), is the most used tool to assess color evaluation, as it depends on the evaluator's training and experience within the study. Another shade guide scale used to evaluate color efficacy is the Vita Bleachedguide 3D-MASTER scale, which has greater sensitivity to detect subtle changes not seen with the Vita Classical scale. Both scales allow calculating the variation in SGU (ΔSGU), which is the difference between color at baseline and assessment periods after treatment. Another common approach to measure color change is using a spectrophotometer, which is an objective method capable of getting the color parameters $L*$ (lightness), $a*$ (red-green axis), and $b*$ (yellow-blue axis) that allows the calculation of ΔE_{ab} using the CIELAB formula[35] or the ΔE_{00} using the CIEDE formula.[70] We also may use these values to calculate the whiteness index (ΔWI_D),[71] another way to measure color change. Measurement with a spectrophotometer provides more accurate results than visual color matching[72] as it is less prone to subjective judgments. However, the results published in ΔE_{ab} are less clinically tangible than those obtained with SGUs. Therefore

ΔE_{ab} is usually compared with the visual perceptibility and acceptability thresholds for color change during bleaching.[73]

Some studies did not report important outcomes, such as the color change expected in bleaching studies. Reducing TS with desensitizers is important, but this effect cannot jeopardize the bleaching efficacy. Even though these agents decrease the concentration of hydrogen peroxide in the tooth structure and may deposit on the enamel surface, they did not negatively interfere with the color change. However, we should point out again that most studies were at high risk of bias.

From a statistical point of view, we could not identify the reasons for the heterogeneity observed in some meta-analyses (Figure 5, I^2 = 48%; Figure 7, I^2 = 64%). From a clinical perspective, the heterogeneity may result from the different bleaching protocols and the different desensitizing products included in our review. Although all studies used CBs, their composition varied. In addition, variations in bleaching protocols (different hydrogen peroxide concentrations, application times, application frequency, and number of clinical sessions) also can affect bleaching-induced TS and, therefore, may affect the magnitude of the effect size. Large RCTs with the most promising desensitizers should be evaluated to minimize these confounding factors.

We should have run the meta-analysis, considering that 19 of 22 studies had a paired design. However, although this was ideal, this was not done in our study because the correlation coefficient of the paired data of these 3 studies was not reported. An alternative would be establishing an arbitrary coefficient correlation for all these split-mouth studies. This would add as much imprecision to the meta-analysis as adding the studies as parallel studies (meaning a correlation coefficient of 0). Authors of primary studies with split-mouth design should be encouraged to report the correlation coefficient of the paired data to allow their future inclusion in systematic reviews and meta-analyses as paired studies.

We have not included studies that evaluated toothpaste with CBs. The decision was made because the contact time of toothpaste with the dental structures is different from that of desensitizers used topically. In most studies, the application time of the calcium-containing desensitizers varied from 5 through 10 minutes. When in

dentifrices, these desensitizers in toothpastes usually remain in contact with the enamel surface for periods less than 3 minutes (toothbrushing time). In addition, they are diluted by saliva, reducing the product's action even further.

Our review is not an update but presents a new research question that includes all bioactive calcium-containing desensitizers for managing bleaching-induced sensitivity. The earlier systematic review[74] on this topic also evaluated the effect of casein phosphopeptide-amorphous calcium phosphate on bleaching TS. However, the authors did not include all available articles (eTable 2, available online at the end of this article).

Apart from that, other methodological flaws put this earlier study[74] at high risk of bias. The study report's structure was confusing, as the authors did not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendation for the article report. The search strategy restrictsed studies by date and language, and the gray literature was not consulted, putting the study at high risk of bias of publication bias. Only 1 operator extracted data from the primary studies, which is different from what the Cochrane Collaboration suggests. Four of 5 studies evaluated the color change via visual inspection. Although this was a secondary outcome registered in Prospective Register of Systematic Reviews, the authors did not present these data, putting the study at a high risk of selective reporting.

Our findings show that the certainty of the evidence was low and very low for the outcomes we evaluated. This result means much needs to be done to improve the quality of the RCTs on bleaching studies. In addition, recognizing this limitation is the quickest step toward enhancing the study project design and implementation. Future RCTs should investigate other types of desensitizing agents to prevent or reduce the adverse effects of bleaching-induced TS. In addition, further investigations could focus on a network meta-analysis to evaluate the various desensitizers on the basis of their composition to complement the findings of our study. This would increase the number of RCTs for a future updated systematic review, increasing the robustness of the conclusions.

We recognize that we conducted the meta-analyses with studies that used different types and concentrations, bleaching agents, and desensitization protocols.

This usually raises criticisms about the feasibility of running a meta-analysis. However, we should consider that the aim of meta-analyses rarely is to synthesize data from a set of identical studies. Systematic literature reviews with a broader research question contain specific diversity between studies, which is inevitable and desirable. This allows researchers to explore the dispersion of studies, using heterogeneity statistics and raising hypotheses that may explain why an intervention may work in some populations and not in others. This heterogeneity is what happens in the real world; therefore, this exploratory question is 1 of the goals of systematic reviews.

Conclusion

We observed a slight reduction of bleaching-induced TS when topical CBs were applied during the bleaching protocol, but the certainty of the evidence was very low. In addition, using these desensitizers did not affect the risks of TS and color changes. However, the certainty of the evidence for risks of TS and color changes was low and very low, respectively.

Acknowledgements

Many thanks to all the authors of the primary articles included in these reviews, for providing their precious time to bring new information about possible problems encountered during the reading of the text. Special thanks to researchers Roberta Basting; Hussam Milly; Oula Yassin and Shaista Rashid.

Refereces

1. Haywood VB, Sword RJ. Tray bleaching status and insights. J Esthet Restor Dent. 2021;33:27-38. https://doi.org/10.1111/jerd.12688.

2. Reis A, da Silva LM, Martins L, Loguercio A. In-office tooth whitening. Clin Dent Rev. 2018;2:1-8. https://doi.org/10.1007/s41894-018-0021-9.

3. Kwon SR, Wertz PW. Review of the Mechanism of Tooth Whitening. J Esthet Restor Dent. 2015;27:240-257. https://doi.org/10.1111/jerd.12152.

4. Favoreto MW, Hass V, Maran BM, et al. At-home Bleaching with a Novel Carbamide Peroxide Polymeric Nanoparticle Gel: A Multicenter Randomized Controlled Trial. Oper Dent. 2022;47:492-502. https://doi.org/10.2341/21-030-C.

5. Esteves LMB, dos Santos PH, Fagundes TC, et al. Effect of bleaching gel volume on color change and postoperative sensitivity: a randomized clinical study. Clin Oral Investig. 2022;26:2527-2536. https://doi.org/10.1007/s00784-021-04220-z.

6. Carneiro TS, Favoreto MW, Bernardi LG, et al. Gingival irritation in patients submitted to at-home bleaching with different cutouts of the bleaching tray: a randomized, single-blind clinical trial. Clin Oral Investig. 2022;26:4381-4390. https://doi.org/10.1007/s00784-022-04401-4

7. Donassollo SH, Donassollo TA, Coser S, et al. Triple-blinded randomized clinical trial comparing efficacy and tooth sensitivity of in-office and at-home bleaching techniques. J Appl Oral Sci. 2021;29:e20200794. https://doi.org/10.1590/1678-7757-2020-0794.

8. Meireles SS, Santos ME, Lustosa Í MC, Leite ELL. Effects of a reduced in-office bleaching protocol with 37.5% hydrogen peroxide on effectiveness and tooth sensitivity: A double-blind randomized clinical trial. J Esthet Restor Dent. 2021;33:824-831. https://doi.org/10.1111/jerd.12744.

9. Kothari S, Jum'ah AA, Gray AR, K ML, Yap M, Brunton PA. A randomized clinical trial investigating three vital tooth bleaching protocols and associated efficacy, effectiveness and participants' satisfaction. J Dent. 2020;95:103322. https://doi.org/10.1016/j.jdent.2020.103322.

10. Martini EC, Favoreto MW, Coppla FM, Loguercio AD, Reis A. Evaluation of reservoirs in bleaching trays for at-home bleaching: a split-mouth single-blind randomized controlled equivalence trial. J Appl Oral Sci. 2020;28:e20200332. https://doi.org/10.1590/1678-7757-2020-0332.

11. de Sá JL, Silva JS, Herkrath FJ, et al. In-office bleaching with complete cervical third protection protocol: A split-mouth, double-blind, randomized clinical trial. Am J Dent. 2021;34:281-285.

12. Parreiras SO, Favoreto MW, Cruz GP, et al. Initial and pulp chamber concentration of hydrogen peroxide using different bleaching products. 2020;23:8. https://doi.org/10.14295/bds.2020.v23i2.1942.

13. Coppla FM, Freire A, Bittencourt B, et al. Influence of simplified, higher-concentrated sodium ascorbate application protocols on bond strength of bleached enamel. J Clin Exp Dent. 2019;11:e21-e26. https://doi.org/10.4317/jced.55153.

14. Coceska E, Gjorgievska E, Coleman NJ, et al. Enamel alteration following tooth bleaching and remineralization. J Microsc. 2016;262:232-244.. https://doi.org/10.1111/jmi.12357.

15. Acuña ED, Parreiras SO, Favoreto MW, et al. In-office bleaching with a commercial 40% hydrogen peroxide gel modified to have different pHs: Color change, surface morphology, and penetration of hydrogen peroxide into the pulp chamber. J Esthet Restor Dent. 2019. https://doi.org/10.1111/jerd.12453.

16. Cavalli V, Rosa DAD, Silva DPD, et al. Effects of experimental bleaching agents on the mineral content of sound and demineralized enamels. J Appl Oral Sci. 2018;26:e20170589. https://doi.org/10.1590/1678-7757-2017-0589.

17. Jager DH, Vieira AM, Ligtenberg AJ, Bronkhorst E, Huysmans MC, Vissink A. Effect of salivary factors on the susceptibility of hydroxyapatite to early erosion. Caries Res. 2011;45:532-537.. https://doi.org/10.1159/000331938.

18. Sa Y, Sun L, Wang Z, et al. Effects of two in-office bleaching agents with different pH on the structure of human enamel: an in situ and in vitro study. Oper Dent. 2013;38:100-110. https://doi.org/100-10. 10.2341/11-173-l.

19. Sa Y, Chen D, Liu Y, et al. Effects of two in-office bleaching agents with different pH values on enamel surface structure and color: an in situ vs. in vitro study. J Dent. 2012;40 Suppl 1:e26-34.. https://doi.org/10.1016/j.jdent.2012.02.010.

20. Parreiras SO, Favoreto MW, Lenz RE, et al. Effect of Prior Application of Desensitizing Agent on the Teeth Submitted to In-Office Bleaching. Braz Dent J. 2020;31:236-243. https://doi.org/10.1590/0103-6440202003365.

21. Kwon SR, Dawson DV, Wertz PW. Time Course of Potassium Nitrate Penetration into the Pulp Cavity and the Effect of Penetration Levels on Tooth Whitening Efficacy. J Esthet Restor Dent. 2016;28 Suppl 1:S14-22. https://doi.org/10.1111/jerd.12192.

22. E Martini EC, Favoreto MW, Rezende M, de Geus JL, Loguercio AD, Reis A. Topical application of a desensitizing agent containing potassium nitrate before dental

bleaching: a systematic review and meta-analysis. Clin Oral Investig. 2021;25:4311-4327. https://doi.org/10.1007/s00784-021-03994-6.

23. Browning WD, Cho SD, Deschepper EJ. Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity. J Esthet Restor Dent. 2012;24:268-276. https://doi.org/10.1111/j.1708-8240.2011.00437.x.

24. de Araújo IDT, de Sousa Santos K, das Neves Peixoto TVO, Costa MJF, de Assunção IV, Borges BCD. The combined use of systemic analgesic/anti-inflammatory drugs and a bioactive topical desensitizer for reduced in-office bleaching sensitivity without jeopardizing the hydrogen peroxide efficacy: a randomized, triple blinded, split-mouth clinical trial. Clin Oral Investig. 2021. https://doi.org/10.1007/s00784-021-03948-y.

25. Mehta D, Jyothi S, Moogi P, Finger WJ, Sasaki K. Novel treatment of in-office tooth bleaching sensitivity: A randomized, placebo-controlled clinical study. J Esthet Restor Dent. 2018;30:254-258. https://doi.org/10.1111/jerd.12374.

26. Oldoini G, Bruno A, Genovesi AM, Parisi L. Effects of Amorphous Calcium Phosphate Administration on Dental Sensitivity during In-Office and At-Home Interventions. Dent J (Basel). 2018;6. https://doi.org/10.3390/dj6040052.

27. Singh M, Mahajan P, Monga P, Mahajan S, Singla D, Kaur NJE. A clinical study is a comparative evaluation of the effectiveness of sodium fluoride and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) in treating postoperative sensitivity associated with in-office vital tooth bleaching. 2017;29:26. https://doi.org/10.4103/endo.endo_118_16

28. Tawfik SS, Khairy MAE, ElBaz MAEJF. Evaluation of post-bleaching hypersensitivity using desensitizing agent before and/or after in-office bleaching: A randomized clinical trial. 2019;8:1762. https://doi.org/10.12688/f1000research.20841.1.

29. Yassin O, Milly H. Effect of CPP-ACP on efficacy and postoperative sensitivity associated with at-home vital tooth bleaching using 20% carbamide peroxide. Clin Oral Investig. 2019;23:1555-1559. https://doi.org/10.1007/s00784-018-2574-z.

30. Ubaldini A, Pascotto RC, Sato F, Soares VO, Zanotto ED, Baesso ML. Effects of Bioactive Agents on Dentin Mineralization Kinetics After Dentin Bleaching. Oper Dent. 2020;45:286-296. https://doi.org/10.2341/18-272-l.

31. Gomes MN, Rodrigues FP, Silikas N, Francci CE. Micro-CT and FE-SEM enamel analyses of calcium-based agent application after bleaching. Clin Oral Investig. 2018;22:961-970. https://doi.org/10.1007/s00784-017-2175-2.

32. Barbosa JG, Benetti F, de Oliveira Gallinari M, et al. Bleaching gel mixed with MI Paste Plus reduces penetration of H(2)O(2) and damage to pulp tissue and maintains bleaching effectiveness. Clin Oral Investig. 2020;24:1299-1309. https://doi.org/10.1007/s00784-019-03009-5.

33. Ma Q, Chen J, Xu X, Wang T. Impact of transparent tray-based application of bioactive glasses desensitizer on the permeability of enamel and dentin to hydrogen peroxide: an in vitro study. BMC oral health. 2020;20:103. https://doi.org/10.1186/s12903-020-01096-5.

34. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed.). 2021;372:n71. https://doi.org/10.1136/bmj.n71.

35. CIE Recommendations on uniform color spaces, color-difference equations, psychometric color terms. Color Research & Application, 1978;2:5-6. https://doi-org/10.1002/j.1520-6378.1977.tb00102.x

36. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic reviews. 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.

37. Ma J, Liu W, Hunter A, Zhang W. Performing meta-analysis with incomplete statistical information in clinical trials. BMC Med Res Methodol. 2008;8:56. https://doi.org/10.1186/1471-2288-8-56.

38. Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.

39. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.). 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.

40. G Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383-394. https://doi.org/10.1016/j.jclinepi.2010.04.026.

41. Bommer C, Flessa HP, Xu X, Kunzelmann KH. Hydroxyapatite and Self-Assembling Peptide Matrix for Non-Oxidizing Tooth Whitening. J Clin Dent. 2018;29:57-63.

42. Tarique N, Awan R, Saleh MI. Vital Tooth Bleaching and Management of Post-Operative Sensitivity: A Clinical Trial Evaluating the Efficacy of Different Desensitizing Materials, 2017;11:1564-1567.

43. Mohamed H, Fayed A, Elkassas D, Hassanien O. Impact of using nano-hydroxyapatite on postoperative hypersensitivity of two bleaching techniques–randomized controlled clinical trial. IOP Conference Series: Materials Science and Engineering. Vol 1046: IOP Publishing; 2021:012004.

44. Martini EC, Parreiras SO, Szesz AL, Coppla FM, Loguercio AD, Reis A. Bleaching-induced tooth sensitivity with application of a desensitizing gel before and after in-office bleaching: a triple-blind randomized clinical trial. Clin Oral Investig. 2020;24:385-394. https://doi.org/10.1007/s00784-019-02942-9.

45. Pierote JJA, Prieto LT, Dias C, et al. Effects of desensitizing products on the reduction of pain sensitivity caused by in-office tooth bleaching: a 24-week follow-up. J Appl Oral Sci. 2020;28:e20190755. https://doi.org/10.1590/1678-7757-2019-0755.

46. Tang B, Millar BJ. Effect of chewing gum on tooth sensitivity following whitening. Br Dent J. 2010;208:571-577. https://doi.org/10.1038/sj.bdj.2010.500.

47. Pierote JJA, Barbosa IF, Prieto LT, Lima D, Paulillo L, Aguiar FHB. Effects of desensitizing dentifrices on the reduction of pain sensitivity caused by in-office dental whitening: a double-blind controlled clinical study. Clin Cosmet Investig Dent. 2019;11:219-226. https://doi.org/10.2147/ccide.S198940.

48. Burey A, Sutil E, Nunez Aldaz MA, et al. Assessment of the effect of experimental bleaching agent with nano-bioactive material on postoperative sensitivity: A randomized, triple blind clinical trial. 2021;33:764-774. https://doi.org/10.1111/jerd.12790

49. Alexandrino LD, Alencar CM, Silveira A, Alves EB, Silva CM. Randomized clinical trial of the effect of NovaMin and CPP-ACPF in combination with dental bleaching. J Appl Oral Sci. 2017;25:335-340. https://doi.org/10.1590/1678-7757-2016-0408.

50. Crescente CL, Pinto CF. Análise da sensibilidade após o uso prévio de dessensibilizantes em clareamento dental, Rev Odonto. 2016;73:34.

51. Da Silva RC, De Melo alenCaR C, Silva BHR, et al. A Clinical, Randomised, Double-Blind Study on the Use of Nano-Hydroxyapatite and Arginine During at-Home Tooth Bleaching. J Clin Diagn Resear. 2018;12. https://doi.org/10.7860/JCDR/2018/37325.12340

52. Gümüştaş B, Dikmen B. Effectiveness of remineralization agents on the prevention of dental bleaching induced sensitivity: A randomized clinical trial. Int J Dent Hyg. 2021. https://doi.org/10.1111/idh.12524.

53. Lima TM, França FMG, Amaral FLB, Turssi CP, Basting RT. The use of desensitizing agents during in-office bleaching might not decrease tooth bleaching sensitivity: a randomized clinical trial. Int J Esthet Dent. 2022;17:100-114.

54. Loguercio AD, Tay LY, Herrera DR, Bauer J, Reis A. Effectiveness of nano-calcium phosphate paste on sensitivity during and after bleaching: a randomized clinical trial. Braz Oral Res. 2015;29:1-7. https://doi.org/10.1590/1807-3107BOR-2015.vol29.0099.

55. Maghaireh GA, Alzraikat H, Guidoum A. Assessment of the effect of casein phosphopeptide-amorphous calcium phosphate on postoperative sensitivity associated with in-office vital tooth whitening. Oper Dent. 2014;39:239-247. https://doi.org/10.2341/12-527-c.

56. Nanjundasetty JK, Ashrafulla M. Efficacy of desensitizing agents on postoperative sensitivity following an in-office vital tooth bleaching: A randomized controlled clinical trial. J Conserv Dent. 2016;19:207-211. https://doi.org/10.4103/0972-0707.181927

57. NCT03026725. Effect of Tri Calcium Phosphate on Efficacy and Sensitivity With Vital Tooth Whitening Using 20% Carbamide Peroxide. https://clinicaltrials.gov/ct2/show/NCT03026725. 2017.

58. Pintado-Palomino K, Peitl Filho O, Zanotto ED, Tirapelli C. A clinical, randomized, controlled study on the use of desensitizing agents during tooth bleaching. J Dent. 2015;43:1099-1105. https://doi.org/10.1016/j.jdent.2015.07.002.

59. Rashid S, ElSalhy M. Efficacy of MI Paste® on Bleaching-Related Sensitivity: Randomized Clinical Trial. Int J Dent. 2021;2021:9963823. https://doi.org/10.1155/2021/9963823.

60. Adil HM, Jouhar R, Ahmed MA, et al. Comparison of Casein Phosphopeptide with Potassium Nitrate and Sodium Monofluorophosphate Desensitizing Efficacy after In-Office Vital Bleaching—A Randomized Trial. 2021;11:9291. https://doi.org/10.3390/app11199291.

61. Vochikovski L, Favoreto MW, Rezende M, et al. Effect of an experimental desensitizing gel on bleaching induced tooth sensitivity after in-office bleaching - a double-blind randomized controlled trial. PREPRINT (Version 1) available at Research Square. 2022. https://doi.org/10.21203/rs.3.rs-1874442/v1.

62. Bizreh Y and Milly H. Effect of bioactive glass paste on efficacy and post-operative sensitivity associated with at-home bleaching using 20% carbamide peroxide: a randomized controlled clinical trial. Eur J Med Res. 2022;27:194. https://doi.org/10.1186/s40001-022-00826-5.

63. Moharam LM, Khadr S, Abdou A, Nagi SM. J Clin Exp Dent. 2022;14:499-505. https://doi.org/10.4317/jced.59423.

64. Markowitz K, Bilotto G, Kim S. Decreasing intradental nerve activity in the cat with potassium and divalent cations. Arch Oral Biol. 1991;36:1-7. https://doi.org/10.1016/0003-9969(91)90047-x.

65. Markowitz K, Kim S. The role of selected cations in the desensitization of intradental nerves. Proc Finn Dent Soc. 1992;88 Suppl 1:39-54.

66. Mena-Serrano AP, Parreiras SO, do Nascimento EM, et al. Effects of the concentration and composition of in-office bleaching gels on hydrogen peroxide

penetration into the pulp chamber. Oper Dent. 2015;40:E76-82. https://doi.org/10.2341/13-352-l.

67. Torres CR, Crastechini E, Feitosa FA, Pucci CR, Borges AB. Influence of pH on the effectiveness of hydrogen peroxide whitening. Oper Dent. 2014;39:E261-268. https://doi.org/10.2341/13-214-l.

68. Balladares L, Alegría-Acevedo LF, Montenegro-Arana A, et al. Effects of pH and Application Technique of In-office Bleaching Gels on Hydrogen Peroxide Penetration into the Pulp Chamber. Oper Dent. 2019;44:659-667. https://doi.org/10.2341/18-148-l.

69. Loguercio AD, Servat F, Stanislawczuk R, et al. Effect of acidity of in-office bleaching gels on tooth sensitivity and whitening: a two-center double-blind randomized clinical trial. Clin Oral Investig. 2017;21:2811-2818. https://doi.org/10.1007/s00784-017-2083-5.

70. Luo MR, Cui G, Rigg B. The development of the CIE 2000 colour-difference formula: CIEDE2000. Color Research & Application, 2001;26:340–350. https://doi-org/10.1002/col.1049

71. Pérez Mdel M, Ghinea R, Rivas MJ, et al. Development of a customized whiteness index for dentistry based on CIELAB color space. Dent Mater, 2016;32:461–467. https://doi/10.1016/j.dental.2015.12.008

72. Ruiz-López J, Perez MM, Lucena C, et al. Visual and instrumental coverage error of two dental shade guides: an in vivo study. Clin Oral Investig; 2022;26:5961–5968. https://doi-org/10.1007/s00784-022-04556-0

73. Paravina RD, Ghinea R, Herrera LJ, et al. Color difference thresholds in dentistry. Journal Esthetic and Restorative Dentistry, 2015;27:1-9. https://doi-org/10.1111/jerd.12149

74. Hussainy N, Govula K. Casein phosphopeptide amorphous calcium phosphate, a potent desensitizing agent, to reduce postoperative sensitivity after vital tooth bleaching -a systematic review and meta-analysis. Inter J Scient Res. 2021;10. https://doi.org/10.36106/ijsr.

Tables

Table 1 – Summary of findings with the certainty of the evidence using the Grading of Recommendations: Assessment, Development and Evaluation approach.

CERTAINTY ASSESSMENT							SUMMARY OF FINDINGS				
Participants (Study Type), No.	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence	Study Event Rates, No. (%)			Anticipated Absolute Effects	
							Without desensitization	With desensitization	Relative effect (95% CI)	Risk without desensitization	Risk difference with desensitization (95% CI)
Risk of Spontaneous Tooth Sensitivity											
652 (11 RCTs*)	Very serious	Not serious	Not serious	Not serious	None	Low	257/297 (86.5)	267/355 (75.2)	Risk ratio, 0.95 (0.90 to 1.01)	865 per 1,000	43 fewer per 1,000 (–87 to 9)
Intensity of Spontaneous Tooth Sensitivity											
703 (14 RCTs)	Very serious	Serious†	Not serious	Not serious‡	None	Very low	368	335	–	The mean intensity of spontaneous TS was 0	MD,§ –0.98 (–1.36 to –0.60)
Vita Classical Units											
459 (9 RCTs)	Serious	Serious	Not serious	Not serious	None	Low	205	254	–	The mean Vita Classical units was 0	MD, 0.28 higher (–0.08 to 0.59)
ΔE_{ab}¶											
265 (6 RCTs)	Serious	Serious#	Not serious	Serious	None	Very low	124	141	–	The mean ΔE_{ab} was 0	MD, –0.92 (–2.09 to 0.24)

* RCT: Randomized controlled trial. † Unexplained heterogeneity in true effects ($I^2 = 48\%$). ‡ A clinically unimportant benefit of the estimate cannot be ruled out.
§ MD: Mean difference. ¶ ΔE_{ab}: Color change. # Unexplained heterogeneity of the true effects ($I^2 = 64\%$).

Figures

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram of study identification.[34] The search strategy was conducted initially on September 17, 2020, updated on October 14, 2021, and updated again on September 19, 2022.

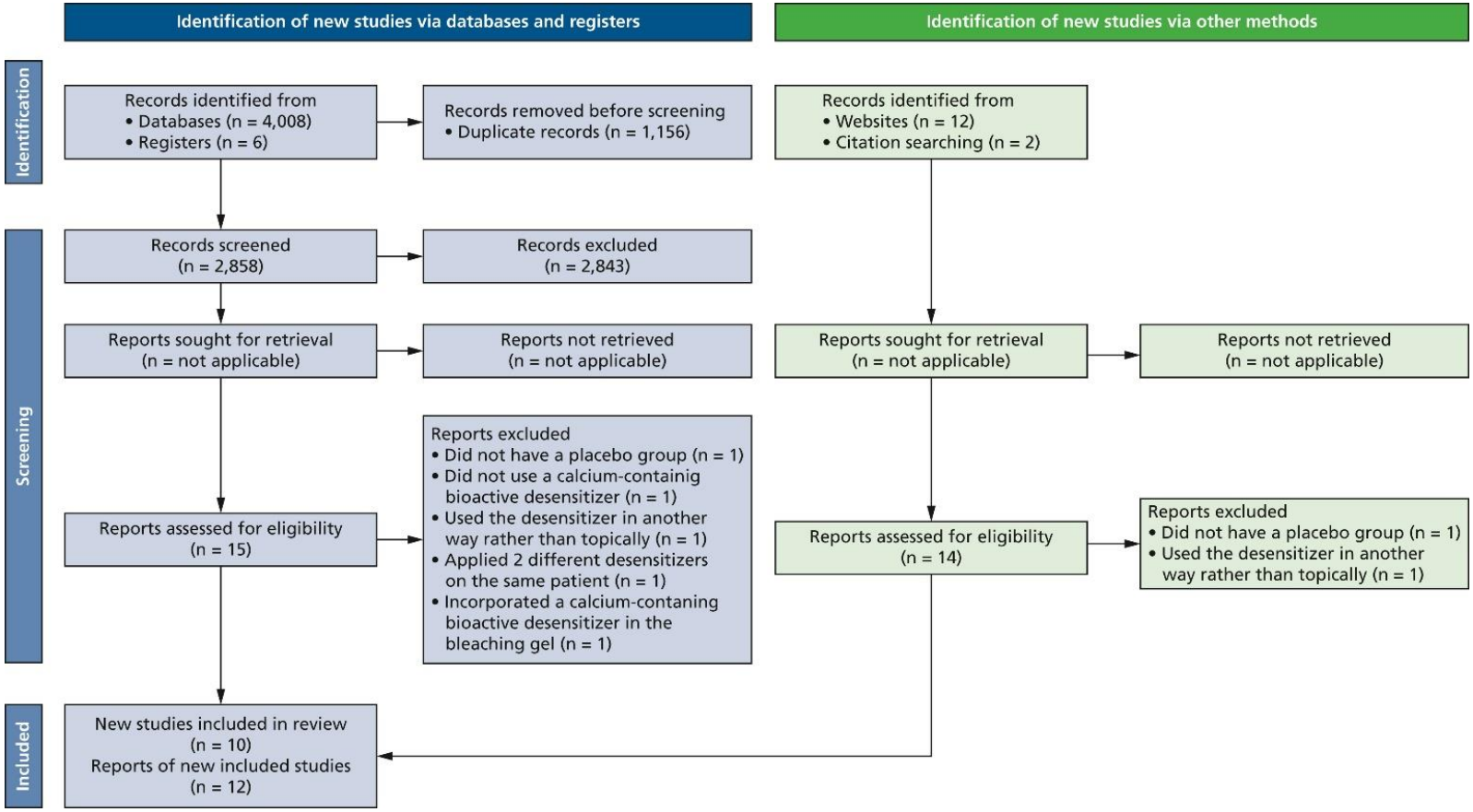


Figure 2. Summary of risk of bias assessment for the risk of tooth sensitivity according to Cochrane Collaboration Risk of Bias tool Version 2.0. Red, green, and yellow refer to high risk of bias, low risk of bias, and some concerns of bias, respectively.

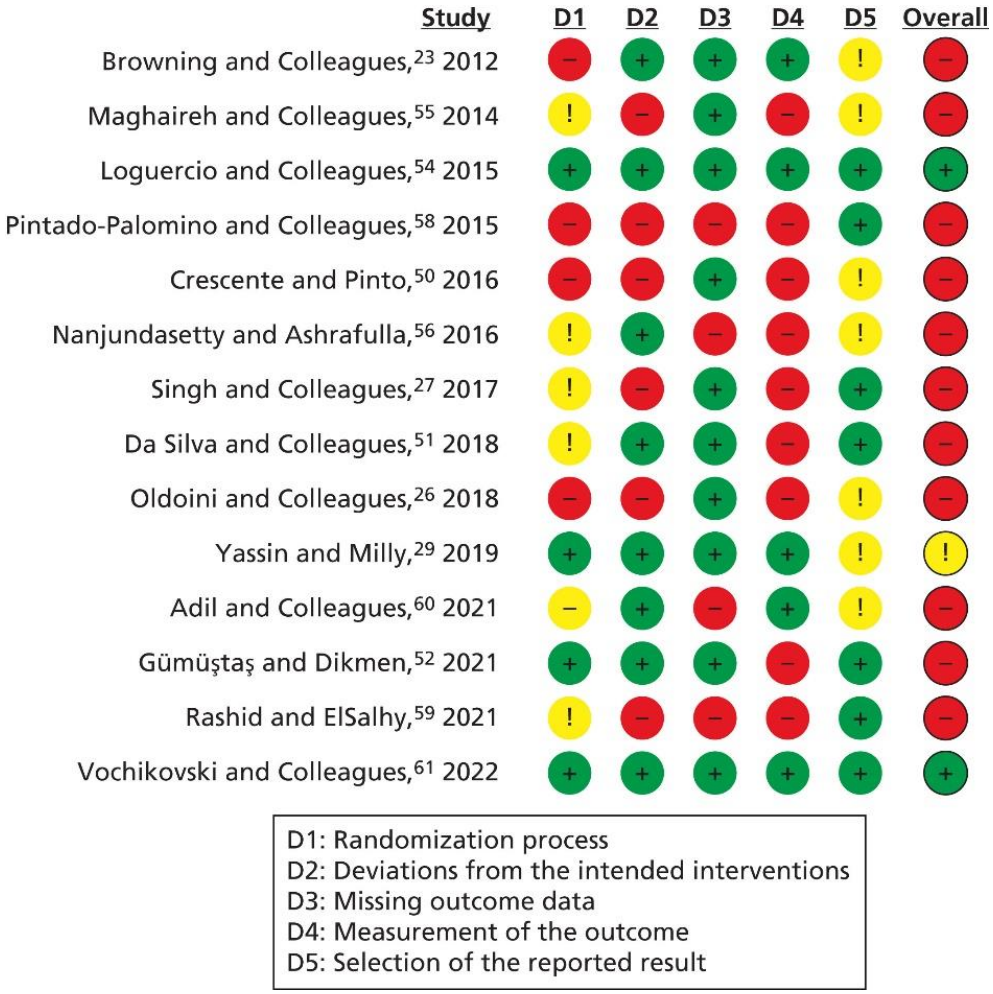


Figure 3. Summary of risk of bias assessment for the intensity of tooth sensitivity according to Cochrane Collaboration Risk of Bias tool Version 2.0. Red, green, and yellow refer to high risk of bias, low risk of bias, and some concerns of bias, respectively.

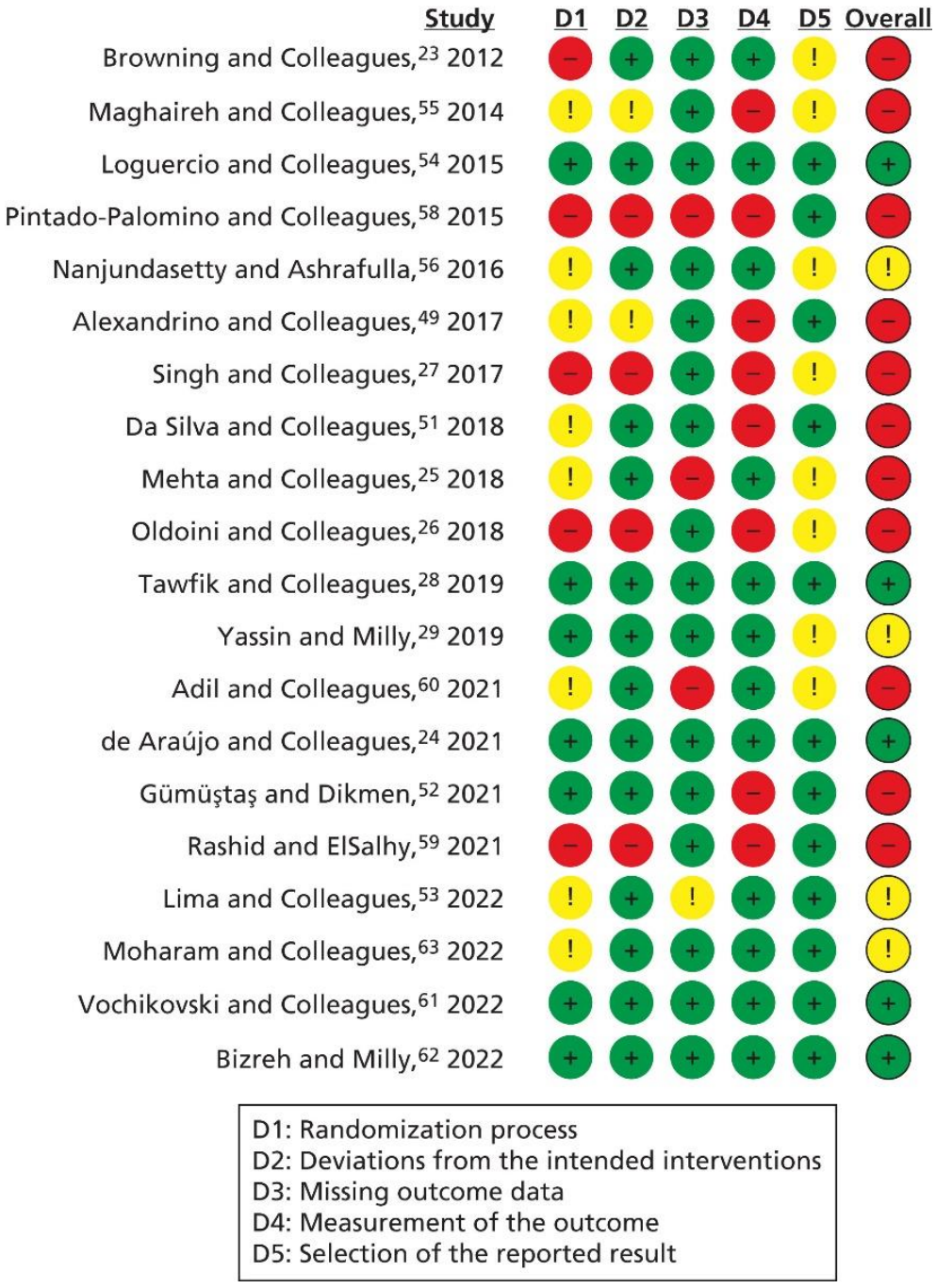


Figure 4. Forest plot of the risk of spontaneous tooth sensitivity for bleaching with desensitization vs without desensitization.

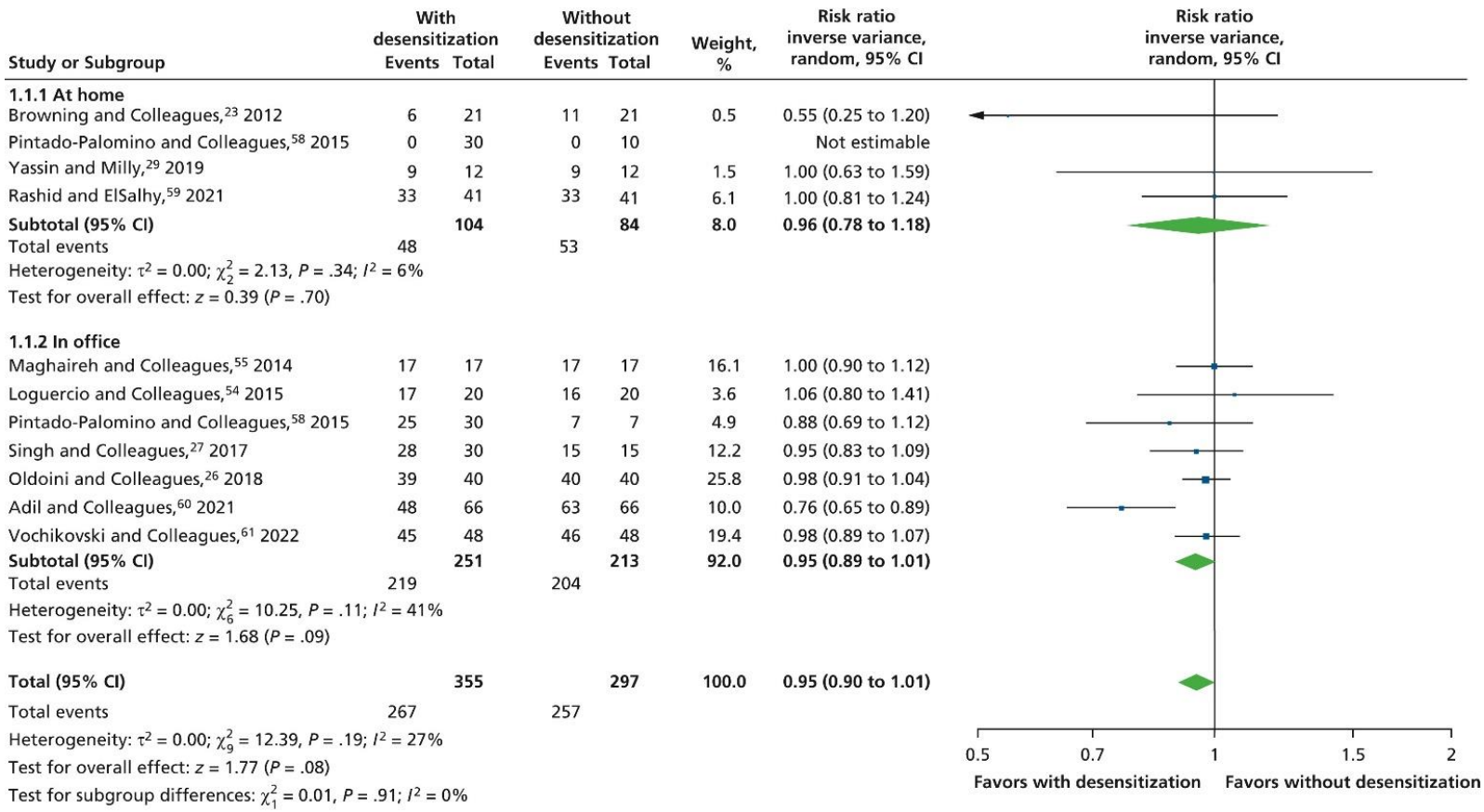


Figure 5. Forest plot of the intensity of spontaneous tooth sensitivity (visual analog scale) for bleaching with desensitization vs without desensitization.

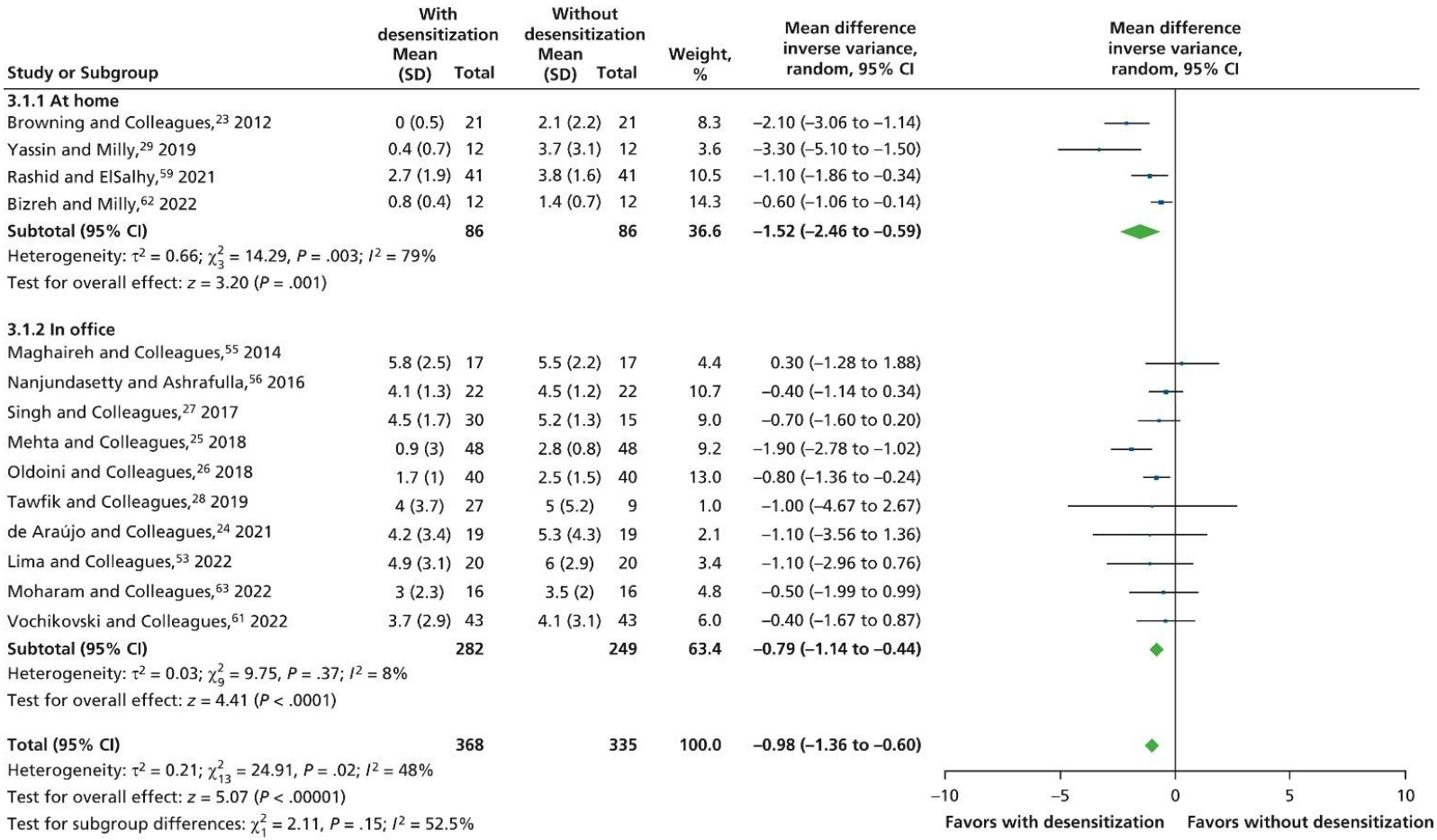


Figure 6. Forest plot of the color change in Vita Classical shade guide units for bleaching with desensitization vs without desensitization.

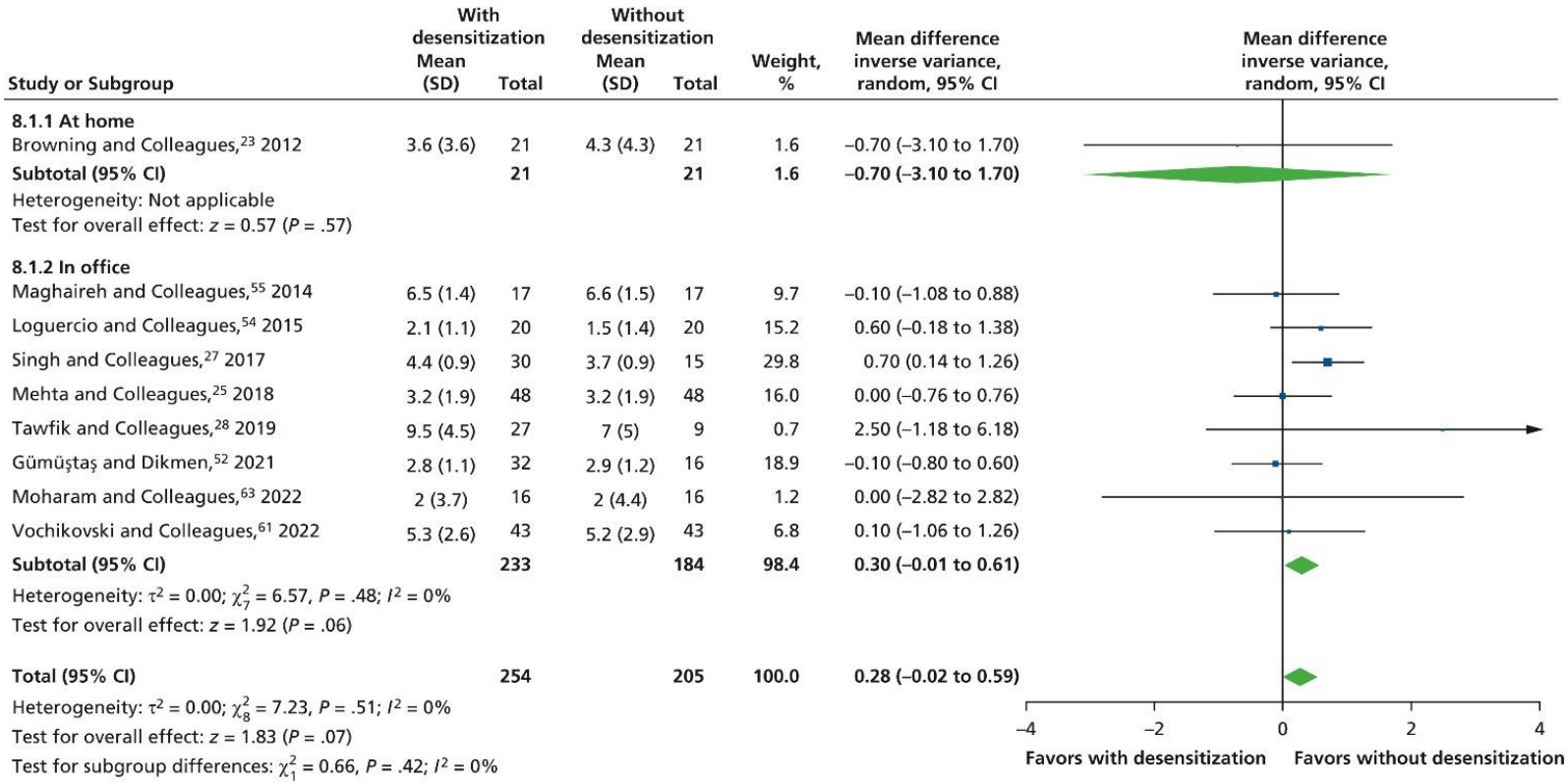
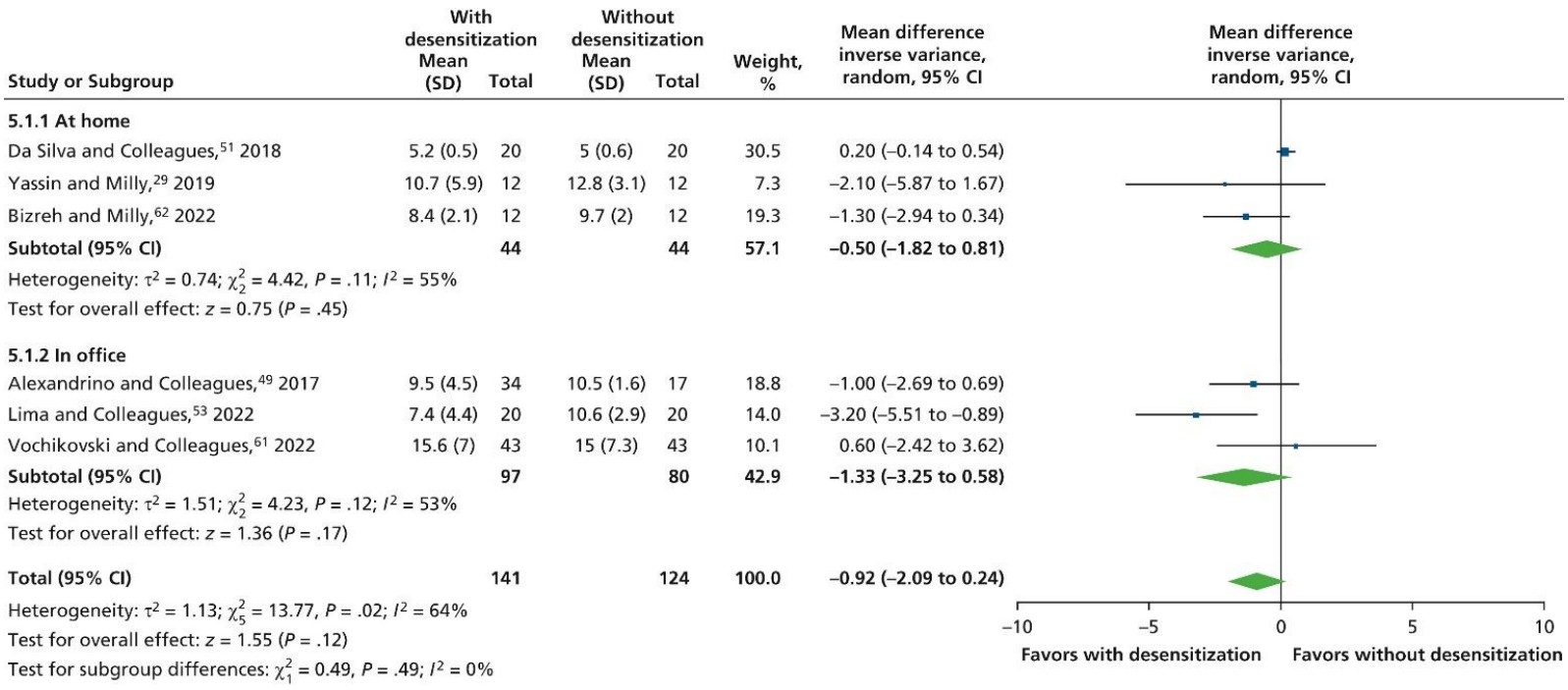


Figure 7. Forest plot of the color change in ΔE_{ab} for bleaching with desensitization vs without desensitization.



Appendix

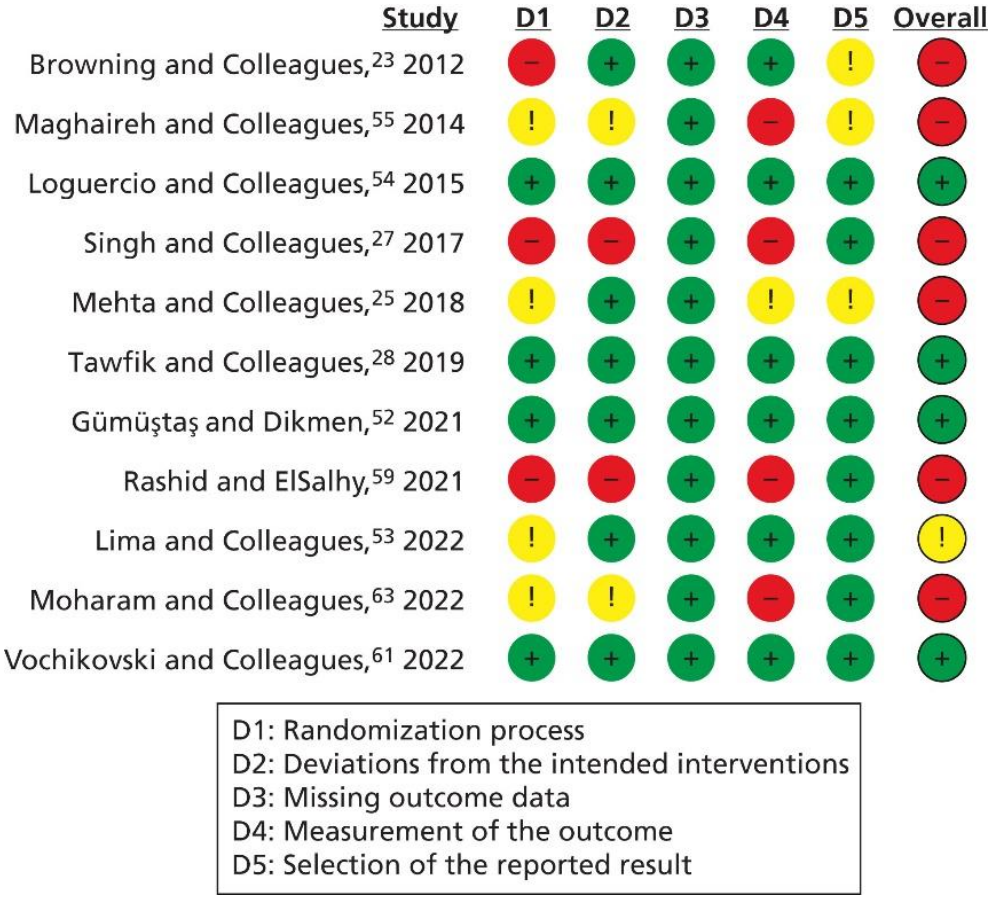
Stimuli-induced tooth sensitivity.

The risk of stimuli-induced tooth sensitivity (TS) was calculated from a total of 3 studies. There was no difference in the risk of TS (P = .50), with a risk ratio of 0.91 (95% CI, 0.68 to 1.21; eFigure 3) with the prediction interval varying from –1.75 through 3.57. Heterogeneity was not detected (P = .23; I^2 = 33%).

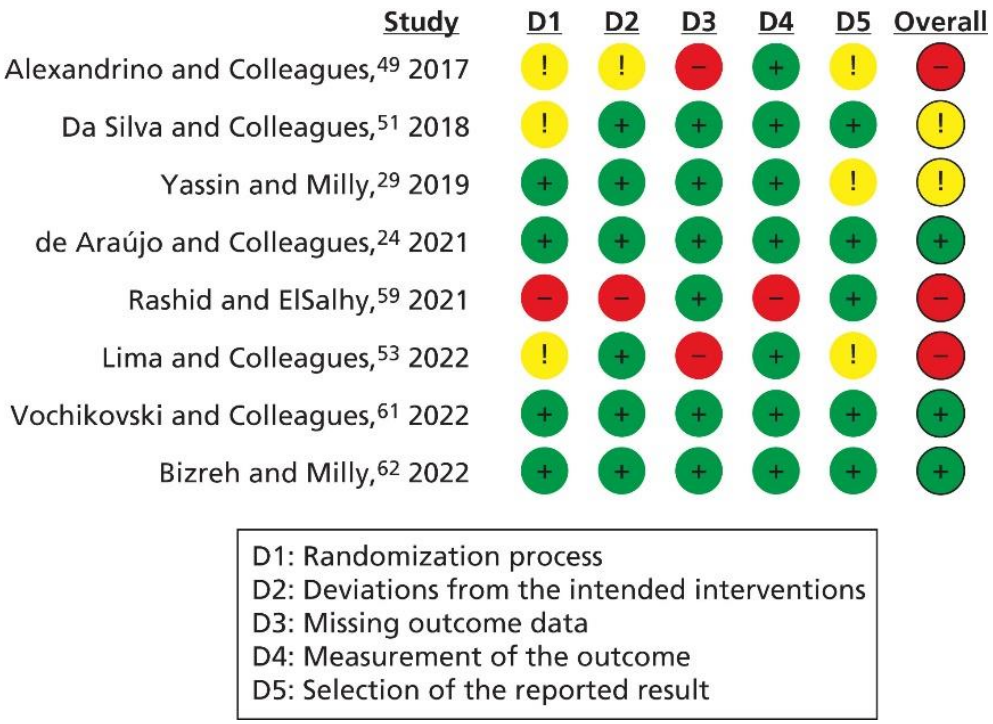
Meta-analysis was performed on the intensity of stimuli-induced TS in the visual analog scale (eFigure 4). Six studies were included in total, giving an average mean difference of –0.78 visual analog scale units (95% CI, –1.95 to 0.39) with no difference between groups (P = .19) and the prediction interval varying from –4.33 through 2.77. Heterogeneity was detected (P < .00001), attributable mainly to variations in the true effect sizes (I^2 = 91%).

Figures Appendix

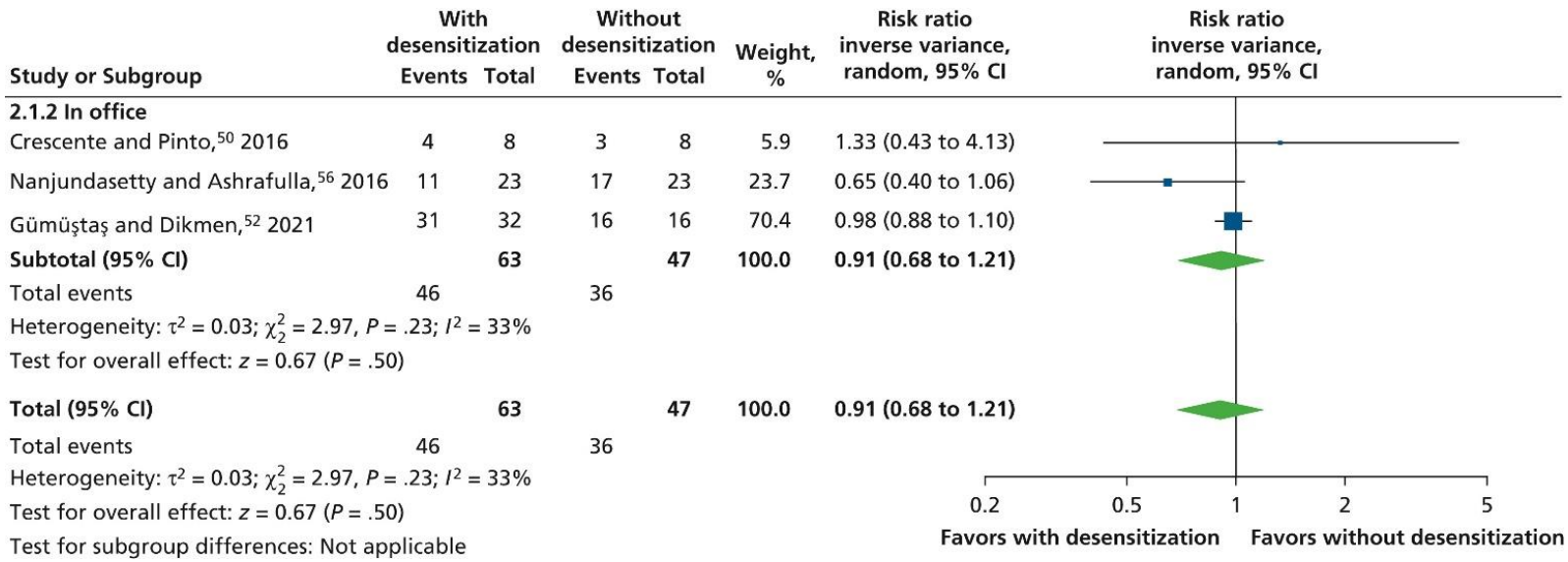
eFigure 1. Summary of risk of bias assessment for color change (subjective) according to Cochrane Collaboration Risk of Bias tool Version 2.0. Red, green, and yellow refer to high risk of bias, low risk of bias, and some concerns of bias, respectively.



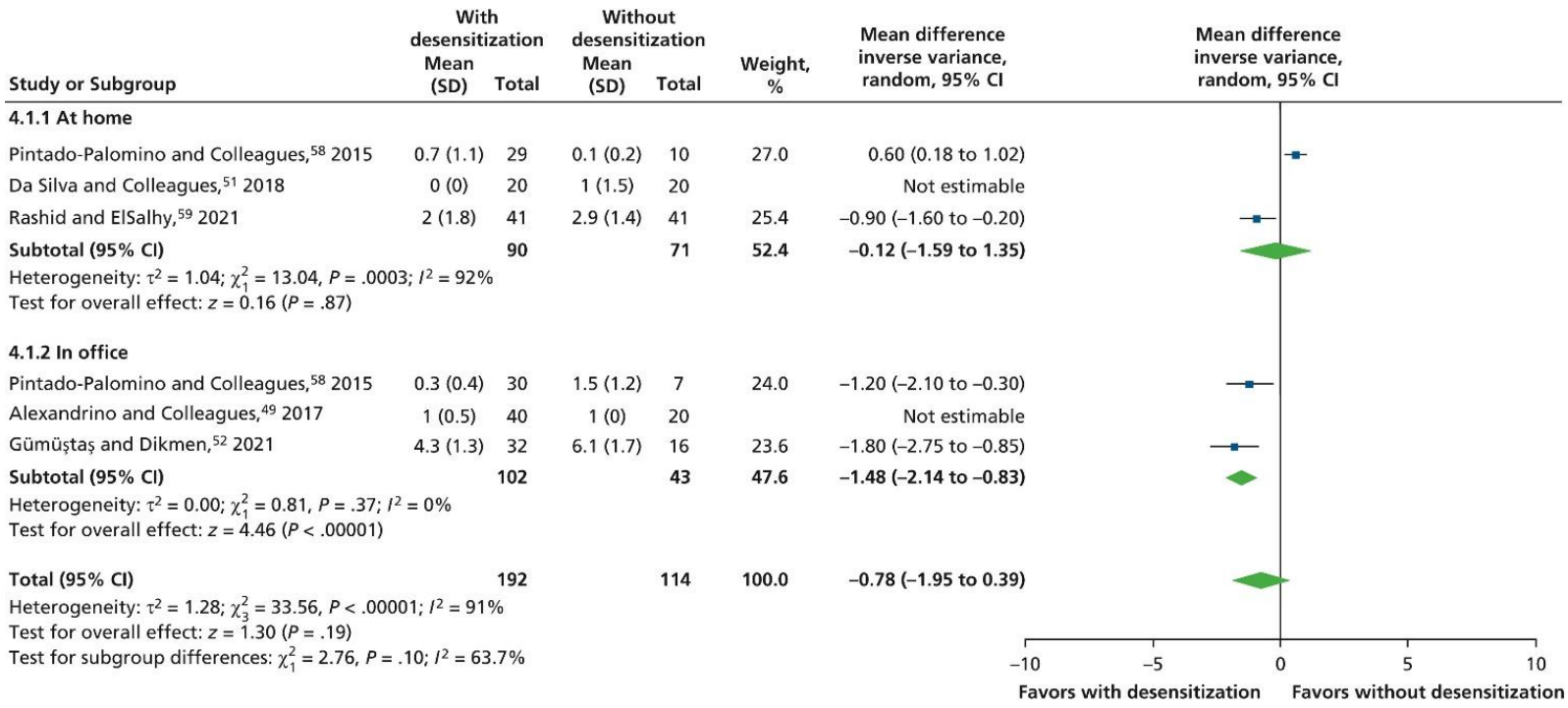
eFigure 2. Summary of risk of bias assessment for color change (objective) according to Cochrane Collaboration Risk of Bias tool Version 2.0. Red, green, and yellow refer to high risk of bias, low risk of bias, and some concerns of bias, respectively.



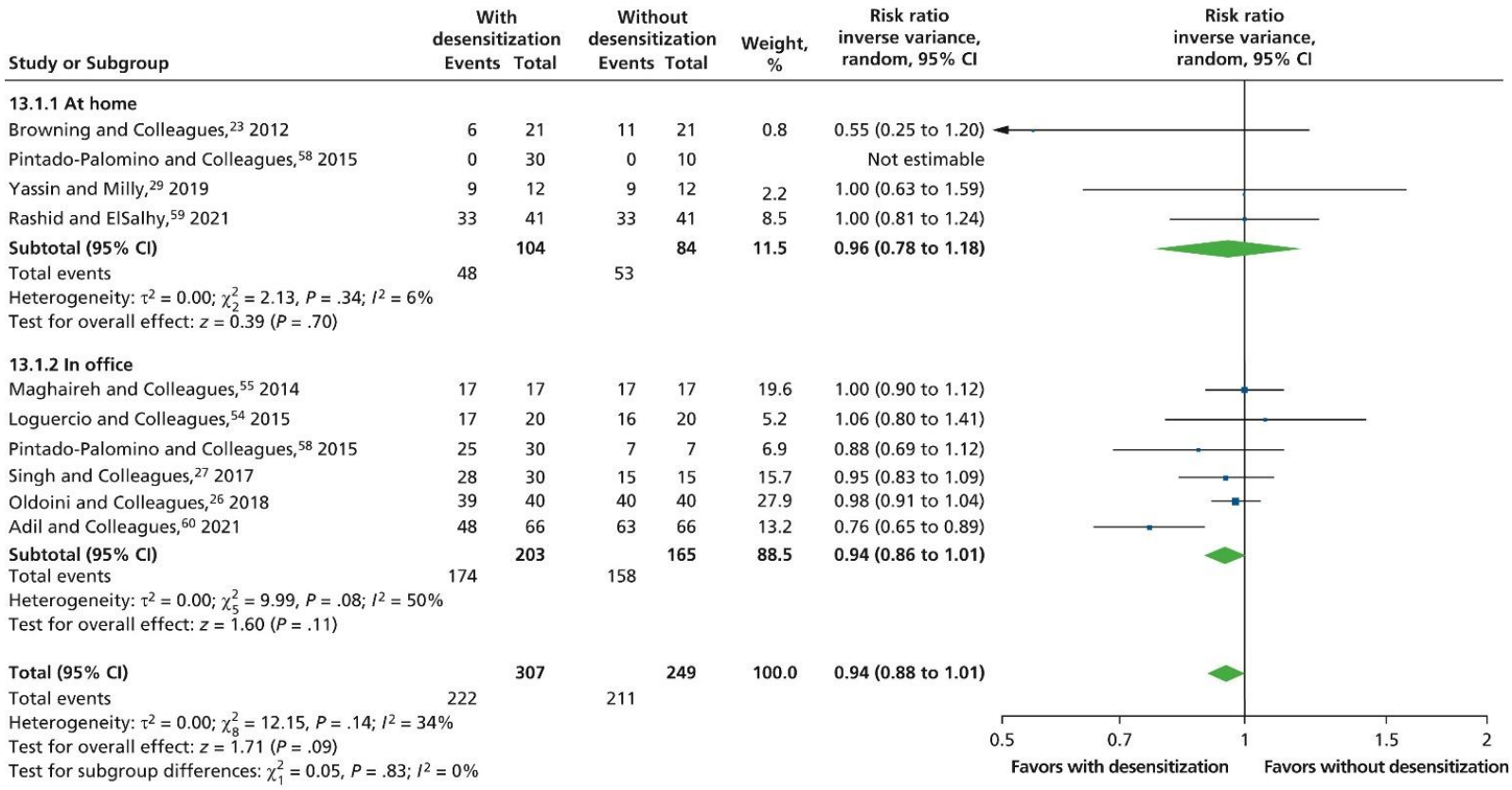
eFigure 3. Forest plot of the risk of stimuli-induced tooth sensitivity for dental bleaching with desensitization vs without desensitization.



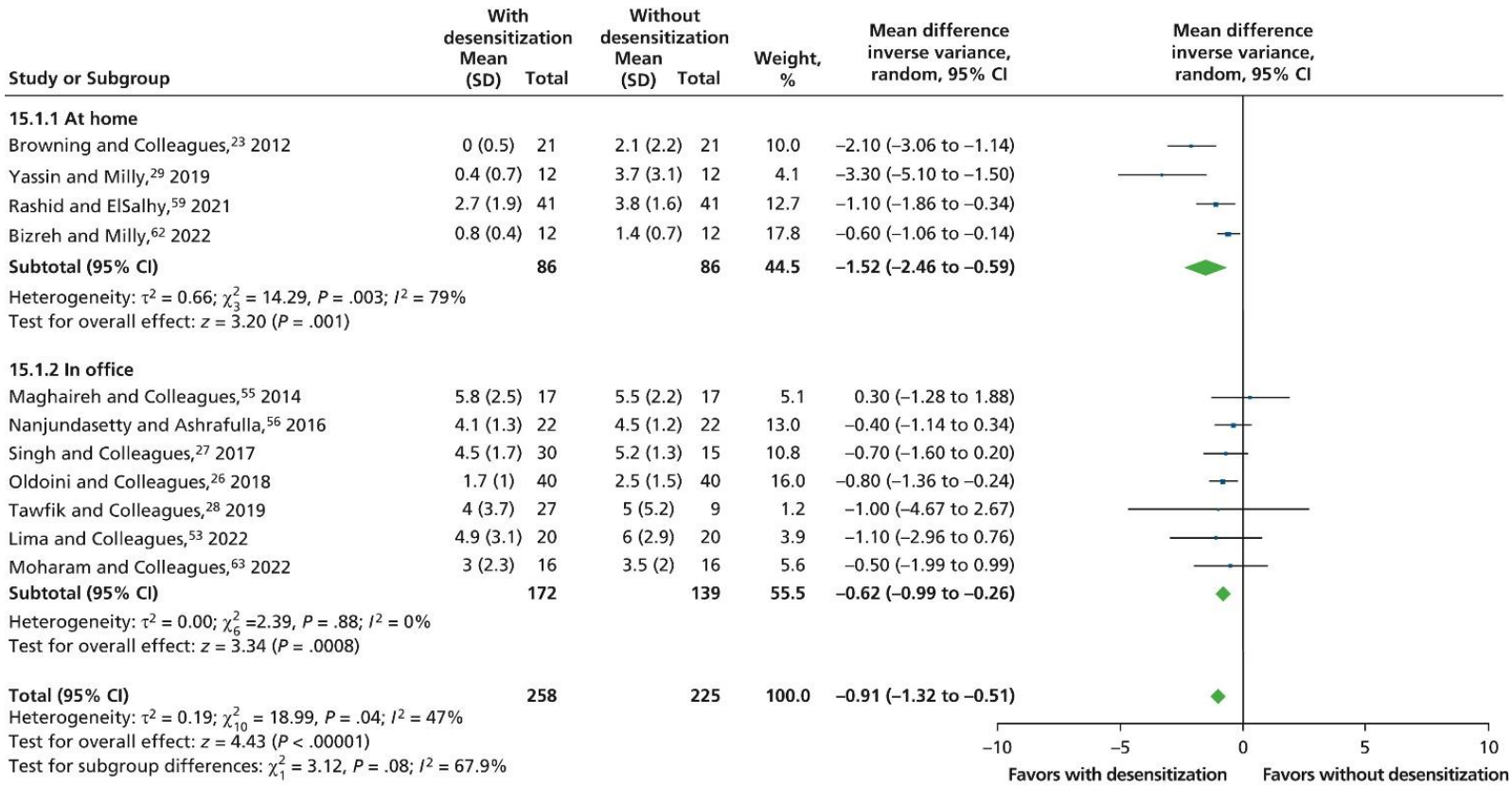
eFigure 4. Forest plot of the stimuli-induced intensity of tooth sensitivity using the visual analog scale for dental bleaching with desensitization vs without desensitization.



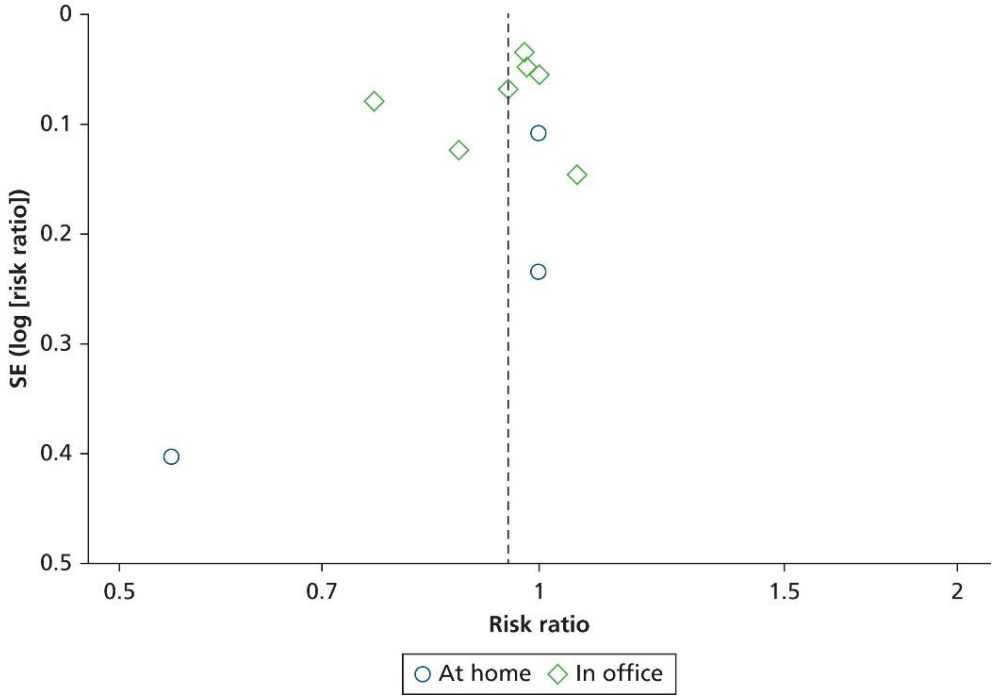
eFigure 5. Forest plot of the risk of spontaneous tooth sensitivity only for parallel studies.



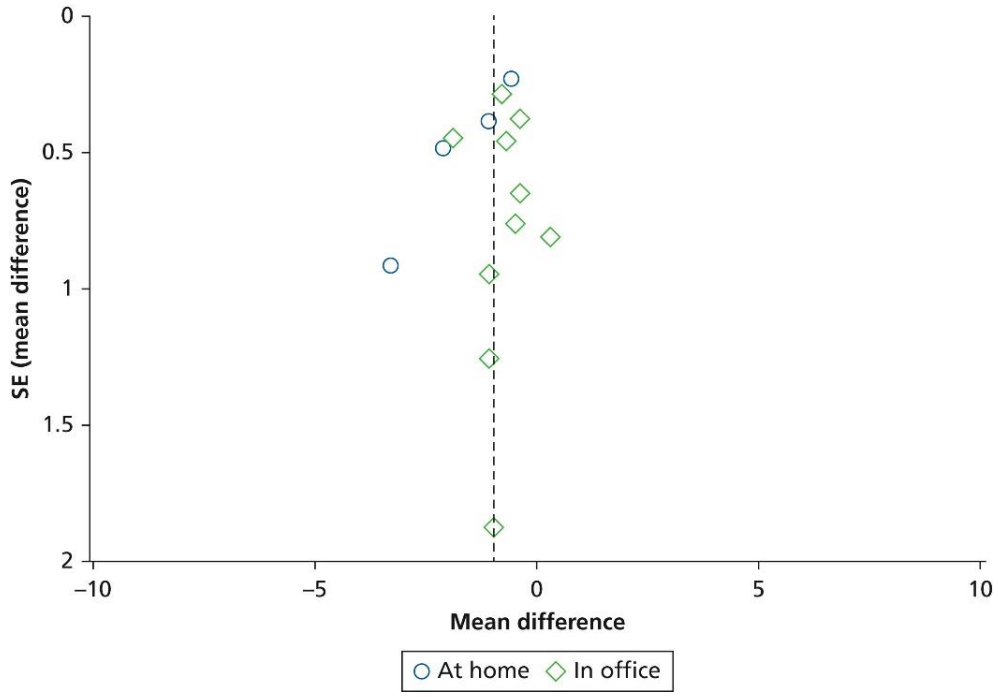
eFigure 6. Forest plot of the intensity of spontaneous tooth sensitivity only for parallel studies.



eFigure 7. Funnel plot of included studies of the risk of spontaneous tooth sensitivity for dental bleaching with desensitization vs without desensitization.



eFigure 8. Funnel plot of included studies of the intensity of spontaneous tooth sensitivity (visual analog scale) for dental bleaching with desensitization vs without desensitization.



eTable 1. Search strategies for electronic databases.*

PUBMED 17/09/2020 = 716		
#1 "Tooth Discoloration"[MeSH Terms] OR "tooth discoloration"[Title/Abstract] OR "tooth staining"[Title/Abstract] OR "teeth staining"[Title/Abstract] OR "tooth stain"[Title/Abstract] OR "stained tooth"[Title/Abstract] OR "stained teeth"[Title/Abstract] OR "teeth discoloration"[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] OR "tooth color"[Title/Abstract] OR "tooth colour"[Title/Abstract] OR "teeth color"[Title/Abstract] OR "teeth colour"[Title/Abstract]	#2 "Tooth Bleaching"[MeSH Terms] OR "Tooth Bleaching Agents"[MeSH Terms] OR "Carbamide Peroxide"[MeSH Terms] OR "Hydrogen peroxide"[MeSH Terms] OR "Dentin Desensitizing Agents"[MeSH Terms] OR "Glutaral"[MeSH Terms] OR "Sodium Fluoride"[MeSH Terms] OR "Calcium Phosphates"[MeSH Terms] OR "Calcium"[MeSH Terms] OR "Apatites"[MeSH Terms] OR "Hydroxyapatites"[MeSH Terms] OR "Potassium Nitrate"[Supplementary Concept] OR "UltraEZ"[Supplementary Concept] OR "Gluma Desensitizer"[Supplementary Concept] OR "Amorphous Calcium Phosphate"[Supplementary Concept] OR "Casein Phosphopeptide-Amorphous Calcium Phosphate nanocomplex"[Supplementary Concept] OR "Tooth Bleaching"[Title/Abstract] OR "Teeth Bleaching"[Title/Abstract] OR bleaching[Title/Abstract] OR whitening[Title/Abstract] OR "at-home"[Title/Abstract] OR "in-office"[Title/Abstract] OR "potassium oxalate"[Title/Abstract] OR "Gluma Desensitizer"[Title/Abstract] OR desensitization[Title/Abstract] OR glutaraldehyde[Title/Abstract] OR "potassium nitrate"[Title/Abstract] OR "hydrogen peroxide"[Title/Abstract] OR "carbamide peroxide"[Title/Abstract] OR "sodium fluoride"[Title/Abstract] OR “Gluma Dentin Desensitizer”[Title/Abstract] OR "calcium	#3 "randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms] OR "clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[Text Word] OR (("singl*"[Text Word] OR "doubl*"[Text Word] OR "trebl*"[Text Word] OR "tripl*"[Text Word]) AND ("mask*"[Text Word] OR "blind*"[Text Word])) OR ("placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "research design"[MeSH Terms:noexp] OR "comparative study"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "follow-up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "control*"[Text Word] OR "prospective*"[Text Word] OR "volunteer*"[Text Word]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

	phosphates"[Title/Abstract] OR "desensitizing agent"[Title/Abstract] OR "desensitizing agents"[Title/Abstract] OR "Amorphous Calcium Phosphate"[Title/Abstract] OR "CPP-ACP"[Title/Abstract] OR "Tooth Mousse"[Title/Abstract] OR "GC Tooth Mousse"[Title/Abstract] OR Recaldent[Title/Abstract] OR "Bioactive Glass"[Title/Abstract] OR "Bioactive Material"[Title/Abstract] OR Hydroxyapatite[Title/Abstract] OR "Teethmate Desensitizer"[Title/Abstract] OR "Casein Phosphopeptide-Amorphous Calcium Phosphate"[Title/Abstract]	
#1 AND #2 AND #3		
SCOPUS 17/09/2020 = 1221		
#1 TITLE-ABS-KEY ("t??th discoloration" OR "t??th staining" OR "tooth stain" OR "stained t??th" OR "t??th discolouration" OR "discolored t??th" OR "discoloured t??th" OR "dental discolo*" OR "t??th color" OR "t??th colour")	**#2** TITLE-ABS-KEY ("Tooth Bleaching" OR "Tooth Bleaching Agents" OR "Carbamide Peroxide" OR "Hydrogen peroxide" OR "Dentin Desensitizing Agents" OR "Glutaral" OR "Sodium Fluoride" OR "Calcium Phosphates" OR "Calcium" OR "Apatites" OR "Hydroxyapatites" OR "Potassium Nitrate" OR "UltraEZ" OR "Gluma Desensitizer" OR "Amorphous Calcium Phosphate" OR "Casein Phosphopeptide-Amorphous Calcium Phosphate nanocomplex" OR "Teeth Bleaching" OR bleaching OR whitening OR "at-home" OR "in-office" OR "potassium oxalate" OR desensitization OR glutaraldehyde OR "sodium fluoride" OR “Gluma Dentin Desensitizer” OR "desensitizing agent" OR "desensitizing agents" OR "Amorphous Calcium Phosphate" OR "CPP-ACP" OR "Tooth Mousse" OR "GC Tooth Mousse" OR Recaldent	**#3** (LIMIT-TO (SUBAREA , "DENT"))

	OR "Bioactive Glass" OR "Bioactive Material" OR "Teethmate Desensitizer" OR "Casein Phosphopeptide-Amorphous Calcium Phosphate")	
#1 AND #2 AND #3		
WEB OF SCIENCE 17/09/2020 = 586		
#1 TS= ("t??th discoloration" OR "t??th staining" OR "tooth stain" OR "stained t??th" OR "t??th discolouration" OR "discolored t??th" OR "discoloured t??th" OR "dental discolo$" OR "t??th color" OR "t??th colour")	**#2** TS= ("Tooth Bleaching" OR "Tooth Bleaching Agents" OR "Carbamide Peroxide" OR "Hydrogen peroxide" OR "Dentin Desensitizing Agents" OR "Glutaral" OR "Sodium Fluoride" OR "Calcium Phosphates" OR "Calcium" OR "Apatites" OR "Hydroxyapatites" OR "Potassium Nitrate" OR "UltraEZ" OR "Gluma Desensitizer" OR "Amorphous Calcium Phosphate" OR "Casein Phosphopeptide-Amorphous Calcium Phosphate nanocomplex" OR "Teeth Bleaching" OR bleaching OR whitening OR "at-home" OR "in-office" OR "potassium oxalate" OR desensitization OR glutaraldehyde OR "sodium fluoride" OR “Gluma Dentin Desensitizer” OR "desensitizing agent" OR "desensitizing agents" OR "Amorphous Calcium Phosphate" OR "CPP-ACP" OR "Tooth Mousse" OR "GC Tooth Mousse" OR Recaldent OR "Bioactive Glass" OR "Bioactive Material" OR "Teethmate Desensitizer" OR "Casein Phosphopeptide-Amorphous Calcium Phosphate")	
#1 AND #2		
LILACS AND BBO 17/09/2020 = 91		
#1 (MH:(Tooth Discoloration)) OR (MH:(Dentition, Permanent)) OR (tw:("tooth color")) OR (tw:("tooth colour")) OR (tw:("teeth color")) OR (tw:("teeth colour")) OR (tw:("tooth staining")) OR (tw:("tooth stain")) OR (tw:("stained tooth")) OR (tw:("stained teeth")) OR (tw:("tooth discoloration")) OR (tw:("tooth discolouration")) OR (tw:("discolored tooth")) OR	**#2 (**MH:(“Tooth Bleaching”)) OR (MH:(“Tooth Bleaching Agents”)) OR (MH:(Peroxides)) OR (MH:(“Hydrogen Peroxide”)) OR (MH:(“Carbamide Peroxide”)) OR (MH:(“Dentin Desensitizing Agents”)) OR (MH:(“Dentin Sensitivity”)) OR (MH:(Glutaral)) OR (MH:(“Sodium Fluoride”)) OR (MH:(Hydroxyapatites)) OR (MH:(Calcium)) OR (tw:(Bleaching)) OR (tw:(Clareamiento)) OR	**#3** db: ("LILACS" OR "BBO")

(tw:("discoloured tooth")) OR (tw:("discolored teeth")) OR (tw:("discoloured teeth")) OR (tw:("teeth discoloration")) OR (tw:("teeth discolouration")) OR (tw:("dental discoloration")) OR (tw:("dental discolouration")) OR (tw:("tooth discolorations")) OR (tw:("color del diente")) OR (tw:("Color de los dientes")) OR (tw:("Manchas en los dientes")) OR (tw:("Manchas dentales")) OR (tw:("Diente manchado")) OR (tw:("dientes manchados")) OR (tw:("Descoloración de los dientes")) OR (tw:("Dientes descoloridos")) OR (tw:("Dientes de descoloración")) OR (tw:("Descoloración dental")) OR (tw:("descoloraciones de los dientes")) OR (tw:("cor dental")) OR (tw:("Cor dos dentes")) OR (tw:("Dente escurecido")) OR (tw:("Dentes escurecidos")) OR (tw:("Dente manchado")) OR (tw:("Dentes manchados")) OR (tw:("Descoloração dos dentes")) OR (tw:("Descoloração dentária")) OR (tw:("Dente descolorido")) OR (tw:("Descoloração dental")) OR (tw:("descolorações dos Dentes"))	(tw:(Blanqueamiento)) OR (tw:("Clareamento Dental")) OR (tw:(Whitening)) OR (tw:("Tooth Sensitivity")) OR (tw:("Sensibilidad Dental")) OR (tw:("Sensibilidade Dental")) OR (tw:("Potassium Oxalate")) OR (tw:("Oxalato de Potasio")) OR (tw:("Oxalato de Potássio")) OR (tw:("GLUMA Desensitizer")) OR (tw:("Desensibilizante GLUMA")) OR (tw:(Desensitization)) OR (tw:(Desensibilización)) OR (tw:(Dessensibilização)) OR (tw:(Glutaraldehyde)) OR (tw:(Glutaraldehído)) OR (tw:(Glutaraldeído)) OR (tw:("Potassium Nitrate")) OR (tw:("Nitrato de Potasio")) OR (tw:("Nitrato de Potássio")) OR (tw:("Dentin Sensitivity")) OR (tw:("Sensibilidad Dentinaria")) OR (tw:("Sensibilidade da Dentina")) OR (tw:("Hydrogen Peroxide")) OR (tw:("Peróxido de Hidrógeno")) OR (tw:("Peróxido de Hidrogênio")) OR (tw:("Carbamide Peroxide")) OR (tw:("Peróxido de Carbamida")) OR (tw:("Sodium Fluoride")) OR (tw:("Fluoruro de Sodio")) OR (tw:("Fluoreto de Sódio")) OR (tw:("Calcium Phosphates")) OR (tw:("Fosfatos de Calcio")) OR (tw:("Fosfatos de Cálcio")) OR (tw:("Calcium Phosphate")) OR (tw:("Fosfato de Cálcio")) OR (tw:("Fosfato de Cálcio")) OR (tw:("Desensitizing Agents")) OR (tw:("Agentes Desensibilizantes")) OR (tw:("Agente Desensibilizante")) OR (tw:("CPP-ACP")) OR (tw:(“Bioactive Glass”)) OR (tw:(“Vidro Bioativo”)) OR (tw:(“Vidrio Bioactivo”)) OR (tw:(“Bioactive Material”)) OR (tw:(“Material Bioativo”)) OR (tw:(“Material Bioactivo”))OR (tw:(Hidroxiapatita)) OR (tw:(Hydroxyapatite))	
#1 AND #2		

COCHRANE LIBRARY 17/09/2020 = 459

#1 MeSH descriptor: [Tooth Discoloration] explode all trees
#2 MeSH descriptor: [Dentition, Permanent] explode all trees
#3 (stain next teeth*):ti,ab,kw (Word variations have been searched)
#4 (tooth next stain*):ti,ab,kw (Word variations have been searched)
#5 (tooth* next discoloration):ti,ab,kw (Word variations have been searched)
#6 (discoloration next tooth*):ti,ab,kw (Word variations have been searched)
#7 (tooth* next color):ti,ab,kw (Word variations have been searched)
#8 (teeth* next discoloration*):ti,ab,kw (Word variations have been searched)
#9 (color next tooth*):ti,ab,kw (Word variations have been searched)
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Tooth Bleaching] explode all trees
#12 MeSH descriptor: [Tooth Bleaching Agents] explode all trees
#13 MeSH descriptor: [Peroxides] explode all trees
#14 MeSH descriptor: [Dentin Desensitizing Agents] explode all trees
#15 MeSH descriptor: [Dentin Sensitivity] explode all trees
#16 MeSH descriptor: [Nitrates] explode all trees
#17 MeSH descriptor: [Glutarates] explode all trees
#18 MeSH descriptor: [Sodium Fluoride] explode all trees
#19 MeSH descriptor: [Hydroxyapatite] explode all trees
#20 MeSH descriptor: [Calcium Phosphates] explode all trees
#21 MeSH descriptor: [Calcium] explode all trees
#22 (bleaching):ti,ab,kw (Word variations have been searched)
#23 (whitening):ti,ab,kw (Word variations have been searched)
#24 (tooth* next sensitivity):ti,ab,kw (Word variations have been searched)
#25 (potassium next oxalate):ti,ab,kw (Word variations have been searched)
#26 (GLUMA next Desensitizer):ti,ab,kw (Word variations have been searched)
#27 (desensitization):ti,ab,kw (Word variations have been searched)
#28 (glutaraldehyde):ti,ab,kw (Word variations have been searched)
#29 (potassium next nitrate):ti,ab,kw (Word variations have been searched)
#30 (dentin next sensitivity):ti,ab,kw (Word variations have been searched)
#31 (carbamide next peroxide):ti,ab,kw (Word variations have been searched)
#32 (hydrogen next peroxide):ti,ab,kw (Word variations have been searched)
#33 (sodium next fluoride):ti,ab,kw (Word variations have been searched)
#34 (calcium next phosphate*):ti,ab,kw (Word variations have been searched)
#35 (desensitizing* next agent*):ti,ab,kw (Word variations have been searched)
#36 (amorphous calcium phosphate):ti,ab,kw (Word variations have been searched)
#37 (hydroxyapatite*):ti,ab,kw (Word variations have been searched)
#38 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
#39 #10 and #38

EMBASE 17/09/2020 = 573

#1 'tooth discoloration'/exp OR 'tooth discoloration' OR 'tooth staining'/exp OR 'tooth staining' OR 'teeth staining' OR 'tooth stain'/exp OR 'tooth stain' OR 'stained tooth' OR 'stained teeth' OR 'teeth discoloration' OR 'tooth discolouration'/exp OR 'teeth discolouration' OR 'discolored tooth' OR 'discolored teeth' OR 'discoloured tooth' OR 'discoloured teeth' OR 'dental discoloration'/exp OR 'dental discoloration' OR 'dental discolouration'/exp OR 'dental discolouration' OR 'tooth color'/exp OR 'tooth color' OR 'tooth colour'/exp OR 'tooth colour' OR 'teeth color' OR 'teeth colour'	#2 'tooth bleaching'/exp OR 'tooth bleaching' OR 'tooth bleaching agents'/exp OR 'tooth bleaching agents' OR 'carbamide peroxide'/exp OR 'carbamide peroxide' OR 'hydrogen peroxide'/exp OR 'hydrogen peroxide' OR 'dentin desensitizing agents'/exp OR 'dentin desensitizing agents' OR 'glutaral'/exp OR 'glutaral' OR 'calcium phosphates'/exp OR 'calcium phosphates' OR 'calcium'/exp OR 'calcium' OR 'apatites'/exp OR 'apatites' OR 'hydroxyapatites'/exp OR 'hydroxyapatites' OR 'potassium nitrate'/exp OR 'potassium nitrate' OR 'ultraez' OR 'gluma desensitizer'/exp OR 'gluma desensitizer' OR 'casein phosphopeptide-amorphous calcium phosphate nanocomplex' OR 'teeth bleaching' OR 'bleaching'/exp OR bleaching OR whitening OR 'at-home' OR 'in-office' OR 'potassium oxalate'/exp OR 'potassium oxalate' OR 'desensitization'/exp OR desensitization OR 'glutaraldehyde'/exp OR glutaraldehyde OR 'sodium fluoride'/exp OR 'sodium fluoride' OR 'gluma dentin desensitizer' OR 'desensitizing agent'/exp OR 'desensitizing agent' OR 'desensitizing agents'/exp OR 'desensitizing agents' OR 'amorphous calcium phosphate'/exp OR 'amorphous calcium phosphate' OR 'cpp-acp' OR 'tooth mousse' OR 'gc tooth mousse' OR recaldent OR 'bioactive glass'/exp OR 'bioactive glass' OR 'bioactive material' OR 'teethmate desensitizer' OR 'casein phosphopeptide-amorphous calcium phosphate'	#3 [embase]/lim
#1 AND #2 NOT MEDLINE		

eTable 2. Summary of the studies selected for qualitative analysis in this systematic review.

Study ID	**Study design [setting]**	**Subjetcs age in means ± SD [range]**	**N°. of subjetcs [% female]**	**Bleaching protocol – bleaching agent: application number x application time [number of sessions] (session interval)**	**Desensitizing protocol application number x application time [number of sessions] (session interval) {Before or After application}**	**Color evaluation criteria / instrument [time assessment]**	**Pain evaluation criteria / instrument [time assessment]**
Adil, 2021	Parallel [University]	25.7 ± 5.15 [25-26]	132 [50]	IO - 35% HP[1]: 3 x 8 min [1] (n.r.)	**Casein phosphopeptide-amorphous calcium phosphate[2]:** 1 x n.r. [6] {After bleaching}	n.r. /n.r. [n.r.]	Risk and Intensity spontaneous/DIS 0-4 [B_o, 24 hours, 36 hours]
Alexandrino, 2017	Parallel [n.r.]	n.r. ± n.r. [18-26]	34 [n.r.]	IO - 35% HP[3]: 1 x 45 min [3] (1 week)	**Calcium sodium phosphosilicate**[4] or **Casein phosphopeptide-amorphous calcium phosphate with fluride[5]:** 1 x 5 minutes [3] (1 week) {After bleaching}	ΔE_{ab} /Spectrophotometer digital[a] [B_o, 24 h, 1st week, 2nd week and 3rd week]	Intensity stimuli-induced/ VAS modified [24 hours]
Bizreh and Milly, 2022	Parallel [n.r.]	23.1 ± 2.6 [18-28]	24 [58]	AT - 20% CP[6]: 1 x 4 hours [7]	**Calcium sodium phosphosilicate[4]:** 1 x 30 minutes [7] {After bleaching}	ΔE_{ab}/ Spectrophotometer digital[a] [B_o, 72 hours, 1st week, 2nd week and 1st month]	Intensity spontaneous/ VAS 0-10 [Daily for 7 days]
Browning, 2012	Parallel [n.r.]	n.r. ± n.r. [n.r.-n.r.]	41 [n.r.]	AT - 7% HP[6]: 2 x 30 minutes [14]	**Nanohydroxyapatite[7]:** 2 x 5 minutes [21] {After bleaching}	SGU and ΔSGU/ Vita Classical[b] and Vita Bleachedguide[c] [B_o, 1st week, 2nd week and 6th week]	Risk and Intensity spontaneous/ VAS 0-10 [B_o, 1st week, 2nd week and 3rd week]

Crescente, 2016	Parallel [n.r.]	22.7 ± n.r. [18-46]	16 [84]	IO - 35% HP[8]: 1 x 40 minutes [3] (1 week)	**Calcium phosphate nanostructured in hydroxyapatite[9]:** 1 x 5 minutes [3] {Before bleaching}	n.r. /n.r. [n.r.]	Risk stimuli-induced/ VAS 0-10 [B_o, Immediately]
da Silva, 2018	Parallel [University]	23.8 ± 2.4 [18-26]	20 [50]	AT - 22% CP[10]: 1 x 2 hours [10]	**Calcium phosphate nanostructured in hydroxyapatite[9]:** 1 x 5 minutes [10] {After bleaching}	ΔE_{ab}/ Spectrophotometer digital[a] [B_o, 24 hours, 1st month, 2nd month and 3rd month]	Intensity stimuli-induced/ VAS modified [B_o, 24 hours, 1st month, 2nd month and 3rd month]
de Araújo, 2021	Split-mouth [n.r]	21.3 ± 2.7 [18-32]	19 [50]	IO - 35% HP[11]: 1 x 20 minutes [2] (1 week)	**Calcium phosphate nanostructured in hydroxyapatite[9]:** 1 x 5 minutes [2] {After bleaching}	ΔE_{00} and ΔWI_D/Spectrophotometer digitsl[d][B_o, immediately sessions, 1st week, 2nd week]	Intensity spontaneous/ VAS 0-10 ([Daily for 14 days]
Gümüştaş and Dikmen, 2021	Parallel [University]	n.r. ± n.r. [18-40]	48 [50]	IO - 38% HP[12]: 3 x 15 minutes [1] (1 week)	**Casein phosphopeptide-amorphous calcium phosphate or nano-hydroxyapatite[13]:** 1 x 4 minutes [1] {Before bleaching}	SGU/ Vitapan Classical[e] [B_o, 24 hours, 1st week]	Risk and Intensity stimuli-induced/ VAS 0-100 modified [B_o, 24 hours, 1st week]
Lima, 2021	Parallel [n.r.]	22.6 ± 3.6 [18-30]	40 [50]	IO - 35% HP[14]: 3 x 15 minutes [3] (1 week)	**Calcium phosphate nanostructured in hydroxyapatite[9]:** 1x 5 minutes [3] {After bleaching}	ΔSGU and ΔE_{ab}/Spectrophotometer digital[a][B_o, after bleaching, 1 week, after 2nd session bleaching, 2 weeks, after 3rd session bleaching and 3 weeks after bleaching]	Intensity spontaneous/ VAS 0-10 [B_o, Immediately, 24 hours and 1 week after sessions]
Loguercio, 2015	Parallel [n.r.]	24.3 ± 5.3 [18-n.r]	40 [55]	IO - 35% HP[14]: 3 x 15 minutes [2] (1 week)	**Calcium phosphate nanostructured in hydroxyapatite[9]:** 1 x 10 minutes [2] {Before bleaching}	SGU/ Vita Lumin[f][B_o, 1st week and 2nd week]	Intensity and Risk spontaneous/ NRS 0-4 [Immediately and 48 hours after 1st and 2nd session]

Maghaireh, 2014	Parallel [n.r.]	23.1 ± n.r. [18-38]	34 [70]	IO - 35% HP[14]: 3 x 15 minutes [1]	**Casein phosphopeptide-amorphous calcium phosphate[13]:** 2 x 3 minutes [14] {After bleaching}	ΔSGU/ Vitapan Classical[e] [B_o, after bleaching, 3 days, 1st week, 2nd week after bleaching]	Intensity and Risk stimuli-induced/ VAS 0-10 [Daily for 14 days]
Mehta, 2018	Split-mouth [n.r]	24 ± n.r. [18-30]	48 [56]	IO - 40% HP[15]: 1 x 15 minutes [1]	**Dicalcium phosphate anhydrate and Tetracalcium phosphate[16]:** 2 x 20 seconds [1] {Before bleaching}	SGU/ Vitapan Classical[e][B_o, Immediately and 48 hours]	Intensity spontaneous/ VAS 0-10 [B_o, during, immediately, 1 hour, 24 hours, 48 hours and 1 week]
Moharam, 2022	Parallel [n.r.]	n.r. ± n.r. [18-55]	64 [60]	IO - 40% HP[15]: 2 x 20 minutes [1]	**Nanohydroxyapatite[17]:** 1 x 30 minutes [1] {Before bleaching}	SGU/ Vitapan Classical[e][B_o, Immediately and 1st week, 2nd week and 3rd week]	Intensity spontaneous/ VAS 0-10 [Immediately, 30 minutes, daily for 7 days, 1st week, 2nd week and 3rd week]
Nanjundasetty and Ashrafulla, 2016	Parallel [n.r.]	n.r. ± n.r. [18-30]	46 [n.r.]	IO - 35% HP[18]: 3 x 15 minutes [2] (1 week)	**Casein phosphopeptide-amorphous calcium phosphate[13]:** 1 x 10 minutes [2] {After bleaching}	n.r./ n.r. [n.r.]	Risk stimuli-induced/ Sceffe´s scale 0-3; Intensity spontaneous/ VAS 0-10 [Sceffe´s: 24 hours and 1st week VAS: Daily for 2 weeks]
NCT03026725, 2017	Parallel [n.r.]	n.r. ± n.r. [18-n.r.]	24 [n.r.]	AT - 20% CP[n.r.]: 4 hours [7]	**Tricalcium phosphate[19]:** 30 minutes [7] {After bleaching}	ΔE_{ab}/ Spectrophotometer digital[a] [B_o, 72 hours, 1st week, 2nd week and 1st month]	Intensity spontaneous/ VAS 0-10 [24 hours, 48 hours, 72 hours and 1st week]
Oldoni, 2018	Parallel [n.r.]	36 ± 12.28 [18-n.r.]	80 [45]	IO - 30% HP[n.r.]: n.r. x n.r. [1]	**Casein phosphopeptide-amorphous calcium phosphate[20]:** n.r. x n.r [1] {Before bleaching}	n.r./ n.r. [n.r.]	Intensity spontaneous/ VAS 0-10 [B_o, Immediately]

Pintado-Palomino, 2015	Parallel [n.r.]	23.9 ± n.r. [18-38]	76 [70]	AT - 16% CP[21]: 4 hours [14] IO - 35% HP[3]: 3 x 15 minutes [1]	**Biosilicate[22]:** 1 x 30s [1] or **Bioglass 45S5[23]:** 1 x 30 seconds [1] or **Calcium phosphate nanostructured in hydroxyapatite[9]:** 1 x 10 seconds [1] {After bleaching}	n.r./ n.r. [n.r.]	Intensity stimuli-induced/ VAS 0-10 Risk spontaneous/ VAS 0-10 [AT: B_o, 24 hours, 3rd day, 6th day, 12th day and 18th day / IO: B_o, Immediately, 24 hours, 3rd day, 6th day and 12th day]
Rashid and ElSalhy, 2021	Cross-over [n.r.]	36.7 ± n.r. [21-52]	41 [56]	AT - 15% CP[24]: 6 – 8 hours [14]	**Casein phosphopeptide-amorphous calcium phosphate[13]:** 5 minutes [14] {After bleaching}	ΔSGU/ Vita Classical[b] and L* Spectrophotometer digital[gF][B_o, 2st week, 4th week]	Risk and Intensity spontaneous/ VAS 0-10 and Intensity stimuli-induced/ NRS 0-3 [Daily for 14 days]
Singh, 2017	Parallel [n.r.]	n.r. ± n.r. [n.r.-n.r.]	45 [n.r.]	IO - 40% HP[15]: 2 x 20 minutes [1]	**Tricalcium phosphate[19]** or **Casein phosphopeptide-amorphous calcium phosphate[13]:** 2 x 3 minutes [14] {After bleaching}	ΔSGU/ Vitapan Classical[e] and Photograph [B_o, 3rd day, 1st week and 2nd week]	Risk and Intensity spontaneous/ VAS 0-10 [Daily for 14 days]
Tawfik, 2019	Parallel [n.r.]	23.9 ± n.r. [18-40]	36 [83]	IO - 30% HP[25]: 3 x 15 minutes [1]	**Casein phosphopeptide-amorphous calcium phosphate[26]:** 1 x 30 minutes [1] {After bleaching or before bleaching or after and before bleaching}	ΔSGU/ Vitapan Classical[e] [B_o, 24 hours, 1st week and 6th month]	Intensity spontaneous/ VAS 0-10 [Immediately, 24 hours, 1st week and 6th month]
Vochikovski, 2022	Split-mouth [University]	23.4 ± 7.5 [18 - n.r.]	48 [60]	IO - 35% HP[27]: 1 x 50 minutes [2] (1 week)	**Calcium Gluconate[28]:** 1 x 10 minutes [2] {Before bleaching}	ΔSGU/ Vita Classical[f] and ΔE_{ab}/Spectrophotometer Easyshade[a] [B_o, 1 week, 2 weeks, and 1st month]	Intensity and Risk spontaneous/ VAS 0-10 and NRS 0-4 [Immediately and 1 hour, 24 hours, and 48 hours after 1st and 2nd session]

Yassin and Milly, 2018	Parallel [n.r.]	n.r. ± n.r. [18-n.r.]	24 [n.r.]	AT - 20% CP[29]: 4 hours [7]	**Casein phosphopeptide-amorphous calcium phosphate[13]:** 30 minutes [7] (After bleaching)	ΔE_{ab}/ Spectrophotometer digital[a] [B_o, 72 hours, 1st week, 2nd week and 1st month]	Intensity and Risk spontaneous/ VAS 0-10 [Daily for 7 days
a Spectrophotometer Easyshade (Vita Easyshade, Vita Zahnfabrik, Bad Säckingen, Germany) b Vita Classical shade guide (Both Vident, Brea, CA, USA) c Vita Bleachedguide 3D shade guides (Both Vident, Brea, CA, USA) d Spectrophotometer ShadeEye NCC™ (Shofu, Tokyo, Japan) e Vitapan shade guide Classical (Vita Zahnfabrik, Bad Säckingen, Germany) f Vita Lumen (Vita Zahnfabrik, Bad Säckingen, Germany) g Spectrophotometer Shade Vision (X-rite Inc, Grand Rapids, MI, USA) h Vita Classical (Vita Zahnfabrik, Bad Säckingen, Germany)			Abbreviations ΔE_{ab}: color difference measured with a spectrophotometer; ΔSGU: color difference measured with a shade guide units; SGU: shade guide units; AT: At Home; Bo: Baseline; CP: Carbamide Peroxide; HP: Hydrogen Peroxide; IO: In Office; n.r.: not reported; NRS: Numerological Rating Scale; VAS: Visual Analog Scale. DIS: Discomfort interval Scale			1 Fluorescent Express White HP35% (Vista Dental, USA) 2 CPP-ACP (n.r.) 3 Whiteness HP 35% (FGM, Joinville, Brazil) 4 NovaMin Repair and Protect (GSK Sensodyne; Brentford, Middlesex, United Kinfdom) 5 CPP-ACPF (GC MI Paste Plus, Recaldent; Hasunuma-Cho, Itabashi-Ku, Tokyo, Japan) 6 7% hydrogen peroxide product (n.r.) 7 Renamel AfterBleach (Sangi Co., Ltd., Tokyo, Japan) 8 Whiteness HP Blue 35% (FGM, Joinville, Brazil) 9 Dessensibilize Nano P (FGM, Joinville, Brazil) 10 Carbamide peroxide 22% (3M™ ESPE™ OMNI™ WHITE&BRITE™ 22% carbamide peroxide tooth whitening system, Sumaré, SP, Brazil) 11 Hydrogen peroxide 35% (Farmaformula™ , Natal, RN, Brazil. 12 Professional Oral Care 38% (Miromed, Chiasso, Switzerland) 13 CPP-ACP GC Tooth Mousse (GC, Tokyo, Japan) 14 Whiteness HP Maxx 35% (FGM, Joinville, Brazil) 15 Opalescence Boost PF 40% (Ultradent Inc., South Jordan, UT, USA) 16 Teethmate AP (TAP, Kuraray Noritake, Dental INc., Okayama, Japan) 17 Nano-sized hydroxyapatite 2.5% (Authors' formulation) 18 Polaoffice 35% (SDI Innovative Dental Products, Australia) 19 Clinpro™ 500 Tooth Creme (3M ESPE, USA) 20 ACP Relief (Philiphs, Seattle, WA, USA) 21 Whiteness Perfect 16% (FGM, Joinville, Brazil) 22 Biosilicate microparticles (Vitrovita, São Carlos, Brazil)	

		23 Bioglass microparticles type 45S5 (Vitrovita, São Carlos, Brazil) 24 TION whitening gel 15% (GC America Inc) 25 Dash™ whitening gel 30% hydrogen peroxide (Discus dental, Culver City, USA) 26 Relief ACP (Discus dental, Culver City, USA) 27 Whiteness Automixx 35% (FGM, Joinville, Brazil) 28 Experimental desensitizing gel containing 10% calcium gluconate, 0.1% dexamethasone acetate, 10% potassium nitrate, and, 5% glutaraldehyde (Authors' formulation) 29 Opalescence PF 20% (Ultradent Products, South Jordan, UT)

6 DISCUSSÃO

Nesta sessão será descrita a discussão de forma resumida, informações detalhadas podem ser encontradas no artigo descrito anterior a sessão, bem como novos tópicos.

Os dessensibilizantes bioativos contendo cálcio são produtos obliterantes, que atuam com maior frequência nos processos de remineralização do tecido dental por meio da saturação superficial. Isso significa que quando esses agentes são aplicados, eles interagem com a superfície dental e podem ser retidos, fornecendo grandes quantidades de cálcio e fosfatos para interação com os tecidos (Parreiras et al. [12] 2020). Esses produtos passaram a ser utilizados antes e após o clareamento devido às alterações na morfologia do esmalte causadas pelos agentes clareadores (Acuña et al. [15] 2019). Embora essa mudança de morfologia seja transitória e reversível pelo efeito da saliva (Jager et al. [17] 2011; Sa et al. [18] 2012; Sa et al. [19] 2013), vários pesquisadores e fabricantes buscam reduzir ainda mais esses possíveis problemas. Outra abordagem que começou a ser avaliada em ECRs foi o impacto que tais produtos bioativos contendo cálcio teriam na redução da SD induzida pelo clareamento, que é o efeito colateral mais indesejável do clareamento dental.

Embora ainda não totalmente elucidado, parece que a SD induzida pelo clareamento é resultado do dano causado pelo PH no tecido conjuntivo vivo da estrutura dental. Devido ao seu baixo peso molecular, forte potencial oxidativo (Kwon e Wertz [4] 2015), rápida difusão, o PH atravessa os tecidos duros dentários e atinge a câmara pulpar (Kwon e Wertz [4] 2015) causando uma reação inflamatória aguda que pode eventualmente causar dor.

Embora não haja uma correlação precisa entre a difusão do PH e os sintomas clínicos, o raciocínio da avaliação de materiais obliterantes para reduzir a SD induzida pelo clareamento baseia-se no fato de que tais problemas podem reduzir a passagem de PH para a polpa, retardando a repostas inflamatória e permitindo mais tempo para a polpa lidar com o PH residual. O presente estudo não mostrou nenhuma redução do risco de SD espontânea, o que significa que esses produtos não podem evitar que os pacientes apresentem SD. De fato, isso está de acordo com achados laboratoriais anteriores que mostraram que nenhum dos dessensibilizadores testados até agora foi capaz de impedir completamente a difusão de PH para o tecido pulpar (Parreiras et al. [12] 2020; Barbosa et al. [31] 2020; Ma et al. [82] 2020).

No entanto, detectamos uma pequena diminuição na intensidade de SD quando dessensibilizantes bioativos contendo cálcio foram empregados. Alguns fatores podem estar envolvidos nesse achado positivo. Outros mecanismos de ação, além da obliteração, foram relatados por dessensibilizadores bioativos contendo cálcio. Alguns estudos *in vitro* demonstram que agentes divalentes de Ca^{2+} podem reduzir a transmissão do impulso nervoso, atuando como um produto dessensibilizante neural.(Markowitz et al. [83] 1991; Markowitz e Kim [84] 1992) No entanto, seu papel na redução da SD induzida pelo clareamento ainda carece de maiores investigações. Além disso, o PH também pode reagir com esses dessensibilizadores bioativos contendo cálcio, levando à formação de outros subprodutos, como o hidróxido de cálcio, reduzindo ainda mais o excesso de PH que se difunde na câmara pulpar (Mena-Serrano et al. [85] 2015).

A formação de produtos alcalinos na estrutura dental pode alterar o pH dos agentes clareadores para mais alcalino e consequentemente quebrar mais moléculas de PH devido a sua constante de dissociação (pka) ser mais alcalino em torno de 11,5 (Torres et al. [35] 2014), não afetando apenas a cinética de degradação, mas também os subprodutos formados na reação de desacoplamento (Torres et al. [35] 2014). Todas essas reações podem diminuir a concentração na polpa e consequentemente a SD (Acuña et al. [15] 2019; Balladares et al. [86] 2019; Loguercio et al. [87] 2017).

Embora a DM na intensidade do SD tenha sido estatisticamente significativa, a relevância desse achado é questionável do ponto de vista clínico. Por exemplo, uma mudança na intensidade do SD de 3 unidades EVA para 2 unidades EVA pode não ser de grande valor clinicamente, considerando que o SD induzido pelo clareamento é transitória e não dura mais de 48 horas. Tomados em conjunto com os achados da SD, podemos dizer que a maioria dos pacientes sentirá algum desconforto durante o tratamento, mas com uma intensidade de SD sutilmente mais baixa. Esse achado, embora positivo em favor dos agentes bioativos contendo cálcio, deve ser interpretado com cautela devido à baixa certeza do corpo de evidências coletado.

Para a avaliação do risco de viés, utilizou-se a ferramenta RoB 2.0 (Sterne et al. [88] 2019), que permite pesquisar em profundidade todas as fontes de informação no estudo publicado que possam levar a vieses. A maioria dos estudos elegíveis apresentou alto risco de viés devido a preocupações no processo de randomização.

A maioria dos estudos não se preocupou em relatar corretamente o processo de randomização. A maioria deles apenas mencionou que o estudo foi randomizado, mas sem maiores informações. A randomização precisa ser planejada a *priori*, escondida com segurança até a implementação e bem descrita no manuscrito final. Falhas na implementação aleatória podem resultar em grupos com características prognósticas desconhecidas e, portanto, a conclusão causa-efeito que os ECRs são capazes de fornecer não pode ser estabelecida. Desvios das intervenções pretendidas foi outra questão problemática nos estudos primários. Os participantes ou avaliadores podem dar atenção diferenciada ao protocolo implementado se estiverem cientes da atribuição do grupo.

Outras questões na metodologia dos estudos elegíveis merecem atenção. Em vez de medir a SD espontânea, alguns autores mediram a SD induzida por estímulos durante ou após o clareamento (Alexandrino et al. [70] 2017; Da Silva et al. [72] 2018; Gümüştaş e Dikmen [73] 2021; Pintado-Palomino et al. [79] 2015; Rashid e ElSalhy [80] 2021). Na opinião dos autores, a SD induzida por estímulos não é um resultado relevante centrado no paciente, uma vez que nem os pacientes nem os operadores induzem a SD de propósito em uma situação clínica. Talvez essa abordagem tenha sido utilizada pelos autores para aumentar o número de eventos no ECR para que o poder do estudo possa ser obtido mesmo com um tamanho amostral baixo. Os autores do presente estudo desencorajam o uso de SD induzida por estímulos em futuros ECRs ou pelo menos relatam os números de SD espontâneos nos achados do estudo.

Alguns estudos não relataram resultados importantes que seriam esperados em estudos de clareamento, como a mudança de cor. A redução da SD com dessensibilizantes contendo cálcio é importante, mas este efeito não pode comprometer a eficácia do clareamento. Em relação à mudança de cor, os dessensibilizantes bioativos contendo cálcio não interferiram negativamente no resultado na avaliação subjetiva e objetiva da mudança de cor. Mas, novamente, devemos ressaltar que a maioria dos estudos apresentou alto risco de viés e este fato junto com a imprecisão e, mas isso não aconteceu, mesmo que esses agentes diminuam a concentração de PH na estrutura dentária, e se depositem na superfície do esmalte, eles não interferem na mudança de cor.

Não incluímos na presente revisão sistemática estudos que avaliaram cremes dentais com dessensibilizantes bioativos contendo cálcio. A decisão foi tomada

porque o tempo de contato dos dentifrícios com as estruturas dentárias é muito diferente daquele utilizado topicamente. Na maioria dos estudos, o tempo de aplicação dos dessensibilizantes contendo cálcio variou de 5 a 10 min. Quando em dentifrícios, esses dessensibilizantes geralmente permanecem em contato com a superfície do esmalte por períodos inferiores a 3 minutos (tempo de escovação) e também são diluídos pela saliva, reduzindo ainda mais a ação do produto.

Nossa revisão não é uma atualização, mas uma nova questão de pesquisa que inclui todos os dessensibilizantes bioativos contendo cálcio para o manejo da SD induzida pelo clareamento. A revisão sistemática anterior (Hussainy e Govula [89] 2021) sobre este tema avaliou o efeito do fosfopeptídeo caseína-fosfato de cálcio amorfo, mas os autores não incluíram todos os artigos disponíveis deste produto que podem ser vistos na Tabela 2 do presente estudo. Além disso, muitas outras falhas metodológicas colocam o estudo em alto risco de viés (Hussainy e Govula [89] 2021).

Nossos achados mostram que a certeza da evidência foi baixa e muito baixa para os desfechos que avaliamos. Este resultado significa que muito precisa ser feito para melhorar a qualidade dos ECRs nos estudos de clareamento. Além disso, reconhecer essa limitação é o passo mais rápido para aprimorar o desenho e a implementação do projeto de estudo. ECRs futuros devem investigar outros tipos de agentes dessensibilizantes para prevenir ou reduzir os efeitos adversos da SD induzida por clareamento. Além disso, investigações adicionais podem se concentrar em uma meta-análise de rede para avaliar os vários dessensibilizantes com base em sua composição para complementar os achados de nosso estudo. Isso aumentaria o número de ECRs para uma futura revisão sistemática atualizada, aumentando a robustez das conclusões.

Reconhecemos que realizamos as meta-análises com estudos que utilizaram diferentes tipos e concentrações, agentes clareadores e protocolos de dessensibilização. Isso geralmente levanta críticas sobre a viabilidade de realizar uma meta-análise. No entanto, devemos considerar que o objetivo das meta-análises raramente é sintetizar dados de um conjunto de estudos idênticos. As revisões sistemáticas da literatura com uma questão de pesquisa mais ampla contêm uma diversidade específica entre os estudos, o que é inevitável e desejável. Isso permite aos pesquisadores explorar a dispersão dos estudos, usando estatísticas de heterogeneidade e levantando hipóteses que podem explicar por que uma intervenção

pode funcionar em algumas populações e não em outras. Essa heterogeneidade é o que acontece no mundo real; portanto, esta questão exploratória é um dos objetivos das revisões sistemáticas.

7 CONCLUSÃO

Observamos uma pequena redução da SD induzida pelo clareamento quando dessensibilizantes bioativos contendo cálcio tópicos foram aplicados durante o clareamento, porém essa redução foi pequena e a certeza da evidência muito baixa. Além disso, o risco de SD e alterações de cor não foram afetados pela aplicação desses dessensibilizantes com baixa e muito baixa certeza de evidência.

REFERÊNCIAS

1. Theobald AH, Wong BK, Quick AN, Thomson WM. The impact of the popular media on cosmetic dentistry. N Z Dent J. 2006; Sep;102(3):58-63.

2. Martel J, Powell E, Murina A. The effect of Instagram and photograph editing on seeking dermatologic care. J Cosmet Dermatol. 2020; Oct;19(10):2732-5.

3. Bonafé E, Rezende M, Machado MM, Lima SNL, Fernandez E, Baldani MMP, et al. Personality traits, psychosocial effects and quality of life of patients submitted to dental bleaching. BMC oral health. 2021; Jan 6;21(1):7.

4. Kwon SR, Wertz PW. Review of the Mechanism of Tooth Whitening. J Esthet Restor Dent. 2015; Sep-Oct;27(5):240-57.

5. Reis A, da Silva LM, Martins L, Loguercio AJCDR. In-office tooth whitening. 2018;2(1):1-8.

6. Haywood VB, Sword RJ. Tray bleaching status and insights. J Esthet Restor Dent. 2021; Jan;33(1):27-38.

7. de Sá JL, Silva JS, Herkrath FJ, Favoreto MW, Reis A, Silva LM, et al. In-office bleaching with complete cervical third protection protocol: A split-mouth, double-blind, randomized clinical trial. Am J Dent. 2021; Oct;34(5):281-5.

8. Donassollo SH, Donassollo TA, Coser S, Wilde S, Uehara JLS, Chisini LA, et al. Triple-blinded randomized clinical trial comparing efficacy and tooth sensitivity of in-office and at-home bleaching techniques. J Appl Oral Sci. 2021;29:e20200794.

9. Kothari S, Jum'ah AA, Gray AR, K ML, Yap M, Brunton PA. A randomized clinical trial investigating three vital tooth bleaching protocols and associated efficacy, effectiveness and participants' satisfaction. J Dent. 2020; Apr;95:103322.

10. Martini EC, Favoreto MW, Coppla FM, Loguercio AD, Reis A. Evaluation of reservoirs in bleaching trays for at-home bleaching: a split-mouth single-blind randomized controlled equivalence trial. J Appl Oral Sci. 2020;28:e20200332.

11. Meireles SS, Santos ME, Lustosa Í MC, Leite ELL. Effects of a reduced in-office bleaching protocol with 37.5% hydrogen peroxide on effectiveness and tooth sensitivity: A double-blind randomized clinical trial. J Esthet Restor Dent. 2021; Jul;33(5):824-31.

12. Parreiras SO, Favoreto MW, Lenz RE, Serra ME, Borges CPF, Loguercio AD, et al. Effect of Prior Application of Desensitizing Agent on the Teeth Submitted to In-Office Bleaching. Braz Dent J. 2020; Jun;31(3):236-43.

13. Coppla FM, Freire A, Bittencourt B, Armas-Vega A, Benítez VE, Calixto AL, et al. Influence of simplified, higher-concentrated sodium ascorbate application protocols on bond strength of bleached enamel. J Clin Exp Dent. 2019; Jan;11(1):e21-e6.

14. Coceska E, Gjorgievska E, Coleman NJ, Gabric D, Slipper IJ, Stevanovic M, et al. Enamel alteration following tooth bleaching and remineralization. J Microsc. 2016; Jun;262(3):232-44.

15. Acuña ED, Parreiras SO, Favoreto MW, Cruz GP, Gomes A, Borges CPF, et al. In-office bleaching with a commercial 40% hydrogen peroxide gel modified to have different pHs: Color change, surface morphology, and penetration of hydrogen peroxide into the pulp chamber. J Esthet Restor Dent. 2019; Feb 20.

16. Cavalli V, Rosa DAD, Silva DPD, Kury M, Liporoni PCS, Soares LES, et al. Effects of experimental bleaching agents on the mineral content of sound and demineralized enamels. J Appl Oral Sci. 2018; Oct 4;26:e20170589.

17. Jager DH, Vieira AM, Ligtenberg AJ, Bronkhorst E, Huysmans MC, Vissink A. Effect of salivary factors on the susceptibility of hydroxyapatite to early erosion. Caries Res. 2011;45(6):532-7.

18. Sa Y, Chen D, Liu Y, Wen W, Xu M, Jiang T, et al. Effects of two in-office bleaching agents with different pH values on enamel surface structure and color: an in situ vs. in vitro study. J Dent. 2012; Jul;40 Suppl 1:e26-34.

19. Sa Y, Sun L, Wang Z, Ma X, Liang S, Xing W, et al. Effects of two in-office bleaching agents with different pH on the structure of human enamel: an in situ and in vitro study. Oper Dent. 2013; Jan-Feb;38(1):100-10.

20. Kwon SR, Dawson DV, Wertz PW. Time Course of Potassium Nitrate Penetration into the Pulp Cavity and the Effect of Penetration Levels on Tooth Whitening Efficacy. J Esthet Restor Dent. 2016; Mar;28 Suppl 1:S14-22.

21. Martini EC, Favoreto MW, Rezende M, de Geus JL, Loguercio AD, Reis A. Topical application of a desensitizing agent containing potassium nitrate before dental bleaching: a systematic review and meta-analysis. Clin Oral Investig. 2021; Jul;25(7):4311-27.

22. Browning WD, Cho SD, Deschepper EJ. Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity. J Esthet Restor Dent. 2012; Aug;24(4):268-76.

23. de Araújo IDT, de Sousa Santos K, das Neves Peixoto TVO, Costa MJF, de Assunção IV, Borges BCD. The combined use of systemic analgesic/anti-inflammatory

drugs and a bioactive topical desensitizer for reduced in-office bleaching sensitivity without jeopardizing the hydrogen peroxide efficacy: a randomized, triple blinded, split-mouth clinical trial. Clin Oral Investig. 2021; Apr 22.

24. Mehta D, Jyothi S, Moogi P, Finger WJ, Sasaki K. Novel treatment of in-office tooth bleaching sensitivity: A randomized, placebo-controlled clinical study. J Esthet Restor Dent. 2018; May;30(3):254-8.

25. Oldoini G, Bruno A, Genovesi AM, Parisi L. Effects of Amorphous Calcium Phosphate Administration on Dental Sensitivity during In-Office and At-Home Interventions. Dent J (Basel). 2018; Oct 1;6(4).

26. Singh M, Mahajan P, Monga P, Mahajan S, Singla D, Kaur NJE. Comparative evaluation of effectiveness of sodium fluoride and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) in treating postoperative sensitivity associated with in-office vital tooth bleaching: A clinical study. 2017;29(1):26.

27. Tawfik SS, Khairy MAE, ElBaz MAEJF. Evaluation of post-bleaching hypersensitivity using desensitizing agent before and/or after in-office bleaching: A randomized clinical trial. 2019;8(1762):1762.

28. Yassin O, Milly H. Effect of CPP-ACP on efficacy and postoperative sensitivity associated with at-home vital tooth bleaching using 20% carbamide peroxide. Clin Oral Investig. 2019; Apr;23(4):1555-9.

29. Gomes MN, Rodrigues FP, Silikas N, Francci CE. Micro-CT and FE-SEM enamel analyses of calcium-based agent application after bleaching. Clin Oral Investig. 2018; Mar;22(2):961-70.

30. Ubaldini A, Pascotto RC, Sato F, Soares VO, Zanotto ED, Baesso ML. Effects of Bioactive Agents on Dentin Mineralization Kinetics After Dentin Bleaching. Oper Dent. 2020; May/Jun;45(3):286-96.

31. Barbosa JG, Benetti F, de Oliveira Gallinari M, Carminatti M, da Silva ABD, Lopes INI, et al. Bleaching gel mixed with MI Paste Plus reduces penetration of H(2)O(2) and damage to pulp tissue and maintains bleaching effectiveness. Clin Oral Investig. 2020; Mar;24(3):1299-309.

32. Haywood VB. History, safety, and effectiveness of current bleaching techniques and applications of the nightguard vital bleaching technique. Quintessence Int. 1992; Jul;23(7):471-88.

33. Haywood VB, Heymann HO. Nightguard vital bleaching. Quintessence Int. 1989; Mar;20(3):173-6.

34. Luque-Martinez I, Reis A, Schroeder M, Muñoz MA, Loguercio AD, Masterson D, et al. Comparison of efficacy of tray-delivered carbamide and hydrogen peroxide for at-home bleaching: a systematic review and meta-analysis. Clin Oral Investig. 2016; Sep;20(7):1419-33.

35. Torres CR, Crastechini E, Feitosa FA, Pucci CR, Borges AB. Influence of pH on the effectiveness of hydrogen peroxide whitening. Oper Dent. 2014; Nov-Dec;39(6):E261-8.

36. Terra R, da Silva KL, Vochikovski L, Sutil E, Rezende M, Loguercio AD, et al. Effect of Daily Usage Time of 4% Hydrogen Peroxide on the Efficacy and Bleaching-induced Tooth Sensitivity: A Single-blind Randomized Clinical Trial. Oper Dent. 2021; Aug 23.

37. Chemin K, Rezende M, Costa MC, Salgado A, de Geus JL, Loguercio AD, et al. Evaluation of At-home Bleaching Times on Effectiveness and Sensitivity with 10% Hydrogen Peroxide: A Randomized Controlled Double-blind Clinical Trial. Oper Dent. 2021; Aug 9.

38. Chemin K, Rezende M, Loguercio AD, Reis A, Kossatz S. Effectiveness of and Dental Sensitivity to At-home Bleaching With 4% and 10% Hydrogen Peroxide: A Randomized, Triple-blind Clinical Trial. Oper Dent. 2018; May/Jun;43(3):232-40.

39. Kiyuna RC, Martins LM, Hanzen TA, Reis A, Loguercio AD, Silva LM. Comparison of the Effect of Agitation on Whitening and Tooth Sensitivity of In-Office Bleaching: A Randomized Clinical Trial. Oper Dent. 2021; Mar 1;46(2):143-50.

40. Maran BM, Vochikovski L, Hortkoff DRA, Stanislawczuk R, Loguercio AD, Reis A. Bleaching sensitivity with a desensitizing in-office bleaching gel: a randomized double-blind clinical trial. Quintessence Int. 2020;51(10):788-97.

41. Watts A, Addy M. Tooth discolouration and staining: a review of the literature. Br Dent J. 2001; Mar 24;190(6):309-16.

42. Sulieman M. An overview of bleaching techniques: I. History, chemistry, safety and legal aspects. Dent Update. 2004; Dec;31(10):608-10, 12-4, 16.

43. Eimar H, Siciliano R, Abdallah MN, Nader SA, Amin WM, Martinez PP, et al. Hydrogen peroxide whitens teeth by oxidizing the organic structure. J Dent. 2012; Dec;40 Suppl 2:e25-33.

44. Eimar H, Marelli B, Nazhat SN, Abi Nader S, Amin WM, Torres J, et al. The role of enamel crystallography on tooth shade. J Dent. 2011; Dec;39 Suppl 3:e3-10.

45. Fattibene P, Carosi A, De Coste V, Sacchetti A, Nucara A, Postorino P, et al. A comparative EPR, infrared and Raman study of natural and deproteinated tooth enamel and dentin. Phys Med Biol. 2005; Mar 21;50(6):1095-108.

46. Kawamoto K, Tsujimoto Y. Effects of the hydroxyl radical and hydrogen peroxide on tooth bleaching. J Endod. 2004; Jan;30(1):45-50.

47. Cardoso PC, Reis A, Loguercio A, Vieira LC, Baratieri LN. Clinical effectiveness and tooth sensitivity associated with different bleaching times for a 10 percent carbamide peroxide gel. J Am Dent Assoc. 2010; Oct;141(10):1213-20.

48. de Geus JL, Wambier LM, Boing TF, Loguercio AD, Reis A. At-home Bleaching With 10% vs More Concentrated Carbamide Peroxide Gels: A Systematic Review and Meta-analysis. Oper Dent. 2018; Jul/Aug;43(4):E210-e22.

49. Sutil E, da Silva KL, Terra RMO, Burey A, Rezende M, Reis A, et al. Effectiveness and adverse effects of at-home dental bleaching with 37% versus 10% carbamide peroxide: A randomized, blind clinical trial. J Esthet Restor Dent. 2020; Nov 10.

50. Abrantes PS, Xavier CM, Melo A, Assunção IV, Borges BC. Efficacy, longevity, and bleaching sensitivity of carbamide and hydrogen peroxides for in-office bleaching: A 6-month randomized, double blind, split-mouth clinical trial. Am J Dent. 2021; Feb;34(1):17-22.

51. Al-Qunaian TA, Matis BA, Cochran MA. In vivo kinetics of bleaching gel with three-percent hydrogen peroxide within the first hour. Oper Dent. 2003; May-Jun;28(3):236-41.

52. Matis BA, Gaiao U, Blackman D, Schultz FA, Eckert GJ. In vivo degradation of bleaching gel used in whitening teeth. J Am Dent Assoc. 1999; Feb;130(2):227-35.

53. Favoreto MW, Hass V, Maran BM, Paula E, Wachter F, Lima SNL, et al. At-home bleaching with a novel carbamide peroxide polymeric nanoparticle gel ? A multicenter randomized controlled trial. Oper Dent. 2022 in press.

54. Kury M, Lins RBE, Resende BA, Picolo MZD, André CB, Cavalli V. The influence of the renewal or the single application of the peroxide gel on the efficacy and tooth sensitivity outcomes of in-office bleaching-A systematic review and meta-analysis. J Esthet Restor Dent. 2021; Oct 8.

55. de Paula EA, Nava JA, Rosso C, Benazzi CM, Fernandes KT, Kossatz S, et al. In-office bleaching with a two- and seven-day intervals between clinical sessions: A randomized clinical trial on tooth sensitivity. J Dent. 2015; Apr;43(4):424-9.

56. Cardenas AFM, Maran BM, Araújo LCR, de Siqueira FSF, Wambier LM, Gonzaga CC, et al. Are combined bleaching techniques better than their sole application? A systematic review and meta-analysis. Clin Oral Investig. 2019; Oct;23(10):3673-89.

57. Guasso B, Salomone P, Nascimento PC, Pozzobon RT. Release time of residual oxygen after dental bleaching with 35% hydrogen peroxide: effect of a catalase-based neutralizing agent. Gen Dent. 2016; May-Jun;64(3):56-9.

58. Markowitz K. Pretty painful: why does tooth bleaching hurt? Med Hypotheses. 2010; May;74(5):835-40.

59. Cooper JS, Bokmeyer TJ, Bowles WH. Penetration of the pulp chamber by carbamide peroxide bleaching agents. J Endod. 1992; Jul;18(7):315-7.

60. Favoreto MW, Madureira MP, Hass V, Maran BM, Parreiras SO, Borges CPF, et al. A novel carbamide peroxide polymeric nanoparticle bleaching gel: Color change and hydrogen peroxide penetration inside the pulp cavity. J Esthet Restor Dent. 2021; Mar;33(2):277-83.

61. Carregosa Santana ML, Leal PC, Reis A, Faria ESAL. Effect of anti-inflammatory and analgesic drugs for the prevention of bleaching-induced tooth sensitivity: A systematic review and meta-analysis. J Am Dent Assoc. 2019; Oct;150(10):818-29.e4.

62. Almassri HNS, Zhang Q, Yang X, Wu X. The effect of oral anti-inflammatory drugs on reducing tooth sensitivity due to in-office dental bleaching: A systematic review and meta-analysis. J Am Dent Assoc. 2019; Oct;150(10):e145-e57.

63. Costa R, Moraes S, Lemos C, SoutoMaior JR, Vasconcelos BDE, Pellizzer EP. Effect of Analgesic Drugs on Tooth Sensitivity Induced by In-office Dental Bleaching: A Systematic Review and Meta-analysis. Oper Dent. 2020; Mar/Apr;45(2):E66-e76.

64. Favoreto MW, Vochikovski L, Terra RMO, Campos VS, Santos ME, Meireles SS, et al. Topical application of Otosporin® before in-office bleaching: a split mouth, triple-blind, multicenter randomized clinical trial. Clin Oral Investig. 2021; Oct 19.

65. Vilela AP, Rezende M, Terra RMO, da Silva KL, Sutil E, Calixto AL, et al. Effect of topical application of nanoencapsulated eugenol on dental sensitivity reduction after

in-office dental bleaching: a randomized, triple-blind clinical trial. J Esthet Restor Dent. 2021; Jun;33(4):660-7.

66. Rezende M, Chemin K, Vaez SC, Peixoto AC, Rabelo JF, Braga SSL, et al. Effect of topical application of dipyrone on dental sensitivity reduction after in-office dental bleaching: A randomized, triple-blind multicenter clinical trial. J Am Dent Assoc. 2018; May;149(5):363-71.

67. de l'Eclairage CIJPC. Recommendations on uniform color spaces, color-difference equations, psychometric color terms. 1978.

68. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons: 2019.

69. Adil HM, Jouhar R, Ahmed MA, Basha S, Ahmed N, Abbasi MS, et al. Comparison of Casein Phosphopeptide with Potassium Nitrate and Sodium Monofluorophosphate Desensitizing Efficacy after In-Office Vital Bleaching—A Randomized Trial. 2021;11(19):9291.

70. Alexandrino LD, Alencar CM, Silveira A, Alves EB, Silva CM. Randomized clinical trial of the effect of NovaMin and CPP-ACPF in combination with dental bleaching. J Appl Oral Sci. 2017; May-Jun;25(3):335-40.

71. Crescente CL, Pinto CFJRBdO. Análise da sensibilidade após o uso prévio de dessensibilizantes em clareamento dental. 2016;73(1):34.

72. Da Silva RC, De Melo alenCaR C, Silva BHR, DE PAULA BLF, BARROS APO, DA SILVEIRA ADS, et al. A Clinical, Randomised, Double-Blind Study on the Use of Nano-Hydroxyapatite and Arginine During at-Home Tooth Bleaching. 2018;12(12).

73. Gümüştaş B, Dikmen B. Effectiveness of remineralization agents on the prevention of dental bleaching induced sensitivity: A randomized clinical trial. Int J Dent Hyg. 2021; May 21.

74. Lima TM, França FMG, Amaral FLB, Turssi CP, Basting RT. The use of desensitizing agents during in-office bleaching might not decrease tooth bleaching sensitivity: a randomized clinical trial. The European Journal of Esthetic Dentistry. 2021 in press.

75. Loguercio AD, Tay LY, Herrera DR, Bauer J, Reis A. Effectiveness of nano-calcium phosphate paste on sensitivity during and after bleaching: a randomized clinical trial. Braz Oral Res. 2015;29:1-7.

76. Maghaireh GA, Alzraikat H, Guidoum A. Assessment of the effect of casein phosphopeptide-amorphous calcium phosphate on postoperative sensitivity associated with in-office vital tooth whitening. Oper Dent. 2014; May-Jun;39(3):239-47.

77. Nanjundasetty JK, Ashrafulla M. Efficacy of desensitizing agents on postoperative sensitivity following an in-office vital tooth bleaching: A randomized controlled clinical trial. J Conserv Dent. 2016; May-Jun;19(3):207-11.

78. NCT03026725. Effect of Tri Calcium Phosphate on Efficacy and Sensitivity With Vital Tooth Whitening Using 20% Carbamide Peroxide. https://clinicaltrialsgov/ct2/show/NCT03026725. 2017.

79. Pintado-Palomino K, Peitl Filho O, Zanotto ED, Tirapelli C. A clinical, randomized, controlled study on the use of desensitizing agents during tooth bleaching. J Dent. 2015; Sep;43(9):1099-105.

80. Rashid S, ElSalhy M. Efficacy of MI Paste® on Bleaching-Related Sensitivity: Randomized Clinical Trial. Int J Dent. 2021;2021:9963823.

81. Vochikovski L, Rezende M, Terra RO, Silva KLd, Favoreto MW, Farago PV, et al. Effect of an experimental desensitizing gel on bleaching induced tooth sensitivity after in-office bleaching - a double-blind randomized controlled trial. 2022 in press.

82. Ma Q, Chen J, Xu X, Wang T. Impact of transparent tray-based application of bioactive glasses desensitizer on the permeability of enamel and dentin to hydrogen peroxide: an in vitro study. BMC oral health. 2020; Apr 10;20(1):103.

83. Markowitz K, Bilotto G, Kim S. Decreasing intradental nerve activity in the cat with potassium and divalent cations. Arch Oral Biol. 1991;36(1):1-7.

84. Markowitz K, Kim S. The role of selected cations in the desensitization of intradental nerves. Proc Finn Dent Soc. 1992;88 Suppl 1:39-54.

85. Mena-Serrano AP, Parreiras SO, do Nascimento EM, Borges CP, Berger SB, Loguercio AD, et al. Effects of the concentration and composition of in-office bleaching gels on hydrogen peroxide penetration into the pulp chamber. Oper Dent. 2015; Mar-Apr;40(2):E76-82.

86. Balladares L, Alegría-Acevedo LF, Montenegro-Arana A, Arana-Gordillo LA, Pulido C, Salazar-Gracez MT, et al. Effects of pH and Application Technique of In-office Bleaching Gels on Hydrogen Peroxide Penetration into the Pulp Chamber. Oper Dent. 2019; Nov/Dec;44(6):659-67.

87. Loguercio AD, Servat F, Stanislawczuk R, Mena-Serrano A, Rezende M, Prieto MV, et al. Effect of acidity of in-office bleaching gels on tooth sensitivity and whitening: a two-center double-blind randomized clinical trial. Clin Oral Investig. 2017; Dec;21(9):2811-8.

88. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2019; Aug 28;366:l4898.

89. Hussainy N, Govula K. CASEIN PHOSPHOPEPTIDE AMORPHOUS CALCIUM PHOSPHATE, A POTENT DESENSITIZING AGENT, TO REDUCE POSTOPERATIVE SENSITIVITY AFTER VITAL TOOTH BLEACHING -A SYSTEMATIC REVIEW AND META-ANALYSIS. International Journal of Scientific Research. 2021;10(03).

ANEXO A

REGISTRO DO PROJETO PELO *INTERNATIONAL PROSPECTIVE REGISTER OF SYSTEMATIC REVIEWS* (PROSPERO)

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Topical application of calcium-based desensitizer in dental bleaching: a systematic review and meta-analysis

Michael Willian Favoreto, Heloise Forville de Andrade, Fabiana Dias Simas Dreweck, Alessandro Dourado Loguercio, Alessandra Reis

Citation

Michael Willian Favoreto, Heloise Forville de Andrade, Fabiana Dias Simas Dreweck, Alessandro Dourado Loguercio, Alessandra Reis. Topical application of calcium-based desensitizer in dental bleaching: a systematic review and meta-analysis. PROSPERO 2020 CRD42020178042 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020178042

Review question

The risk and intensity of tooth sensitivity in adults submitted to dental bleaching are lower when a calcium-based desensitizer is used compared to the bleaching without desensitization?

Searches

To identify trials to be included for this review, we will search on the electronic databases MEDLINE via

PubMeb, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database

(LILACS), Brazilian Library in Dentistry (BBO), EMBASE and Cochrane Library. 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 without restrictions to publication date or languages. No restrictions will be placed on

the publication date or languages, and all relevant studies will be translated and reviewed. We will search the

abstracts of the annual conference of the International Association for Dental Research (IADR) and their

regional divisions (1990–2020) 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 theses using the ProQuest Dissertations and Theses Fulltext 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 plataform (http://apps.who.int/trialsearch/), the ClinicalTrials.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

Randomized controlled trials that compare the risk and intensity of tooth sensitivity produced by dental bleaching with and without application of calcium-based desensitizers. We will include parallel, split-month or cross-over clinical trials in humans.

Quality assessments of the included trials will be evaluated by two independent reviewers using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. The assessment criteria contains six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. All these domains will be evaluated at the study level.

During data extraction and risk of bias assessment, any disagreements between the reviewers will be resolved through discussion, and if needed, by consulting a third reviewer.

For each aspect of the quality assessment, the risk of bias of each domain will be scored following the recommendations of the Cochrane Handbook for Systematic reviews of Interventions 5.1.0 (http://handbook.cochrane.org). The judgment for each entry will involve recording 'yes' indicating low risk of bias, 'no' indicating high risk of bias, and 'unclear' indicating either lack of information or uncertainty over the potential for bias.

Only studies classified as low or unclear risk of bias will be included.

Strategy for data synthesis

The extracted data will be analyzed using Revman (Review Manager version 5.3 software, Cochrane

Collaboration, Copenhagen, Denmark). Data from eligible studies will be either dichotomous (absolute risk of

pain) or continuous (pain intensity and color change). The outcomes will be summarized by the mean difference for the continuous data and the risk ratio for dichotomous data. For both summary measures, the 95% confidence interval (CI) will be calculated. We will apply the random-effect model for all meta-analysis using the inverse variance method.

Analysis of subgroups or subsets

In case studies differ in their risk of bias, subgroup analysis grouping low/unclear risk vs high risk of bias will be performed. Other possible subgroup analysis may be based on the type of dental bleaching (at-home and in-office).

Contact details for further information

Michael Willian Favoreto
michaelfavoreto@hotmail.com

Organisational affiliation of the review

State University of Ponta Grossa
www.uepg.br

Review team members and their organisational affiliations

Mr Michael Willian Favoreto. Universidade Estadual de Ponta Grossa
Mrs Heloise Forville de Andrade. Universidade Estadual de Ponta Grossa
Professor Fabiana Dias Simas Dreweck. Centro de Ensino Superior de Campos Gerais
Professor Alessandro Dourado Loguercio. Universidade Estadual de Ponta Grossa
Alessandra Reis. Universidade Estadual de Ponta Grossa

Type and method of review

Intervention, Meta-analysis, Systematic review

Anticipated or actual start date

06 April 2020

Anticipated completion date

30 September 2020

Funding sources/sponsors

None

Condition or domain being studied
Bleaching-induced tooth sensitivity.

Participants/population
Inclusion criteria: Adults 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 pathological conditions such as dental caries, need of endodontics, orthodontics or periodontal treatment. Patients that already underwent dental bleaching and with poor oral hygiene.

Intervention(s), exposure(s)
Dental bleaching with the application of calcium-based desensitizing agents.

Comparator(s)/control
Dental bleaching without application of any type of desensitizing agent

Main outcome(s)
1) Risk of tooth sensitivity (percentage of patients that experienced bleaching induced tooth sensitivity at least once during the treatment)

2) Tooth sensitivity intensity (measured with any pain scale)

* Measures of effect

Risk of tooth sensitivity = we will use the risk ratio

Tooth sensitivity intensity = preferably we will employ the mean difference for VAS scale. However, if many different primary studies report tooth sensitivity using other pain scales, we will include them and use the standardized mean difference as the effect measure.

Additional outcome(s)
Color change in Delta E - CIELab system obtained in a spectrophotometer (e.g., Vita Easyshade, Vita Zahnfabrik). Color change in shade guide units (e.g. Vita Classical Shade Guide or Vita Bleachedguide).

In both cases, we will take the color change taken soon after bleaching in periods ranging from 1 week post bleaching up to 3 months post bleaching. In case a study report more than one study follow-up we will choose the most recent one within this period range.

* Measures of effect

For each color instrument, we will use the mean difference. Preferably we will include color change in Delta E and Delta SGU measured with Vita Classical shade guide.

Data extraction (selection and coding)
Articles will be selected by title and abstracts according to the previously described search strategy. Articles that appear in more than one database will be considered only once. Full-text articles will also be obtained when the title and abstract have insufficient information to make a clear decision. Subsequently, three reviewers will classify those that met the inclusion criteria. To handle with such a large number of studies, we will use a study ID for each eligible study, combining first author and year of publication. Any disagreement between the reviewers over the eligibility of particular studies will be resolved through discussion with a fourth reviewer.

Risk of bias (quality) assessment

Conflicts of interest

Language
English

Country
Brazil

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
05 July 2020

Date of first submission
08 April 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
05 July 2020