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AVALIAÇÃO DE PROTOCOLOS DE CLAREAMENTO ATRAVÉS DE ENSAIOS CLÍNICOS RANDOMIZADOS, REVISÕES SISTEMÁTICAS E META-ANÁLISES

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

Orientadora: Profª. Drª. Alessandra Reis

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BIANCA MEDEIROS MARAN

Avaliação de protocolos de clareamento através de ensaios clínicos randomizados, revisões sistemáticas e meta-análises.

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

Ponta Grossa, 8 de junho de 2018

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Dedico este trabalho ao meu esposo, Luan Maran, que de forma especial e carinhosa me deu força e coragem, me apoiando nos momentos de dificuldades.

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DADOS CURRICULARES

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RESUMO

Maran, B.M. **Avaliação de protocolos de clareamento através de ensaios clínicos randomizados, revisões sistemáticas e meta-análises.** [Tese] Doutorado em Dentística Restauradora. Ponta Grossa: Universidade Estadual de Ponta Grossa; 2018.

Objetivos: Avaliar a eficácia e sensibilidade dental (SD) utilizando agentes dessensibilizantes incorporados ao gel no clareamento caseiro (1) e em consultório (2), no uso da ativação com luz no clareamento em consultório com alta e baixa concentração de peróxido de hidrogênio (3 e 4); no clareamento combinado (consultório e caseiro) vs. isolado (5), além de avaliar a conformidade dos estudos clínicos randomizados (ECRs) de clareamento com o CONSORT e o risco de viés desses estudos pela ferramenta Cochrane (6). **Metodologias:** Para este trabalho, foram feitos seis estudos: dois ECRs e quatro revisões sistemáticas (RSs), sendo que o estudo (4) foi uma RS de comparação mista de tratamentos (MTC). Os ECRs (1 e 2) foram triplo-cegos, boca-dividida e o tratamento clareador foi realizado em 120 pacientes livres de cárie, conforme critérios de inclusão e exclusão, sendo 60 em cada estudo. Os agentes dessensibilizantes incorporados ao gel foram, 3% de nitrato de potássio e 0,2% de fluoreto de sódio (1), e 5% de nitrato de potássio (2). No estudo (1) uma moldeira foi usada três horas diariamente por 21 dias, no estudo (2) foi feita uma aplicação única de 50 minutos em duas sessões com intervalo de sete dias entre elas. Foram avaliados o risco absoluto e a intensidade da SD por meio das escalas visual analógica 0-10 cm e de classificação numérica 0-4 durante três semanas no estudo (1) e durante e até 48 horas após cada sessão no estudo (2); a alteração de cor foi registrada utilizando as escalas de cor Vita Classical, Bleachedguide (ΔUEV) e espectrofotômetro Easyshade (ΔE*) antes, durante e após 30 dias do término de cada tratamento. O risco absoluto e a intensidade da SD foram avaliadas pelos testes de *McNemar* e *Wilcoxon Signed Rank*, respectivamente ($\alpha = 0,05$), a eficácia do clareamento foi avaliada pelos testes de *Wilcoxon Signed Rank* (ΔUEV) e teste t para dados pareados (ΔE*) ($\alpha = 0,05$). Nas RSs (3-6) foram feitas buscas por termos específicos sobre o tema em diferentes bases de dados e literatura cinzenta. O risco de viés foi avaliado usando a ferramenta de Colaboração Cochrane. Meta-análises foram conduzidas para mudança de cor (ΔE*, ΔSGU), risco e intensidade de SD, usando modelo de efeitos aleatórios. A heterogeneidade foi avaliada com o teste Q de Cochran e a estatística I^2. A qualidade de evidência (GRADE) foi avaliada nos estudos (3) e (5). **Resultados:** No estudo (1), não houve diferenças entre os grupos na cor, no risco e intensidade da SD ($p > 0,05$), já no estudo (2) foram observadas diferenças apenas na redução da intensidade da SD para o grupo com agente dessensibilizante nas primeiras 24 horas ($p < 0,01$). Nas RSs após a busca dos estudos, restaram 21 (3), 28 (4), 11 (5), 185 (6) ECRs. Na RS (3) não houve diferença na cor e na SD ($p > 0,05$), e a qualidade de evidencia foi graduada como moderada para ΔE* e risco de SD, e muito baixa e baixa para ΔUEV e intensidade da SD, respectivamente. Na RS de MTC (4), não houve diferença na cor sem o uso da luz ou com diferentes fontes de luz usadas. Na RS (5) não houve diferença na cor no clareamento combinado vs. em consultório ($p > 0,05$) e não foram obtidos dados disponíveis para avaliação do risco e intensidade da SD; no clareamento combinado vs. caseiro não foram observadas diferenças para ΔE*, ΔSGU e risco de SD, porém, menor intensidade de SD foi detectada no clareamento caseiro isolado com diferença de média padronizada de 0,86 (IC 95% 0,31-1,41), e a qualidade de evidência foi

graduada como moderada para alteração de cor em ΔE*, e baixa ou muito baixa para as demais análises. Na RS (6) na classificação de adesão ao CONSORT dos estudos, a média geral foi 16,7 ± 5,4 pontos (de 32 pontos no total) e apenas 7,6% foram julgados como baixo risco de viés. **Conclusões:** A incorporação dos agentes dessensibilizantes nos géis clareadores usados neste trabalho não afetou a cor e não reduziu a SD no clareamento caseiro (1), porém diminuiu a intensidade da SD no clareamento em consultório (2). O uso da ativação com luz no clareamento em consultório não melhorou a cor nem afetou a SD independente da concentração de peróxido de hidrogênio utilizada (3) e igualmente não afetou a cor no estudo (4). No clareamento combinado vs. isolado (5), baixa intensidade de SD foi encontrada no clareamento caseiro, quando este foi realizado isoladamente. E no estudo (6) concluiu-se que a adesão ao CONSORT em ECRs de diferentes técnicas de clareamento é baixa e possuem alto risco de viés.

Palavras-Chaves: Clareamento dental. Clareadores. Peróxido de hidrogênio. Dessensibilizantes dentinários. Sensibilidade da dentina. Estudo clínico. Revisão sistemática.

ABSTRACT

Maran, B.M. **Evaluation of clinical protocols for dental bleaching through randomized clinical trials, systematic reviews and meta-analysis**. **[**Thesis] Doctorate in Restorative Dentistry. Ponta Grossa: State University of Ponta Grossa; 2018.

Objectives: To evaluate efficacy and tooth sensitivity (TS) through the use of desensitizing agents incorporated into the gel in the at-home (1) and in the in-office bleaching (2), in the use of light activation in the in-office bleaching with high and low hydrogen peroxide concentration (3 and 4); in combined (at-home and in-office) vs. isolated bleaching (5), in addition to assessing the conformity of the randomized clinical trials (RCTs) of bleaching with CONSORT and the risk of bias of these studies by the Cochrane tool (6). **Methodologies:** Six studies: two RCTs and four systematic reviews (SRs) were made for this work, the study (4) was a mixed-treatment comparison (MTC). The RCTs (1 and 2) were triple-blind, split-mouth and the bleaching treatment was performed on 120 caries-free patients, according to inclusion and exclusion criteria, of which 60 were in each study. The desensitizing agents incorporated into the gel were 3% potassium nitrate and 0.2% sodium fluoride (1), and 5% potassium nitrate in study (2). In study (1) a tray was used three hours daily for 21 days, in study (2) a single application of 50 minutes was made in two sessions with 7-days intervals between them. Were assessed the absolute risk and the intensity of TS using the 0-10 cm visual analog and 0-4 numerical rating scales for 21 days in the study (1) and during 48 hours after each study session (2); the color change was recorded using the Vita Classical, Bleachedguide (ΔSGU) and Easyshade spectrophotometer (ΔE*) color scales before, during and after 30 days of the end of each treatment. The absolute risk and intensity of TS were assessed by the McNemar and Wilcoxon Signed Rank tests, respectively ($\alpha = 0.05$), the color change was assessed by Wilcoxon Signed Rank (ΔSGU) and t-test for paired data (ΔE*) ($\alpha = 0.05$). In the SRs (3-6) were searched for specific terms about the topic on databases and grey literature. The risk of bias was assessed using the Cochrane Collaboration tool. Meta-analysis were conducted for color change (ΔE*, ΔSGU), risk and intensity of TS using random effects model. Heterogeneity was assessed with the Cochran Q test and the I^2 statistic. The quality of evidence (GRADE) was evaluated in the studies (3) and (5). **Results:** In the study (1), there were no differences between groups in color, risk and intensity of SD ($p > 0.05$); in the study (2) differences were observed only in the reduction the intensity of TS for the group with desensitizing agent in the first 24 hours ($p < 0.01$). In the SRs after the search of the studies, there were 21 (3), 28 (4), 11 (5), 185 (6) RCTs. In SR (3) there were no differences in color and TS ($p > 0.05$), and the quality of evidence was graded as moderate for ΔE* and risk of TS, and very low and low for ΔSGU and intensity of TS, respectively. In MTC SR (4), there were no differences in color without the use of light or with different light sources used. In SR (5) there was no difference in color in the combined vs. in-office bleaching ($p > 0.05$), and no data were available to assess the risk and intensity of TS; in combined vs. at-home bleaching no differences were observed for ΔE*, ΔSGU and risk of TS; however, lower intensity of TS was detected in the sole at-home bleaching with a standardized mean difference of 0.86 (95% CI, 0.31-1.41); and the quality of evidence was graded as moderate for color change in ΔE*, and low or very low for the other analysis. In the SR (6) in the CONSORT classification of the studies, the general mean was

16.7 ± 5.4 points (out of 32 points in total) and only 7.6% were judged as low risk of bias. **Conclusions:** The incorporation of the desensitizing agents in the bleaching gels used in this study did not affect the color and did not reduce the TS in the at-home bleaching (1), but it decreased the intensity of TS in the in-office bleaching (2). The use of light activation in the in-office bleaching did not improve color or affect TS regardless of the concentration of hydrogen peroxide used (3) and also did not affect color in the study (4). In combined vs. isolated bleaching (5), low intensity of TS was found in sole at-home bleaching. And in the study (6) it was concluded that adherence to CONSORT in RCTs of different bleaching techniques is low and with high risk of bias.

Keywords: Tooth bleaching. Bleaching agents. Hydrogen peroxide. Dentin desensitizing agents. Dentin sensitivity. Clinical study. Systematic review.

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LISTA DE ABREVIATURAS E SIGLAS

ΔE*	Variação de cor nos parâmetros CIELAB
ΔUEV	Variação de Unidades da Escala Vita
a*	Mensuração da faixa vermelho-verde
b*	Mensuração da faixa amarelo-azul
BBO	Biblioteca Brasileira de Odontologia
COEP	Comitê de Ética em Pesquisa
CONSORT	CONsolidação Padronizada de Estudos Clínicos Randomizados
ECN	Escala de Classificação Numeríca
ECRs	Estudos Clínicos Randomizados
EVA	Escala Visual Analógica
GRADE	*Grading of Recommendations: Assessment, Development, and Evaluation*
IC	Intervalo de confiança
L*	Luminosidade do 0 (preto) ao 100 (branco)
LILACS	Literatura Latino-Americana em Ciências da Saúde
MTC	Comparação de Tratamento Misto
PC	Peróxido de Carbamida
PH	Peróxido de Hidrogênio
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*
PROSPERO	*International Prospective Register of Systematic Reviews*
ReBEC	Registro Brasileiro de Ensaios Clínicos
RSs	Revisões Sistemáticas
SD	Sensibilidade Dental
SUCRA	Superfície sob a Curva de Classificação Cumulativa
TCLE	Termo de Consentimento Livre e Esclarecido
UEPG	Universidade Estadual de Ponta Grossa
Vs.	Versus

SUMÁRIO

1 INTRODUÇÃO

O clareamento dental, tornou-se um dos tratamentos de escolha para solucionar a insatisfação com a cor dos dentes da maioria dos pacientes, associado ainda ao impacto na qualidade de vida dos mesmos. Possui facilidade de técnica, além de ser considerado um tratamento não-invasivo [1]. Meireles e colaboradores [2] mostraram em um estudo realizado em 2014, que a maioria dos participantes avaliados tinha como queixa principal prévia ao tratamento, a coloração dental, e que após finalizado o clareamento dental, nenhum dos participantes apresentou queixa da cor dos seus dentes. Em outro estudo conduzido no Chile, em 2017 [3] que avaliou a satisfação dos pacientes após o tratamento clareador, por meio de um score de 1 (totalmente insatisfeito) a 5 (muito satisfeito), mostrou que uma semana após o tratamento, a satisfação do paciente foi quantificada com uma média de 4, com o ressalve que, a característica que eles queriam com o tratamento era uma mudança moderada na coloração dental, a qual foi alcançada.

No entanto, no mesmo estudo de Meireles citado acima [2], a sensibilidade dental (SD) após o tratamento, foi reportada por um grande número de pacientes. Sendo a SD considerada o principal efeito adverso do clareamento dental [4]. Contudo, o mecanismo que causa este resultado doloroso ainda não está totalmente compreendido, mas parece estar associado à capacidade do peróxido de hidrogênio (PH) penetrar na estrutura dental e alcançar a câmara pulpar [5-7], gerando um maior estresse oxidativo no tecido pulpar [8-10]. Sabe-se que a sensibilidade dental ocorre entre 55% e 90% da população após o tratamento clareador; e o seu risco é igual para clareamento em consultório e caseiro, sendo que a intensidade difere numa escala numérica de 0 à 4, 2,8 no clareamento em consultório e 0,5 no caseiro [10,11].

Com a intenção de se tentar diminuir a SD, alguns artifícios são utilizados, como o uso de agentes dessensibilizantes, que podem estar presentes na composição do gel [12,13] ou aplicados tópicamente prévio ao procedimento clareador, um exemplo é o nitrato de potássio e fluoreto de sódio, ou ainda por meio da administração de analgésicos, drogas anti-inflamatórias, anti-inflamatórios não-seletivos, antioxidantes e corticosteróides [8,14-16]. Entretanto, ainda não foram encontrados na literatura estudos que tenham reduzido de forma considerável o risco e intensidade de SD. Um dos fatores para isso está relacionado as características morfológicas da dentina, que podem modular a quantidade de droga que alcança os fluidos do plasma, tornando estas abordagens não tão eficazes [17].

A adição de agentes dessensibilizantes no gel clareador, como o nitrato de potássio e fluoreto de sódio, seja no gel de tratamento caseiro ou em consultório, pode ser uma maneira

eficiente de reduzir a SD sem adicionar um passo extra no protocolo. Os íons de potássio reduzem a ativação do nervo sensorial, pois previne a repolarização da fibra nervosa e o flúor oblitera os túbulos dentinários atuando na redução do movimento do fluido na polpa [8,15]. Na literatura consultada há poucos estudos que compararam géis de clareamento com ou sem agentes dessensibilizantes, sendo que os mesmos apresentaram resultados conflitantes [12,13,18-20].

Contudo, tendo em vista que o principal objetivo do tratamento clareador é a alteração da cor dos dentes, ou seja, o clareamento dos mesmos, um artifício utilizado para melhorar sua eficácia, é a ativação do gel com luz, com diferentes fontes, tais como lasers, diodos emissores de luz, lâmpadas de arco de plasma e lâmpadas halógenas [21]. Na teoria, a luz aquece o PH, aumentando a energia cinética e decompõe-se em oxigênio e radicais livres. Assim, quando realizada a ativação com luz no clareamento, pensa-se que há um aumento de SD, pois há um aumento da temperatura intrapulpar [22,23]. He e colaboradores, em 2012 [24], fizeram uma revisão sistemática, avaliando o clareamento com e sem ativação com luz e o resultado mostrou que há um clareamento mais efetivo imediatamente após com o uso da luz e com menor concentração de PH, no entanto a luz aumentou a SD. Porém, após este estudo, novos estudos clínicos randomizados (ECRs) com este objetivo foram publicados [7,23,25]. Portanto, uma atualização da revisão sistemática, torna-se necessária, para estabelecer se existem diferenças baseadas em evidências na eficácia de clareamento e SD realizados com e sem luz usando concentrações baixas e altas de PH.

Ainda, além de uma revisão sistemática da literatura de análise direta, uma comparação mista de tratamentos para comparar diferentes tipos de fontes de luz, nos quais o padrão-ouro é desconhecido, por meio da realização de uma combinação de evidência diretas e indiretas, torna-se importante, comparando diferentes protocolos com um comparador comum (como o clareamento sem luz) [26].

Outra prática clinica comum para obter um efeito de clareamento mais rápido, melhor estabilidade de cor e níveis reduzidos de SD é combinar técnicas de clareamento caseiro e em consultório [27-29]. Dentro desse contexto, uma única sessão de clareamento em consultório é geralmente realizada em primeiro lugar para fornecer um efeito inicial na alteração de cor [30,31], e em seguida, o paciente continua o protocolo em casa com uma moldeira personalizada usando produtos de baixa concentração até a tonalidade desejada ser obtida [28,29,32].

No entanto, antes de tomar uma decisão de qual o melhor protocolo a ser seguido, os leitores devem avaliar previamente cada ECR da literatura, e esta avaliação depende de uma boa redação dos métodos e resultados, os quais devem seguir o CONSORT (Consolidação Padronizada de Estudos Clínicos Randomizados). Sendo assim, necessário avaliar os estudos de clareamento já existentes na literatura independente da técnica utilizada, além de avaliar o risco de viés dos mesmos por meio da ferramenta Cochrane.

Dessa forma, o objetivo desse trabalho foi avaliar a eficácia e SD por meio do uso de agentes dessensibilizantes incorporados ao gel no clareamento caseiro (PC 10%) e em consultório (PH 35%); o uso da ativação com luz no clareamento em consultório; o clareamento combinado (consultório e caseiro); além de avaliar a conformidade dos ECRs de clareamento com o CONSORT e o risco de viés dos mesmos; por meio de dois estudos clínicos e quatro revisões sistemáticas.

2 PROPOSIÇÃO

2.1 EXPERIMENTO 1

2.1.1 Proposição geral

Realizar um ECR com o objetivo de responder a seguinte pergunta foco no formato PICO: “A aplicação de gel clareador com agente dessensibilizante 3% de nitrato de potássio e 0,2% de fluoreto de sódio tem melhor eficácia e menor sensibilidade dental no clareamento caseiro comparado ao gel sem agente dessensibilizante em pacientes adultos com indicação de tratamento clareador?”

2.1.2 Proposição específica

1 – Avaliar o risco absoluto e a intensidade da SD durante 3 semanas no clareamento caseiro com e sem agente dessensibilizante com gel clareador de peróxido de carbamida 10% em um estudo de boca-dividida.

2 – Avaliar a eficácia do clareamento durante três semanas e após 30 dias do término do tratamento no clareamento caseiro com e sem agente dessensibilizante com gel clareador de peróxido de carbamida 10% em um estudo de boca-dividida.

2.2 EXPERIMENTO 2

2.2.1 Proposição geral

Realizar um ECR com o objetivo de responder a seguinte pergunta foco no formato PICO: “A aplicação de gel clareador com agente dessensibilizante 5% de nitrato de potássio tem melhor eficácia e menor sensibilidade dental no clareamento em consultório comparado ao gel sem agente dessensibilizante em pacientes adultos com indicação de tratamento clareador?”

2.2.2 Proposição específica

1 – Avaliar o risco absoluto e a intensidade da SD durante e após 48 horas de cada sessão no clareamento em consultório com e sem agente dessensibilizante com gel clareador de peróxido de hidrogênio 35% em um estudo de boca-dividida.

2 – Avaliar a eficácia do clareamento durante duas sessões e após 30 dias do término do tratamento no clareamento em consultório com e sem agente dessensibilizante com gel clareador de peróxido de hidrogênio 35% durante em um estudo de boca-dividida.

2.3 EXPERIMENTO 3

2.3.1 Proposição geral

Realizar uma RS e meta-análise da literatura com o objetivo de responder a seguinte pergunta foco no formato PICO: “A ativação com luz no clareamento em consultório tem uma maior eficácia comparada ao clareamento sem luz quando realizado em adultos?”

2.3.2 Proposição específica

1 – Avaliar se existem diferenças baseadas em evidências na eficácia do clareamento em consultório com e sem uso da luz usando concentrações altas e baixas de peróxido de hidrogênio por meio de uma revisão sistemática e meta-análise.

2 – Avaliar se existem diferenças baseadas em evidências no risco e na intensidade da SD do clareamento com e sem uso da luz usando concentrações baixas e altas de peróxido de hidrogênio por meio de uma revisão sistemática e meta-análise.

2.4 EXPERIMENTO 4

2.4.1 Proposição geral

Realizar uma RS e meta-análise da literatura de comparação mista de tratamentos com o objetivo de responder a seguinte pergunta foco no formato PICO: “Há algum protocolo de ativação com luz capaz de melhor a eficácia do clareamento em consultório quando realizado em adultos?”

2.4.2 Proposição específica

1 – Avaliar se existem diferenças baseadas em evidências na eficácia do clareamento em consultório com diferentes tipos de luz e sem o uso da mesma, com concentrações altas e baixas de peróxido de hidrogênio por meio de uma revisão sistemática e meta-análise de comparação mista de tratamentos.

2.5 EXPERIMENTO 5

2.5.1 Proposição geral

Realizar uma RS e meta-análise da literatura com o objetivo de responder a seguinte pergunta foco no formato PICO: “A combinação do clareamento em consultório e caseiro tem uma melhor eficácia comparada somente ao clareamento isolado em consultório ou caseiro realizado em adultos?”

2.5.2 Proposição específica

1 – Avaliar se existem diferenças baseadas em evidências na eficácia do clareamento combinado (consultório e caseiro) comparado só ao clareamento em consultório ou caseiro por meio de uma revisão sistemática e meta-análise.

2 – Avaliar se existem diferenças baseadas em evidências no risco e na intensidade da SD do clareamento combinado (consultório e caseiro) comparado só ao clareamento em consultório ou caseiro por meio de uma revisão sistemática e meta-análise.

2.6 EXPERIMENTO 6

2.6.1 Proposição geral

Avaliar a conformidade dos estudos clínicos randomizados de clareamento dental com o CONSORT e o risco de viés desses estudos pela ferramenta Cochrane por meio de uma revisão sistemática.

2.6.2 Proposição específica

1 – Avaliar os estudos clínicos randomizados de clareamento dental se estão em conformidade com a declaração do CONSORT.

2 – Avaliar o risco de viés dos estudos clínicos randomizados de clareamento dental por meio da ferramenta de colaboração Cochrane.

3 MATERIAL E MÉTODOS

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

3.1 EXPERIMENTO 1

O projeto deste estudo clínico foi aprovado pelo Comitê de Ética em Pesquisa (COEP) da Universidade Estadual de Ponta Grossa através do parecer nº 1.762.164 e registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC) sob o número RBR-4M6YR2 (ANEXO – p. 246 e 247). A metodologia detalhada deste experimento está descrita no Artigo 1 (p. 43-47).

3.1.1 Seleção dos pacientes

Foram selecionados 60 voluntários que procuraram atendimento nas clínicas odontológicas da Universidade Estadual de Ponta Grossa (UEPG), que tinham interesse em realizar o clareamento dental e que se enquadraram nos critérios de inclusão e exclusão dos estudos. Os caninos superiores deveriam ser classificados como cor A2 ou mais escuros, por comparação com a escala Vita Classical (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 243). Todos os voluntários assinaram um Termo de Consentimento Livre e Esclarecido (TCLE) antes de participarem do estudo (APÊNDICE – p. 253).

3.1.2 Randomização e ocultação da sequência aleatória

Neste estudo boca-dividida, foi realizada uma randomização simples no site *www.sealedenvelope.com*. Os quais foram númerados sequencialmente em envelopes opacos e selados, de forma que o operador e paciente só saberiam qual gel seria aplicado em cada hemi-arco no momento da intervenção quando o envelope fosse aberto.

3.1.3 Cegamento

Foi um estudo triplo-cego, onde nem o operador, avaliador e examinador sabiam a atribuição dos grupos. Ambos os geis foram entregues em seringas idências codificadas em “A” ou “B”, os quais possuim a mesma consistência e cor. Apenas o coordenador da pequisa sabia o sistema de codificação.

3.1.4 Procedimento clareador

A técnica utilizada foi o clareamento dental caseiro com gel peróxido de carbamida (PC) 10% (Whiteness Perfect – FGM, Joinville, SC, Brasil) com agente dessensibilizante 3% de nitrato de potássio e 0,2% de fluoreto de sódio e sem agente dessensibilizante, por meio do uso de uma moldeira. Os pacientes foram instruídos a utilizar o gel clareador no seu respectivo hemi-arco, pelo período de três horas diariamente, durante 21 dias.

3.1.5 Avaliação da sensibilidade dental

Foi avaliado o risco absoluto e intensidade da SD avaliada por meio da Escala Visual Analógica (EVA) 0-10 cm (ANEXO – p. 241) e Escala de Classificação Numérica (ECN) 0-4 (ANEXO – p. 242) durante três semanas no clareamento caseiro.

3.1.6 Avaliação da cor

A cor foi avaliada inicialmente, durante o tratamento clareador e 30 dias após o término do mesmo, por meio das escalas de cor Vita Classical (Vita Classical Shade, Vita Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 243), Vita Bleachedguide 3D-Master (BG, VITA Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 244), e com o espectrofotômetro Vita Easyshade (VITA Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 245), de acordo com o sistema Vita e CIEL*a*b*. A área de mensuração da cor foi o terço médio da face vestibular dos caninos superiores.

3.1.7 Análise estatística

Os dados de cor foram tabulados no Programa Sigma Plot (Systat Software Inc., San Jose, CA, EUA) e avaliados. O risco absoluto de SD e sua intensidade foram avaliados pelo teste de McNemar e pelo Wilcoxon Signed Rank test, respectivamente ($\alpha = 0,05$). A eficácia do clareamento foi avaliada pelos testes de Wilcoxon Signed Rank (ΔUEV) e teste t para dados pareados (ΔE^*) ($\alpha = 0,05$).

3.2 EXPERIMENTO 2

O projeto deste estudo clínico foi aprovado pelo COEP da UEPG através do parecer nº 1.756.984 e registrado no ReBEC sob o número RBR-4TKYS8 (ANEXO – p. 248 e 249). A metodologia detalhada deste experimento está descrita no Artigo 2 (p. 67-72).

3.2.1 Seleção dos pacientes

Foram selecionados 60 voluntários que procuraram atendimento nas clínicas odontológicas da UEPG, que tinham interesse em realizar o clareamento dental e que se enquadraram nos critérios de inclusão e exclusão dos estudos. Os caninos superiores deveriam ser classificados como cor A2 ou mais escuros, por comparação com a escala Vita Classical (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 243). Todos os voluntários assinaram o TCLE antes de participarem do estudo (APÊNDICE – p. 254).

3.2.2 Randomização e ocultação da sequência aleatória

Neste estudo boca-dividida, foi realizada uma randomização simples no site *www.sealedenvelope.com*. Os quais foram números sequencialmente em envelopes opacos e selados, de forma que o operador e paciente só saberiam qual gel seria aplicado em cada hemi-arco, no momento da intervenção quando o envelope fosse aberto.

3.2.3 Cegamento

Foi um estudo triplo-cego, onde nem o operador, avaliador e examinador sabiam a atribuição dos grupos. Ambos os geis foram entregues em seringas idências codificadas em “A” ou “B”, os quais possuim a mesma consistência e cor. Apenas o coordenador da pequisa sabia o sistema de codificação.

3.2.4 Procedimento clareador

A técnica utilizada foi o clareamento dental em consultório com o gel peróxido de hidrogênio 35% (Whiteness HP AutoMixx – FGM, Joinville, Brasil) com agente dessensibilizante 5% de nitrato de potássio e sem agente dessensibilizante. Foi feita uma aplicação do gel no seu respectivo hemi-arco em aplicação única de 50 minutos realizadas em duas sessões com intervalos de sete dias entre elas.

3.2.5 Avaliação da sensibilidade dental

Foi avaliado o risco absoluto e intensidade da SD avaliada por meio da EVA 0-10 cm (ANEXO – p. 241) e ECN 0-4 (ANEXO – p. 242) durante e até 48 horas após cada sessão no clareamento em consultório.

3.2.6 Avaliação da cor

A cor foi avaliada inicialmente, uma semana após cada sessão e 30 dias após o término do mesmo, por meio das escalas de cor Vita Classical (Vita Classical Shade, Vita Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 243), Vita Bleachedguide 3D-Master (BG, VITA Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 244), e com o espectrofotômetro Vita Easyshade (VITA Zahnfabrik, Bad Säckingen, Alemanha) (ANEXO – p. 245), de acordo com o sistema Vita e CIEL*a*b*. A área de mensuração da cor foi o terço médio da face vestibular dos caninos superiores.

3.2.7 Análise estatística

Os dados de cor foram tabulados no Programa Sigma Plot (Systat Software Inc., San Jose, CA, EUA) e avaliados. O risco absoluto de SD e sua intensidade foram avaliados pelo teste de McNemar e pelo Wilcoxon Signed Rank test, respectivamente ($\alpha = 0,05$). A eficácia do clareamento foi avaliada pelos testes de Wilcoxon Signed Rank (ΔUEV) e teste t para dados pareados (ΔE^*) ($\alpha = 0,05$).

3.3 EXPERIMENTO 3

Este protocolo de revisão sistemática e meta-análise foi registrado no banco de dados PROSPERO – CRD42016037630 (ANEXO – p. 250). Foram seguidas as recomendações da declaração *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) para a realização desta revisão sistemática. A metodologia detalhada deste experimento está descrita no Artigo 3 (p. 91-94).

3.3.1 Fontes de informação e estratégia de busca

O vocabulário controlado e palavras-chave livres na estratégia de busca foram definidos com base na seguinte pergunta foco no formato PICOS:

1. População (P): pacientes adultos que foram submetidos ao clareamento clareador de dentes vitais;

2. Intervenção (I): clareamento em consultório com luz;

3. Comparação (C): clareamento em consultório sem luz;

4. Resultado (O): alteração de cor nas unidades da escala vita (ΔUEV) e espectrofotômetro (ΔE^*), bem como o risco e intensidade de SD após o clareamento dental;

5. Estudos (S): estudos clínicos randomizados.

Para identificar os estudos a serem incluídos nesta revisão, foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, Biblioteca Cochrane, Biblioteca Brasileira de Odontologia (BBO), Literatura Latino-Americana em Ciências da Saúde (LILACS) e bancos de dados de citações (*Scopus* e *Web of Science*), também foi realizada uma busca na literatura cinzenta e nos Registros de Estudos Clínicos. As listas das referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições na data de publicação ou idiomas.

3.3.2 Critério de elegibilidade

Foram incluídos ECRs paralelos ou boca-dividida, que comparavam o clareamento dental em consultório com e sem luz em pacientes adultos de qualquer faixa etária. Os ECRs foram excluídos se: 1) os estudos compararam apenas diferentes técnicas de clareamento ativados por luz em consultório e 2) os estudos compararam o clareamento dental em consultório com clareamento combinado (consultório e caseiro).

3.3.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara. Posteriormente, três revisores classificaram aqueles que preencheram os critérios de inclusão. Detalhes sobre o estudo, como métodos e os resultados foram extraídos utilizando formulários de extração personalizados.

3.3.4 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs.

O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como alto, baixo ou incerto risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0 (*http://handbook.cochrane.org*).

3.3.5 Meta-análise

A meta-análise foi realizada em estudos classificados como baixos e incertos risco de viés, de acordo com a classificação final dos componentes de avaliação de validade.

3.3.6 GRADE

A qualidade de evidência foi classificada para cada resultado em todos os estudos (corpo de evidência) usando a Classificação de Recomendações: Avaliação, Desenvolvimento e Avaliação (GRADE) (*http://www.gradeworkinggroup.org/).*

3.4 EXPERIMENTO 4

Este protocolo de revisão sistemática e meta-análise foi registrado no banco de dados PROSPERO – CRD42017078743 (ANEXO – p. 251). Foram seguidas as recomendações da declaração PRISMA para a realização desta revisão sistemática. A metodologia detalhada deste experimento está descrita no artigo 4 (p. 124-127).

3.4.1 Fontes de informação e estratégia de busca

O vocabulário controlado e palavras-chave livres na estratégia de busca foram definidos com base na seguinte pergunta foco no formato PICOS:

1. População (P): pacientes adultos que foram submetidos ao clareamento clareador de dentes vitais;

2. Intervenção (I): clareamento em consultório com diferentes tipos de ativação com luz;

3. Comparação (C): clareamento em consultório sem luz;

4. Resultado (O): alteração de cor nas unidades da escala vita (ΔUEV) e espectrofotômetro (ΔE*), bem como o risco e intensidade de SD após o clareamento dental;

5. Estudos (S): estudos clínicos randomizados.

Para identificar os estudos a serem incluídos nesta revisão, foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, Biblioteca Cochrane, BBO, LILACS e bancos de dados de citações (*Scopus* e *Web of Science*), também foi realizada uma busca na literatura cinzenta e nos Registros de Estudos Clínicos. As listas das referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições na data de publicação ou idiomas.

3.4.2 Critério de elegibilidade

Foram incluídos ECRs paralelos ou boca-dividida, que comparavam o clareamento dental em consultório com e sem luz em pacientes adultos de qualquer faixa etária. Os ECRs foram excluídos se: 1) estudos compararam o clareamento dental em consultório com clareamento combinado (consultório e caseiro).

3.4.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara. Posteriormente, três revisores classificaram aqueles que preencheram os critérios de inclusão. Detalhes sobre o estudo, como métodos e os resultados foram extraídos utilizando formulários de extração personalizados

3.4.4 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs.

O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como alto, baixo ou incerto risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0 (*http://handbook.cochrane.org*).

3.4.5 Meta-análise

A metodologia MTC foi escolhida para a análise estatística, a fim de avaliar simultaneamente os efeitos dos diferentes tratamentos, utilizando o software estatístico R (*https://cran.r-project.org*) e a inferência bayesiana foi realizada utilizando JAGS (*http://mcmc-jags.sourceforge.net*).

Neste estudo, o comparador comum foi o tratamento de clareamento sem luz, no qual duas análises foram feitas. Primeiramente, foi realizada uma meta-análise tradicional da evidência direta, a partir dos estudos que compararam diferentes métodos terapêuticos, derivando uma diferença de média e um intervalo de confiança (IC) de 95%. A heterogeneidade foi avaliada usando o teste Q de Cochran e estatística I^2. Subsequentemente, a meta-análise de rede foi realizada, o comparador comum foi os grupos que não utilizaram luz e os grupos de tratamento de luz foram tratados como grupos diferentes.

No caso de diferenças entre tratamentos, uma abordagem Bayesiana usando valores de probabilidade será resumida como Superfície sob a Curva de Classificação Cumulativa (SUCRA) para avaliar a probabilidade do tratamento mais efetivo ou seguro. Quanto maior o valor da SUCRA, melhor o grau de intervenção.

3.5 EXPERIMENTO 5

Este protocolo de revisão sistemática e meta-análise foi registrado no banco de dados PROSPERO – CRD42016036555 (ANEXO – p. 252). Foram seguidas as recomendações da declaração PRISMA para a realização desta revisão sistemática. A metodologia detalhada deste experimento está descrita no Artigo 5 (p. 151-154).

3.5.1 Fontes de informação e estratégia de busca

O vocabulário controlado e palavras-chave livres na estratégia de busca foram definidos com base na seguinte pergunta foco no formato PICOS:

1. População (P): pacientes adultos que foram submetidos ao clareamento clareador de dentes vitais;

2. Intervenção (I): clareamento combinado (consultório e caseiro);

3. Comparação (C): clareamento isolado consultório ou caseiro;

4. Resultado (O): alteração de cor nas unidades da escala vita (ΔUEV) e espectrofotômetro (ΔE*), bem como o risco e intensidade de SD após o clareamento dental;

5. Estudos (S): estudos clínicos randomizados.

Para identificar os estudos a serem incluídos nesta revisão, foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, BBO, LILACS e bancos de dados de citações (*Scopus* e *Web of Science*), também foi realizada uma busca na literatura cinzenta e nos Registros de Estudos Clínicos. As listas das referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições na data de publicação ou idiomas.

3.5.2 Critério de elegibilidade

Foram incluídos ECRs paralelos ou boca-dividida, que comparavam o clareamento dental em consultório com e sem luz em pacientes adultos de qualquer faixa etária. Os ECRs foram excluídos se: 1) os estudos compararam apenas com diferentes técnicas de clareamento combinado.

3.5.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara. Posteriormente, três revisores classificaram aqueles que preencheram os critérios de inclusão. Detalhes sobre o estudo, como métodos e os resultados foram extraídos utilizando formulários de extração personalizados.

3.5.4 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs.

O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como alto, baixo ou incerto risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0 (*http://handbook.cochrane.org*).

3.5.5 Meta-análise

A meta-análise foi realizada em estudos classificados como baixos e incertos risco de viés, de acordo com a classificação final dos componentes de avaliação de validade.

3.5.6 GRADE

A qualidade de evidência foi classificada para cada resultado em todos os estudos (corpo de evidência) usando a Classificação de Recomendações GRADE (*http://www.gradeworkinggroup.org/*).

3.6 EXPERIMENTO 6

Este protocolo de revisão sistemática não foi registrado pois não existem registros com essa metodologia. A medotodologia está descrita no Artigo 6 (p. 180-182).

3.6.1 Fontes de informação e estratégia de busca

Foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, Biblioteca Cochrane, BBO, LILACS) e bancos de dados de citações (*Scopus* e *Web of Science*), também foi realizada uma busca na literatura cinzenta e nos Registros de Estudos Clínicos. As listas de referência de todos os estudos primários foram pesquisadas manualmente para publicações

relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições nos idiomas e com data posterior a 1196.

3.6.2 Critério de elegibilidade

Foram incluídos ECRs em paralelo ou boca-dividida que avaliaram a eficácia, sensibilidade dental, toxicidade e diferentes técnicas de clareamento dental de qualquer faixa etária. Os ECRs foram excluídos se fossem: 1) estudos laboratoriais 2) resumos de congressos 3) teses 4) relatos de casos clínicos 5) estudos que não foram publicados em jornais periódicos.

3.6.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara.

3.6.4 Aderência à declaração CONSORT

Um total de 12 itens da declaração CONSORT foram incluídos nesta ferramenta de avaliação. Como alguns desses itens foram subdivididos, um total de 16 itens foram avaliados (desenho do estudo; critérios de eligibilidade; local e data; intervenção; desfechos; tamanho amostral; geração de sequência; ocultação da sequência; cegamento; teste de hipótese; tamanho de efeito; fluoxograma; perdas/exclusões; dados iniciais; números analisados e registro e protocolo). A pontuação dada por item variou de 0 a 2. Em palavras gerais, 0 = sem descrição, 1 = descrição ruim e 2 = descrição adequada,

3.6.5 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs.

O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como alto, baixo ou incerto risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0 (*http://handbook.cochrane.org*).

4 ARTIGOS

4.1 Tooth sensitivity with a desensitizing-containing at-home bleaching gel – a randomized, triple-blind clinical trial

4.2 Tooth sensitivity with a desensitizing-containing in-office bleaching gel – a randomized, triple-blind clinical trial

4.3 In-office dental bleaching with light vs. without light: a systematic review and meta-analysis

4.4 Different light activation to dental bleaching: a systematic review and a mixed treatment comparison meta-analysis

4.5 Are combined bleaching techniques better than at-home or in-office bleaching? A systematic review and meta-analysis

4.6 Randomized clinical trials of dental bleaching – compliance with the consort statement: A systematic review

Artigo 1

TÍTULO: TOOTH SENSITIVITY WITH A DESENSITIZING-CONTAINING AT-HOME BLEACHING GEL – A RANDOMIZED, TRIPLE-BLIND CLINICAL TRIAL

STATUS: PUBLICADO

REVISTA: JOURNAL OF DENTISTRY

4.1 ARTIGO 1 – TOOTH SENSITIVITY WITH A DESENSITIZING-CONTAINING AT-HOME BLEACHING GEL – A RANDOMIZED, TRIPLE-BLIND CLINICAL TRIAL

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ABSTRACT

Objectives: Desensitizing agents are usually included in the composition of bleaching agents to reduce bleaching-induced tooth sensitivity (TS). This randomized clinical trial (RCT) evaluated the risk and intensity of TS and color change after at-home bleaching with a desensitizing-containing (3% potassium nitrate and 0.2% sodium fluoride) and desensitizing-free 10% carbamide peroxide (CP) gel (Whiteness Perfect, FGM).

Methods: A triple-blind, within-person RCT was conducted on 60 caries-free adult patients. Each participant used the gel in a bleaching tray for three hours daily for 21 days in both the upper and lower dental arches. The absolute risk and intensity of TS were assessed daily through the 0-10 VAS and 0-4 NRS scale for 21 days. Color change was recorded using shade guides (Vita Classical and Vita Bleachedguide) and the Easyshade spectrophotometer at baseline, weekly and 30 days after the end of the bleaching. The risk and intensity of TS were evaluated by the McNemar and Wilcoxon Signed Rank tests, respectively. Color change (ΔSGU and ΔE*) were evaluated by the Wilcoxon Signed Rank test and a paired t-test, respectively ($\alpha = 0.05$).

Results: No difference in the TS and color change was observed ($p > 0.05$).

Conclusions: The incorporation of potassium nitrate and sodium fluoride in 10% carbamide peroxide at-home bleaching gel tested in this study did not reduce the TS and did not affect color change (RBR-4M6YR2).

Clinical Relevance: Bleaching gel composed of 10% carbamide peroxide containing potassium nitrate and sodium fluoride does not have reduced risk and intensity of bleaching-induced tooth sensitivity.

Keywords: Tooth bleaching agents. Desensitizing Agents. Dentin Sensitivity.

INTRODUCTION

The increased search for esthetic procedures may be attributed to advertising and general media that emphasize the need for a pleasing appearance. Consequently, esthetic treatments have become a priority in dental practice, making esthetics as important as function, structure and biology [1]. This was evident in a survey conducted in Ankara, Turkey [2]; the authors investigated the factors involved with patient satisfaction and observed that 55.1% of them were dissatisfied with dental discoloration, followed by dental appearance (42.7%) and poor alignment of the teeth (29.9%). When the patients were asked about what kind of treatment they would like to receive, half reported dental bleaching, followed by esthetic restorations (25.4%), orthodontic treatment (24.5%) and prosthetic restorations (16.9%).

Dental bleaching is a very conservative alternative for the treatment of dental discolorations, and among the bleaching protocols, at-home bleaching is the one most commonly used due to its clinical effectiveness, safety and acceptance by patients and professionals [3-5].

Although this bleaching protocol requires the use of low-concentrate oxidizing agents, tooth sensitivity (TS) is still present and can be considered the main adverse effect of the bleaching technique [6]. A recent retrospective study that collected data from eleven RCTs showed that the risk of TS reported by patients who submitted to at-home bleaching is approximately 51% (95% CI 41 to 61%) [7], and this variation may depend on the active bleaching agent [8-10]. Studies that compared different gel concentrations for at-home technique showed higher TS levels for more concentrated gels [9,10].

The higher the concentration of the peroxide, the greater the oxidative stress generated in the pulp tissue [11,12], which in turn may be the factor responsible for the TS. This oxidative stress generates an inflammatory process with the release of inflammatory mediators, such as adenosine triphosphate and prostaglandins, that excite the nociceptors and trigger the bleaching-induced TS [13,14].

Although some studies have shown that the use of desensitizing agents before tooth whitening can minimize the intensity of TS [15,16], this technique adds another clinical step to the bleaching process. Theoretically, adding desensitizing agents in the composition of the bleaching gel, such as 3% potassium nitrate and 0.2% sodium fluoride, could be an efficient way to reduce TS without adding an extra step to the protocol. Potassium ions reduce the activation of the sensory nerve by preventing the repolarization of the nerve fiber and fluoride blocks dentin tubules that might be exposed and reducing its fluid flow [17,18].

To the extent of the author's knowledge, few studies have compared desensitizing-containing and desensitizing-free bleaching gels, and they show conflicting results [19-23]. Thus, the objective of this study was to compare the risk and intensity of TS and color change in patients who submitted to at-home bleaching and used a desensitizing-containing or desensitizing-free 10% carbamide peroxide gel.

MATERIAL AND METHODS

Ethics approval and protocol registration

The clinical investigation was approved (protocol number 1.762.164) by the scientific review committee and by the committee for the protection of human participants of the local university. It was registered in the Brazilian clinical trials registry (ReBEC) under the identification number RBR-4M6YR2. We prepared this article using the protocol established by the Consolidated Standards of Reporting Trials (CONSORT) Statement with an extension for within-person designs [24].

Trial design, settings and locations of data collection

This study was a randomized, within-person, triple-blind clinical trial, in which the patient, operator, and evaluator were masked to the group assignment. A third researcher, who was not involved in the evaluation process, was responsible for the randomization process. All participants were informed about the nature and objectives of the study. The study was performed from November 01, 2016, to March 31, 2017, in the Clinics of the School of Dentistry from the local university.

Recruitment

Recruitment was performed by posting written advertisements on the university walls. All volunteer participants signed an informed consent form before being enrolled in the study.

Eligibility criteria

Based on pre-established criteria, we selected 60 subjects volunteered for this study. Participants included in the present RCT should be at least 18–50 years old and in good general and oral health. The participants were required to have at least six maxillary anterior teeth free of caries and restorations, with canine shade A2 or darker, as judged by comparison with a value-oriented shade guide (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Germany).

Participants with dental prostheses, orthodontics apparatus or severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth, etc.) were not included in the study. In addition, pregnant and lactating women, participants with bruxism or any pathology that

could cause sensitivity (such as recession, dentinal exposure and visible cracks in teeth), anti-inflammatory or analgesic drug users, smokers, or participants who had undergone tooth-whitening procedures were also excluded.

Sample size calculation

The primary outcome of this study was the absolute risk of TS. The absolute risk of TS (that is, the number of patients [percent] who reported pain at some point during dental bleaching) was considered for the calculation of the sample size. The absolute risk of TS for at-home bleaching was reported to be 61% in an earlier study [7]. Using an alpha of 0.05, 90% power and a two-sided test, the minimum sample size in this equivalence trial was 60 patients in order to detect a 30% difference in the risk of TS between groups.

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

Randomization and allocation concealment

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

Blinding

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

Both bleaching gels (with the desensitizing agent) and the control (without the desensitizing agent) were delivered in identical syringes coded as “A” and “B”. Both gels had similar consistency and color. Only the research coordinator knew the coding system.

Study Intervention

The bleaching procedure was done by three clinical dentists with a clinical experience of more than 3 years. We made alginate impressions of each subject's maxillary and mandibular arch, and these were filled with dental stone. We did not apply block-out material to the labial surfaces of teeth of the stone model teeth. A 1 mm soft vinyl material provided by the manufacturer (FGM Dental Products, Joinville, SC, Brazil) was used to fabricate the custom-fitted tray to hold the bleaching gel. We trimmed the bleaching tray 1 mm beyond the marginal gingiva, and we identified the right and left sides of the bleaching tray. The participant received both bleaching products with the respective instructions on which side each product was to be applied. Both the bleaching product and the corresponding side of the bleaching tray had identical coding to facilitate the patient's identification, but they were masked to hide the product that was used on each side of the dental arch.

The whitening gel that was used in this study was 10% Whiteness Perfect Carbamide Peroxide (FGM, Joinville, SC Brazil). In the experimental group (desensitizing-containing), the commercial product itself was employed, being composed of 3% potassium nitrate and 0.2% sodium fluoride. In the control group (desensitizing-free), the company manufactured the same bleaching agent but without the desensitizing active agents (Table 4.1-1). The wearing instructions are depicted in Table 4.1-1. After each daily use, the patient should remove the bleaching tray, wash it under tap water and brush their teeth routinely.

Outcomes

Tooth Sensitivity evaluation

The patients were instructed to fill out a form to record the TS daily during bleaching for 21 days. Before starting the bleaching, each patient received a paper form with a mouth drawn on it that contained the teeth of the upper arch and should describe their degree of pain using two pain scales. Using a five-point Numeric Rating Scale (NRS) where 0 = none, 1 = mild, 2 = moderate, 3 = considerable and 4 = severe, the patient was instructed to indicate the numerical value of the degree of sensitivity on each side of the dental arch. Additionally, we instructed them to express their tooth sensitivity degree using the Visual Analogue Scale (VAS). The VAS scale is a 10-cm horizontal line with scores of 0 and 10 at their ends, where 0 = no sensitivity and 10 = severe sensitivity. The patient should mark with a vertical line across the horizontal line of the scale the intensity of the TS. Then, the distance in mm from the zero ends was measured with the aid of a millimeter ruler.

The patients were not instructed to point out the painful teeth in the present study, although they would be able to accomplish this goal if requested. They were told to fill out the

form every time they felt pain. We also explained to them that if they did not feel any TS, their intensity would be zero. These forms were returned to the researcher on the next appointment (1 week later).

If the participant scored 0 (no sensitivity) in all time assessments, this participant was considered to be insensitive to the bleaching protocol. In all other circumstances, the participants were considered to have bleaching-induced TS. This dichotomization allowed us to calculate the absolute risk of TS, which is the percentage of patients who reported tooth sensitivity at least once during treatment.

To calculate the TS intensity, we took the worst score from the NRS scale and the highest numerical value obtained in the VAS scale reported by each patient, so that only a single value per patient was taken from the 3-week treatment.

Color evaluation

Two experienced and calibrated dentists (kappa statistics higher than 80% after previous calibration; data not shown) not involved in the randomization procedures performed clinical assessments at baseline, weekly during the 3-week treatment, and 1 month after the bleaching treatment. We performed the color evaluation using the shade guides VITA Classical (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Germany), the VITA Bleachedguide 3D-MASTER (BG, VITA Zahnfabrik, Bad Säckingen, Germany) and the spectrophotometer VITA Easyshade (VITA Zahnfabrik, Bad Säckingen, Germany).

The Vita Classical scale was arranged in 16 tabs from highest (B1) to lowest (C4) value: B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4 and C4. Although this scale is not linear in the truest sense, color changes were considered as continuous and linear changes as in several clinical studies of tooth whitening [9,25-28]. The VITA Bleachedguide 3D-MASTER contains lighter shade tabs, and it is already organized from highest (0M1) to lowest (5M3) values.

The tooth matching area was the middle third of the buccal surface of the upper canines [29-32]. Color changes were calculated from the beginning of the active phase up to the individual recall times by calculating the change in the number of shade guide units (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs. In case of disagreement between operators, they should reach a consensus.

For color measurement with the spectrophotometer, the examiner took an impression of the maxillary arch with dense silicone paste (Coltoflax and Perfil Cub Kit, Vigodent, Rio de Janeiro, Rio de Janeiro, Brazil). The impression was extended to the maxillary canines and

served as a standard color measurement guide for the spectrophotometer. For each tooth to be evaluated, we created a window on the buccal surface of the silicone guide using a metal device with a radius of 6 millimeters, which is exactly the diameter of the tip of the spectrophotometer. The tip of the device was then inserted into the silicone guide, and we obtained the L*, a* and b* parameters of color from the spectrophotometer. The L* value represents the luminosity (value from 0 [black] to 100 [white]), a* value represents the measurement along the red-green axis, and b* value represents the measurement along the yellow–blue axis. The color change (ΔE*) before (baseline) and after each treatment (in each assessment period) is given by differences between the two colors measured with the spectrophotometer—which is calculated using the formula $\Delta E^* = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$.

Statistical methods

The analysis followed the intent-to-treat protocol and involved all participants, who were randomly divided (Figure 4.1-1). The statistician was also blinded to the groups. Each arch was analyzed separately. The absolute risk of TS of both groups were compared by means of the McNemar's exact test ($\alpha = 0.05$, test for proportion of dependent data ratio). The relative risk as well as the confidence interval (CI) for the effect size was also calculated.

The TS intensity data sets for both the VAS and NRS scales were plotted in histograms and inspected for normal distributions. As data did not have normal distribution, the groups were compared using the Wilcoxon Signed Rank test ($\alpha = 0.05$).

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

RESULTS

Characteristics of included participants

A total of 112 participants were examined according to the inclusion and exclusion criteria (Figure 4.1-1), but only 60 participants remained for the clinical trial. The baseline color of the participants and the distribution of the genders were described in Table 4.1-2. No hypothesis testing was performed for baseline features, as any difference between these features are attributed to chance alone.

All participants attended the recall visits during the bleaching protocol, and none quit the treatment. Figure 4.1-1 depicts the participant flow diagram in the different phases of the study design.

Risk of tooth sensitivity

In upper arch, a total of 38 patients (absolute risk: 63%, 95% CI 51 to 74%) presented pain in the desensitizing-free group, and from these, only 5 patients reported pain exclusively in the desensitizing-free group. Forty patients (absolute risk: 66%, 95% CI 54 to 77%) reported pain in the desensitizing-containing group, and from these, seven experienced pain only in the desensitizing-containing group. In comparative terms, the odds ratio for pain was 1.4 (0.4 to 5.6; Table 4.1-3), and it did not reach statistical significance ($p = 0.77$).

In the lower arch, a total of 33 patients (absolute risk: 55%, 95% CI 42 to 67%) presented pain in the desensitizing-free group, and from these, only 6 patients reported pain exclusively in the desensitizing-free group. Thirty-one patients (absolute risk: 52%, 95% CI 39 to 64%) reported pain in the desensitizing-containing group, and from these, four experienced pain only in the desensitizing-containing group. In comparative terms, the odds ratio for pain was 0.67 (0.14 to 2.8; Table 4.1-3), and it was not statistically significant ($p = 0.75$).

The Spearman correlation coefficient for pairs of binary data was moderate and significant for the upper ($r = 0.56$; $p < 0.0001$) and the lower arches ($r = 0.67$; $p< 0.0001$).

Intensity of tooth sensitivity

No significant difference in the TS intensity was observed between groups in any of the pain scales for the upper and lower dental arches ($p > 0.16$ for NRS and $p > 0.31$; for VAS). Pain was positively correlated in both groups. For the upper arch, the correlation was weak and significant for the NRS ($r = 0.47$; $p < 0.001$) scales and moderate for the VAS scales ($r = 0.52$; $p < 0.001$). For the lower dental arch, the correlation was moderate for the NRS ($r = 0.68$; $p < 0.001$) and strong for the VAS scale ($r = 0.76$, $p < 0.001$) (Table 4.1-4 and 5).

Color change

Significant whitening was detected by the three different color measurement tools for both study groups (Table 4.1-6). A bleaching of approximately 7 units of color in the Vita Classical scale and in the Vita Bleachedguide and approximately 12 units in the ΔE^* was observed (Table 4.1-6). No significant difference of color change was observed between groups (Table 4.1-6; $p > 0.66$).

DISCUSSION

A recent systematic review of literature conducted by our research group has attempted to answer the same research question as this randomized clinical trial [33]. After an extensive literature search, we found eight RCT [19-23,34-37] that compared desensitizing-containing vs desensitizing-free at-home bleaching products. All of these studies were judged to be at unclear

risk of bias, as they all lacked allocation concealment, and six of them [19,20,22,34,36,37] did not perform an adequate description of the random allocation sequence; this means that no reliable conclusions can be obtained on the basis of the previous published RCTs.

This RCT was performed under rigorous control of the randomization and blinding. This avoids the conscious or subconscious choice of the intervention and prevents allocation bias. Adequate blinding was also conducted to avoid performance and detection bias by both operators and participants. We selected a split-mouth design so that within-patient, tooth-related and patient-habit variables, which are commonly observed in the bleaching treatment [8,38,39] and are difficult to balance even in randomized designs, can be controlled, as the two treatments are simultaneously applied in the same patient. Within-paired designs allows the use of powerful statistical methods of analysis which take advantage of repeated measures within a subject with reduction of within subject variability [40].

In agreement with the aforementioned systematic review of the literature, we observed that the incorporation of desensitizing agents, specifically 3% potassium nitrate and 0.2% sodium fluoride, does not reduce the risk of bleaching-induced TS. These desensitizing components were reported to be effective in minimizing bleaching-induced TS by reducing the excitability of the pulpal nerve fibers (potassium nitrate) and/or occluding the dentinal tubules by precipitation of calcium fluoride crystals or hydroxyapatite crystals (fluoride) [22,41]. However, the successful reports regarding these desensitizing agents were observed when they were applied before the application of an in-office bleaching product and not simultaneously [28,41-45] .

The idea behind the incorporation of desensitizing agents into the composition of bleaching products is to reduce TS without increasing a clinical step of treatment [20]. Nevertheless, when the desensitizing agent is incorporated into the bleaching gel, both the oxidizing agent and the desensitizing agent travel within the dental structure simultaneously. However, hydrogen peroxide has a lower molecular mass than potassium nitrate and can reach the pulp tissue faster [46]. Therefore, by the time potassium nitrate arrives to the pulp to reduce the transmission of the pain stimuli [28,34], hydrogen peroxide could have already caused damage and triggered an inflammatory response and the transmission of the pain impulses. Whether or not this hypothesis is applicable to a high-concentrate hydrogen peroxide in-office products is yet to be addressed.

For the upper arch, the absolute risk of pain for both at-home protocols was around 63%, which was similar to some studies [22,47,48]. Differences in this absolute risk of TS for at-

home bleaching vary in the literature, which leads readers to question if it is not too high. However, these differences depend on how studies calculated them. In this study, if one patient reported a single episode of TS during treatment, the patient was counted as having pain. Perhaps other researchers did not interpret data in the same manner, though they did not report clearly how they calculated their risks in their published papers [8,34,49,50]. Comparisons in such situations may be misleading. Authors are therefore encouraged to make this clearer in future publications.

In regard to the pain intensity, the results of the present study showed low TS intensity, which is in agreement with other studies that evaluated at-home bleaching [10,51-53]. In a 0–10 scale, the mean pain intensity is around 1.9 units, or in a NRS scale, the mean is approximately 0.9 units. This is related to the use of a low concentration of carbamide peroxide. The results of a recent systematic review of the literature are in line with these findings [54]. The authors showed that 10% carbamide peroxide showed similar bleaching efficacy, lower risk and intensity of TS than did more concentrated carbamide peroxide gels [54].

Regarding color change, the bleaching procedure outcome depends on the concentration of the bleaching agent, age of the patient, the ability of the agent to oxidize the organic component of dentin, the number of times the agent is in contact with dental tissue and the duration of the contact [3]. The presence or absence of the desensitizing agent in the bleaching gel does not jeopardize the bleaching efficacy. This was observed in the present study and was also concluded in a systematic review of the literature that revised the same research question [33].

The mean of the age of the patients in this study was quite young, and this can also increase the effectiveness of tooth whitening [7]. The color of the teeth will be determined by characteristics of dentin, and this is correlated with age, due to constant changes that occur in dental tissues, it means that older patients do not have as effective whitening as younger patients, beyond, due to occlusion of the dentinal tubules by mineral deposition and consequent thickening of the peritubular dentine or the lower permeability of the enamel to hydrogen peroxide due to the increase of hydroxyapatite crystals [55,56].

Various methods may be used to assess color changes. The Vita 3D Master scale has a greater number of shades (29 shades vs 16 for the Vita Classical scale), which makes it adequate for use in bleaching studies due to greater uniformity between shades and the presence of lighter shades [57]. However, it still reduced the number of authors who have adhered to this color measurement tool in their studies, which makes comparison difficult. Vita Classical is

frequently used by dentists to compare color at the beginning and after the end of treatment. The objective method used in this study (spectrophotometer) provides both a systematic and an objective color assessment and prevents the influence of external factors on shade matching, such as illumination and human physiological variabilities [58-60].

Another characteristic of this study was that the color evaluation was done in the canines rather than incisors; the advantage of this choice is that it makes the recruitment of patients easier, as it is quite difficult to find participants with incisors darker than A2 who also meet the inclusion criteria [29-32]. In study of Hasegawa et al. in 2000 [61], at the end of the bleaching treatment, no significant differences of color was observed among teeth, as bleaching produces homogenization of the dental color. This means that the bleaching effect is higher in darker teeth, so there was greater variation of color in the canines if compared with incisors [62-65]. This is a great benefit for bleaching studies, as it allows the evaluation of color changes more effectively.

Finally, the limitations of this study should be reported. We have only evaluated one bleaching product, but variations in the acidity of the gel, concentration and other additives may also have an impact on the bleaching-induced TS. Future studies should focus on the incorporation of more than one desensitizing agent or on the increase of the concentration of the potassium nitrate in the bleaching gel.

CONCLUSIONS

The incorporation of potassium nitrate and sodium fluoride to 10% carbamide peroxide at-home bleaching gel tested in this study did not reduce the risk and intensity of tooth sensitivity and did not affect color change. It is worth mentioning that this may not be true for other bleaching gel compositions.

Conflict of interest

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

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Table 4.1-1. Bleaching gel (manufacturer, composition, groups and application method).

Manufacturer	Composition	Groups	Application method
Carbamide peroxide 10% (Whiteness Perfect, FGM, Joinville, SC Brazil)	Carbamide peroxide 10%, neutralized carbopol, glycerin and distilled water	Desensitizing-containing (batch number – 210916): The gel contains 3% potassium nitrate and sodium fluoride 0.2%	Apply one drop of gel to each tooth in the tray, in the regions corresponding to the buccal surfaces of the teeth to be bleached;
		Desensitizing-free (batch number – 091116): The gel did not desensitizing agent	Daily use for three hours for 21 days.

Table 4.1-2. Baseline characteristics of the participants.

Baseline color (SGU; mean ± SD*)		10.4 ± 2.1
Age (years; mean ± SD)		22.4 ± 4.4
Gender (female; %)		71.7
Race	White (%)	85.0
	Black (%)	3.3
	Mulatto (%)	5.0
	Yellow (%)	6.7

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

Table 4.1-3. Matched tabulation of the absolute risk of tooth sensitivity for both groups along with the odds ratio.

Upper arch		Desensitizing-free			Odds ratio (95% CI interval)*
		Positive	Negative	Total	
Desensitizing-containing	Positive	33	7	40	1.4 (0.4 to 5.6)
	Negative	5	15	20	
	Total	38	22	60	
Lower arch		**Desensitizing-free**			**Odds ratio (95% CI interval)****
		Positive	Negative	Total	
Desensitizing-containing	Positive	27	4	31	0.67 (0.14 to 2.8)
	Negative	6	23	29	
	Total	33	27	60	

*McNemar's test ($p = 0.77$). Correlation coefficient between paired data = 0.56; $p < 0.0001$.
**McNemar's test ($p = 0.75$). Correlation coefficient between paired data = 0.67; $p < 0.0001$.

Table 4.1-4. Means and standard deviations of the tooth sensitivity for both groups as well as for the difference of the paired means and the correlation coefficient of the paired data.

	Pain scale	Desensitizing-containing	Desensitizing-free	Difference of the paired means	Correlation coefficient (p-value*)
Upper arch	NRS 0-4	1.0± 1.1	0.8 ± 1.0	0.2 ± 0.9	0.47 ($p < 0.001$)
	VAS 0-10	1.9 ± 2.6	1.7 ± 2.3	0.2 ± 2.2	0.52 ($p < 0.001$)
Lower arch	NRS 0-4	0.9 ± 1.2	0.9 ± 1.3	0.0 ± 0.8	0.68 ($p < 0.001$)
	VAS 0-10	2.0 ± 2.9	1.8 ± 2.8	0.2 ± 1.9	0.76 ($p < 0.001$)

*The p-value described is from the correlation coefficient.

Table 4.1-5. Medians and interquartile ranges of the tooth sensitivity intensity for both groups using the two pain scales.

	Pain scale	Desensitizing-containing	Desensitizing-free	p-value*
Upper arch	NRS 0-4	1 (0-1.7)	1 (0-1)	0.16
	VAS 0-10	0.7 (0-3.1)	0.7 (0-2.3)	0.36
Lower arch	NRS 0-4	0 (0-2)	0 (0-1)	0.52
	VAS 0-10	0 (0-3)	0.2 (0-2.6)	0.31

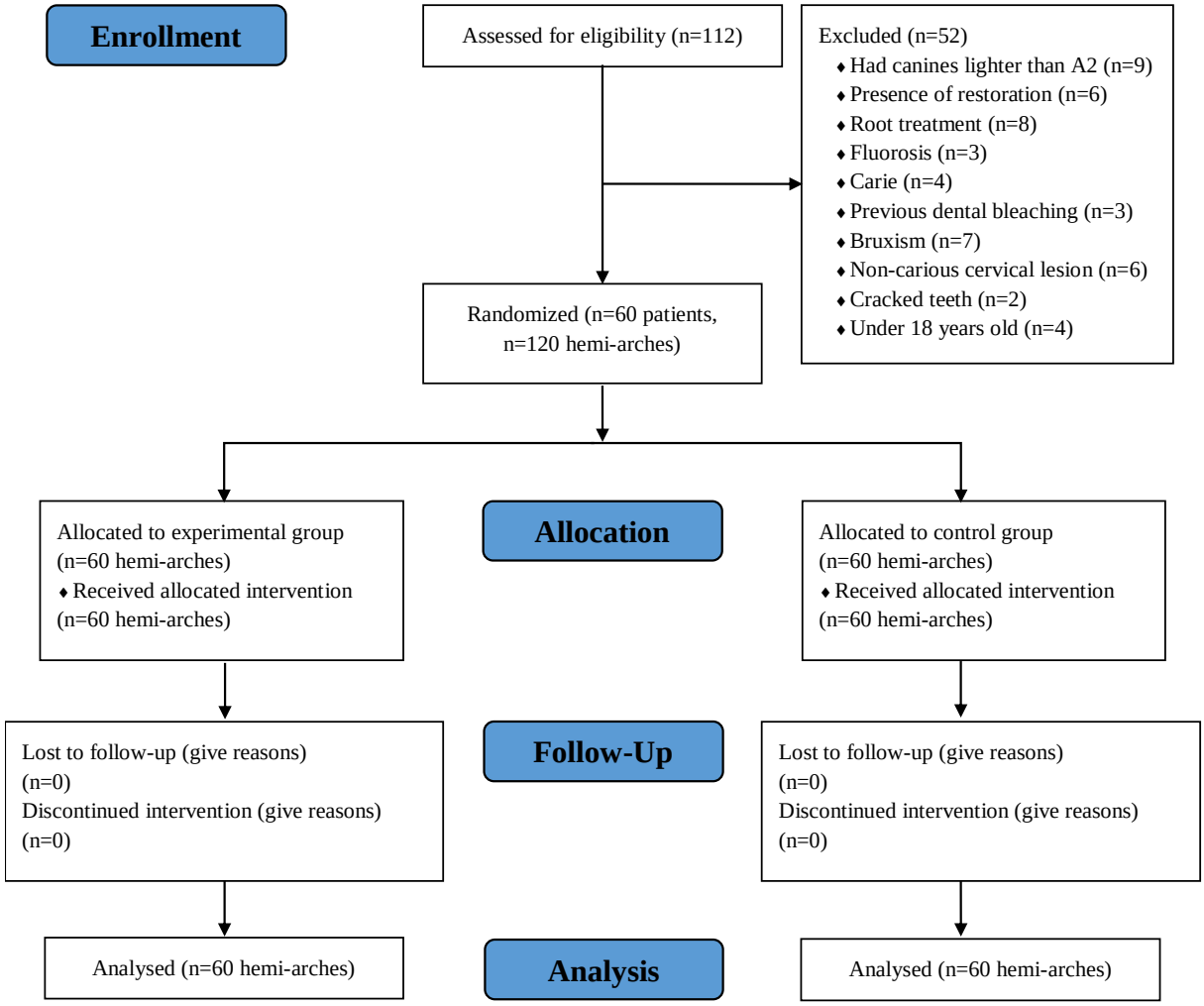
*Wilcoxon Signed Rank test.

Table 4.1-6. Means and standard deviations of ΔSGU obtained with the Vita Classical and Vita Bleachedguide and ΔE* obtained by spectrophotometer between baseline vs. 1-month post-bleaching along with the effect size (95% confidence interval) as well as the p-value of the pairwise comparison.

Color evaluation tool	Groups		Mean difference (95% CI)	p-value
	Desensitizing-containing	Desensitizing-free		
Vita Classical	7.2 ± 2.3	7.2 ± 2.3	0.0 (-0.1 to 0.2)	0.84*
Vita Bleached	7.8 ± 3.4	7.8 ± 3.3	0.0 (-0.1 to 0.2)	0.66*
ΔE*	12.0 ± 5.6	12.1 ± 5.7	-0.2 (-1.8 to 1.4)	0.82**

* Wilcoxon Signed Rank test.
** Paired t-test.

Figure 4.1-1. Flow diagram of study design phases, including enrollment and allocation criteria.



REFERENCES

[1] G.R. Samorodnitzky-Naveh, S.B. Geiger, L. Levin, Patients' satisfaction with dental esthetics, The Journal of the American Dental Association, 138 (2007) 805-808.
[2] Z.Z. Akarslan, B. Sadik, H. Erten, E. Karabulut, Dental esthetic satisfaction, received and desired dental treatments for improvement of esthetics, Indian J Dent Res, 20 (2009) 195-200.
[3] J.E. Dahl, U. Pallesen, Tooth bleaching - a critical review of the biological aspects, Critical Reviews in Oral Biology & Medicine, 14 (2003) 292-304.
[4] J.L. De Geus, M. Rezende, L.S. Margraf, M.C. Bortoluzzi, E. Fernandez, A.D. Loguercio, et al., Evaluation of genotoxicity and efficacy of at-home bleaching in smokers: A single-blind controlled clinical trial, Oper Dent, 40 (2015) E47-55.
[5] J.L. De Geus, L.M. Wambier, S. Kossatz, A.D. Loguercio, A. Reis, At-home vs in-office bleaching: A systematic review and meta-analysis, Oper Dent, (2016)
[6] M. Kashima-Tanaka, Y. Tsujimoto, K. Kawamoto, N. Senda, K. Ito, M. Yamazaki, Generation of free radicals and/or active oxygen by light or laser irradiation of hydrogen peroxide or sodium hypochlorite, J Endod, 29 (2003) 141-143.
[7] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[8] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[9] J.K. Bernardon, M. Vieira Martins, G. Branco Rauber, S. Monteiro Junior, L.N. Baratieri, Clinical evaluation of different desensitizing agents in home-bleaching gels, J Prosthet Dent, 115 (2016) 692-696.
[10] S.S. Meireles, S.S. Heckmann, F.L. Leida, S. Dos Santos Ida, A. Della Bona, F.F. Demarco, Efficacy and safety of 10% and 16% carbamide peroxide tooth-whitening gels: A randomized clinical trial, Oper Dent, 33 (2008) 606-612.
[11] D.G. Soares, F.G. Basso, J. Hebling, C.A. De Souza Costa, Concentrations of and application protocols for hydrogen peroxide bleaching gels: Effects on pulp cell viability and whitening efficacy, J Dent, 42 (2014) 185-198.
[12] D.G. Soares, F.G. Basso, E.C.V. Pontes, L.D.R. Garcia, J. Hebling, C. Costa, Effective tooth-bleaching protocols capable of reducing h2o2 diffusion through enamel and dentine, J Dent, 42 (2014) 351-358.
[13] K. Markowitz, Pretty painful: Why does tooth bleaching hurt?, Medical Hypotheses, 74 (2010) 835-840.
[14] P. Charakorn, L. Cabanilla, W. Wagner, W. Foong, J. Shaheen, R. Pregitzer, et al., The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching, Oper Dent, 34 (2009) 131-135.
[15] R.V. Armênio, F. Fitarelli, M.F. Armênio, F.F. Demarco, A. Reis, A.D. Loguercio, The effect of fluoride gel use on bleaching sensitivity, The Journal of the American Dental Association, 139 (2008) 592-597.
[16] C. Kose, A. Reis, L.N. Baratieri, A.D. Loguercio. Clinical effects of at-home bleaching along with desensitizing agent application. Am J Dent; 2011. p. 379-382.
[17] J. Peacock, R. Orchardson, Action potential conduction block of nerves in vitro by potassium citrate, potassium tartrate and potassium oxalate, J Clin Periodontol, 26 (1999) 33-37.
[18] V.B. Haywood, W.F. Caughman, K.B. Frazier, M.L. Myers, Tray delivery of potassium nitrate--fluoride to reduce bleaching sensitivity, Quintessence Int, 32 (2001)
[19] J.R. Gallo, J.O. Burgess, A.H. Ripps, M.J. Bell, D.E. Mercante, J.M. Davidson, Evaluation of 30% carbamide peroxide at-home bleaching gels with and without potassium nitrate--a pilot study, Quintessence Int, 40 (2009)
[20] C. Navarra, B. Reda, M. Diolosà, I. Casula, R. Di Lenarda, L. Breschi, et al., The effects of two 10% carbamide peroxide nightguard bleaching agents, with and without desensitizer, on enamel and sensitivity: An in vivo study, Int J Dent Hyg, 12 (2014) 115-120.
[21] M. Giniger, J. Macdonald, S. Ziemba, H. Felix. The clinical performance of professionally dispensed bleaching gel with added amorphous calcium phosphate. J Am Dent Assoc; 2005. p. 383-392.

[22] W.D. Browning, D.C. Chan, M.L. Myers, W.W. Brackett, M.G. Brackett, D.H. Pashley, Comparison of traditional and low sensitivity whiteners, Oper Dent, 33 (2008) 379-385.
[23] J.B. Da Costa, R. Mcpharlin, T. Hilton, J.L. Ferracane, M. Wang, Comparison of two at-home whitening products of similar peroxide concentration and different delivery methods, Oper Dent, 37 (2012) 333-339.
[24] N. Pandis, B. Chung, R.W. Scherer, D. Elbourne, D.G. Altman, Consort 2010 statement: Extension checklist for reporting within person randomised trials, BMJ, 357 (2017) j2835.
[25] Q. Alomari, E. Daraa. A randomized clinical trial of in-office dental bleaching with or without light activation. The journal of contemporary dental practice; 2010. p. E017-024.
[26] J.L. De Geus, M.B. De Lara, T.A. Hanzen, E. Fernandez, A.D. Loguercio, S. Kossatz, et al., One-year follow-up of at-home bleaching in smokers before and after dental prophylaxis, J Dent, 43 (2015) 1346-1351.
[27] E.A. De Paula, S. Kossatz, D. Fernandes, A.D. Loguercio, A. Reis, Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: A randomized tripleblind clinical trial, Oper Dent, 39 (2014) 128-135.
[28] L.Y. Tay, C. Kose, A.D. Loguercio, A. Reis, Assessing the effect of a desensitizing agent used before in-office tooth bleaching, J Am Dent Assoc, 140 (2009) 1245-1251.
[29] A. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, 41 (2016) 455-464.
[30] J.C. Ontiveros, R.D. Paravina, Color change of vital teeth exposed to bleaching performed with and without supplementary light, J Dent, 37 (2009) 840-847.
[31] N.U. Wetter, E.P. Branco, A.M. Deana, J.E. Pelino, Color differences of canines and incisors in a comparative long-term clinical trial of three bleaching systems, Lasers Med Sci, 24 (2009) 941-947.
[32] O. Polydorou, M. Wirsching, M. Wokewitz, P. Hahn. Three-month evaluation of vital tooth bleaching using light units-a randomized clinical study. Oper Dent; 2013. p. 21-32.
[33] M. Rezende, F. Coppla, K. Chemin, A.C. Chibinski, A.D. Loguercio, A. Reis, Tooth sensitivity after dental bleaching with a desensitizing-containing and a desensitizing-free bleaching gel: A systematic review and meta-analysis, Oper Dent, (2018)
[34] V. Alonso De La Peña, O. Balboa Cabrita. Comparison of the clinical efficacy and safety of carbamide peroxide and hydrogen peroxide in at-home bleaching gels. Quintessence Int; 2006. p. 551-556.
[35] M. Giniger, J. Macdonald, M. Spaid, H. Felix, A 180-day clinical investigation of the tooth whitening efficacy of a bleaching gel with added amorphous calcium phosphate, J Clin Dent, 16 (2005) 11-16.
[36] D. Ziebolz, K. Helms, C. Hannig, T. Attin. Efficacy and oral side effects of two highly concentrated tray-based bleaching systems. Clin Oral Investig; 2007. p. 267-275.
[37] L. Tam, Effect of potassium nitrate and fluoride on carbamide peroxide bleaching, Quintessence Int, 32 (2001)
[38] S. Al Shethri, B.A. Matis, M.A. Cochran, R. Zekonis, M. Stropes. A clinical evaluation of two in-office bleaching products. Oper Dent; 2003. p. 488-495.
[39] E. Lesaffre, B. Philstrom, I. Needleman, H. Worthington, The design and analysis of split-mouth studies: What statisticians and clinicians should know, Stat Med, 28 (2009) 3470-3482.
[40] A.A. Antczak-Bouckoms, J. Tulloch, C.S. Berkey, Split-mouth and cross-over designs in dental research, J Clin Periodontol, 17 (1990) 446-453.
[41] Y. Wang, J. Gao, T. Jiang, S. Liang, Y. Zhou, B.A. Matis, Evaluation of the efficacy of potassium nitrate and sodium fluoride as desensitizing agents during tooth bleaching treatment - a systematic review and meta-analysis, J Dent, 43 (2015) 913-923.
[42] S. Kossatz, G. Martins, A.D. Loguercio, A. Reis. Tooth sensitivity and bleaching effectiveness associated with use of a calcium-containing in-office bleaching gel. J Am Dent Assoc; 2012. p. e81-87.
[43] G.C. Martins, A.C.S.D.A. Izidoro, L.M.B. Meister, S. Kossatz, O.M.M. Gomes, A.D. Loguercio, et al., Avaliação clínica do uso de um dessensibilizante antes do clareamento de consultório, Rev Assoc Paul Cir Dent, 65 (2011) 119-123.

[44] M. Pale, J.R. Mayoral, J. Llopis, M. Valles, J. Basilio, M. Roig, Evaluation of the effectiveness of an in-office bleaching system and the effect of potassium nitrate as a desensitizing agent, Odontol, 102 (2014) 203-210.
[45] E. Bonafe, A.D. Loguercio, A. Reis, S. Kossatz, Effectiveness of a desensitizing agent before in-office tooth bleaching in restored teeth, Clin Oral Investig, 18 (2014) 839-845.
[46] S. Kwon, D. Dawson, D. Schenck, J. Fiegel, P. Wertz, Spectrophotometric evaluation of potassium nitrate penetration into the pulp cavity, Oper Dent, 40 (2015) 614-621.
[47] L. Tam, Clinical trial of three 10% carbamide peroxide bleaching products, J Can Dent Assoc, 65 (1999) 201-207.
[48] R.H. Leonard Jr, V.B. Haywood, C. Phillips, Risk factors for developing tooth sensitivity and gingival irritation associated with nightguard vital bleaching, Quintessence Int, 28 (1997)
[49] K.A. Karpinia, I. Magnusson, P.A. Sagel, X. Zhou, R.W. Gerlach. Vital bleaching with two at-home professional systems. Am J Dent; 2002. p. 13a-18a.
[50] M. Bizhang, Y.H. Chun, K. Damerau, P. Singh, W.H. Raab, S. Zimmer, Comparative clinical study of the effectiveness of three different bleaching methods, Oper Dent, 34 (2009) 635-641.
[51] L.Y. Tay, C. Kose, D.R. Herrera, A. Reis, A.D. Loguercio, Long-term efficacy of in-office and at-home bleaching: A 2-year double-blind randomized clinical trial, Am J Dent, 25 (2012) 199-204.
[52] S. Morgan, A.A. Jum'ah, P. Brunton, Assessment of efficacy and post-bleaching sensitivity of home bleaching using 10% carbamide peroxide in extended and non-extended bleaching trays, Br Dent J, 218 (2015) 579-582.
[53] B.A. Matis, M.A. Cochran, G.J. Eckert, J.I. Matis, In vivo study of two carbamide peroxide gels with different desensitizing agents, Oper Dent, 32 (2007) 549-555.
[54] J.L. De Geus, L.M. Wambier, T.F. Boing, A.D. Loguercio, A. Reis, At-home bleaching with 10% vs. More concentrated carbamide peroxide gels: A systematic review and meta-analysis., Oper Dent, (2018)
[55] D.R. Morse, Age-related changes of the dental pulp complex and their relationship to systemic aging, Oral Surgery, Oral Medicine, Oral Pathology, 72 (1991) 721-745.
[56] B. He, S. Huang, C. Zhang, J. Jing, Y. Hao, L. Xiao, et al., Mineral densities and elemental content in different layers of healthy human enamel with varying teeth age, Archives of Oral Biology, 56 (2011) 997-1004.
[57] R.D. Paravina, W.M. Johnston, J.M. Powers, New shade guide for evaluation of tooth whitening--colorimetric study, J Esthet Restor Dent, 19 (2007) 276-283; discussion 283.
[58] M. Rezende, E. Bonafe, L. Vochikovski, P.V. Farago, A.D. Loguercio, A. Reis, et al., Pre- and postoperative dexamethasone does not reduce bleaching-induced tooth sensitivity a randomized, triple-masked clinical trial, J Am Dent Assoc, 147 (2016) 41-49.
[59] J. Da Costa, E. Lubisich, J. Ferracane, T. Hilton, Comparison of efficacy of an in-office whitening system used with and without a whitening priming agent, J Esthet Restor Dent, 23 (2011) 97-104.
[60] E. Fernandez, C. Bersezio, J. Bottner, F. Avalos, I. Godoy, D. Inda, et al., Longevity, esthetic perception, and psychosocial impact of teeth bleaching by low (6%) hydrogen peroxide concentration for in-office treatment: A randomized clinical trial, Oper Dent, (2016)
[61] A. Hasegawa, A. Motonomi, I. Ikeda, S. Kawaguchi, Color of natural tooth crown in japanese people, Color Res Appl, 25 (2000) 43-48.
[62] M. Tavares, J. Stultz, M. Newman, V. Smith, R. Kent, E. Carpino, et al., Light augments tooth whitening with peroxide, J Am Dent Assoc, 134 (2003) 167-175.
[63] S. Kossatz, A.P. Dalanhol, T. Cunha, A. Loguercio, A. Reis, Effect of light activation on tooth sensitivity after in-office bleaching, Oper Dent, 36 (2011) 251-257.
[64] L.S. Machado, R.B. Anchieta, P.H. Dos Santos, A.L. Briso, N. Tovar, M.N. Janal, et al., Clinical comparison of at-home and in-office dental bleaching procedures: A randomized trial of a split-mouth design, Int J Periodontics Restorative Dent, 36 (2016) 251-260.
[65] L.C. Almeida, H. Riehl, P.H. Santos, M.L. Sundfeld, A.L. Briso. Clinical evaluation of the effectiveness of different bleaching therapies in vital teeth. The International journal of periodontics & restorative dentistry; 2012. p. 303-309.

Artigo 2

TÍTULO: TOOTH SENSITIVITY WITH A DESENSITIZING-CONTAINING IN-OFFICE BLEACHING GEL – A RANDOMIZED TRIPLE-BLIND CLINICAL TRIAL

STATUS: SUBMETIDO

REVISTA: JOURNAL OF DENTISTRY

4.2 ARTIGO 2 – TOOTH SENSITIVITY WITH A DESENSITIZING-CONTAINGIN IN-OFFICE BLEACHING GEL – A RANDOMIZED TRIPLE-BLIND CLINICAL TRIAL

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ABSTRACT

Objective: Desensitizing agents can be incorporated into bleaching gels to reduce the bleaching-induced tooth sensitivity (TS) of in-office bleaching. This randomized clinical trial (RCT) evaluated the risk and intensity of TS and color change after in-office bleaching with a desensitizing (5% potassium nitrate) and a desensitizing-free 35% hydrogen peroxide (HP) gel (Whiteness HP AutoMixx, FGM).

Methods: A triple-blind, split-mouth RCT was conducted on 60 caries-free adult patients, who received two bleaching sessions with 35% HP gel at 1-week intervals. The absolute risk and intensity of TS were assessed with a Visual Analogue Scale and a Numerical Rating Scale up to 48 h after each session. Color change was recorded using shade guides (Vita Classical and Vita Bleachedguide) and the Easyshade spectrophotometer at baseline and 30 days after bleaching. The risk of TS was evaluated with the McNemar's test and the intensity of TS was evaluated with the Wilcoxon Signed Rank. Color change (ΔSGU and ΔE*) was evaluated with the Wilcoxon Signed Rank test and paired t-test ($\alpha = 0.05$).

Results: No difference in the absolute risk of TS was observed, but the intensity of TS was lower in the desensitizing-group in all time assessments up to 24 h ($p < 0.05$). No difference in color change was observed between the groups ($p > 0.05$).

Conclusion: The incorporation of 5% potassium nitrate into in-office bleaching gels did not affect color change but reduced the intensity of TS.

Clinical Relevance: The incorporation of potassium nitrate in an in-office bleaching gel does not reduce the risk of tooth sensitivity but reduce its intensity without jeopardizing color change.

Keywords: Tooth bleaching agents. Hydrogen Peroxide. Dentin Sensitivity.

INTRODUCTION

A survey conducted in 2015 by the American Academy of Cosmetic Dentistry [1] has shown that the search for cosmetic procedures in dentistry has grown significantly. One of the main reasons that patients seek dental work is dissatisfaction with the appearance of their teeth. This was supported by a study conducted by Israeli authors [2], from a total of 407 interviewed patients, 89.3% complained about their dental discoloration, followed by their dental appearance (37.3%) and poor alignment of the teeth (23.7%).

Dental bleaching is the treatment of choice to reduce dissatisfaction among patients with dental discoloration, since it is an inexpensive, conservative and non-invasive technique. Bleaching has been well accepted by patients and professionals, given its effectiveness and safety [3].

Regardless of the type of bleaching technique selected, bleaching-induced tooth sensitivity is a very common adverse side effect [4,5]. Clinical studies show that the risk of bleaching-induced TS, as reported by patients, can vary from 55% to 90% [5-7]. Although the risk of tooth sensitivity is similar for at-home and in-office bleaching, their intensities are different, with the in-office technique having much higher intensity [5,8].

The higher intensity of tooth sensitivity for in-office bleaching is likely the result of the concentration of hydrogen peroxide used, which diffuses into the dental structure and induces the release of cell-derived factors such as adenosine triphosphate (ATP) and prostaglandins, which can excite or sensitize nociceptors [8,9]. In addition, the presence of hydrogen peroxide damages the pulp, generating an inflammatory response with consequent pain stimuli [10-12].

Anti-inflammatory, analgesic, antioxidant and corticosteroids drugs have been evaluated as alternatives to minimize tooth sensitivity; however, clinical studies indicate that the use of oral drugs does not reduce the risk and intensity of tooth sensitivity [7,13-16] as synthesized in a recent systematic review [17]. Instead, a promising approach to minimizing bleaching-induced tooth sensitivity is the application of topical desensitizers before in-office bleaching procedures [18-22] such as 5% potassium nitrate and 2% sodium fluoride gel [8]. Potassium nitrate reduces bleaching-induced tooth sensitivity by increasing the concentration of potassium ions around the nerve fibers, which prevents repolarization of the sensory nerve. Yet, despite its promising results in reducing the risk and intensity of tooth sensitivity, this technique adds another clinical step to the bleaching process [18,20,23].

One way of reducing this extra clinical step would be to add this desensitizing agent to the bleaching gel. However, few available studies have compared desensitizing and desensitizing-free gels; these studies tested the gels in the at-home protocol and showed conflicting results [24,25]. To the best of the authors' knowledge, no study has compared in-office bleaching gels with and without desensitizing agents.

Thus, the objective of this randomized, split-mouth, triple-blind clinical study was to compare the risk and intensity of tooth sensitivity among patients who submitted to in-office bleaching desensitizing-containing 5% potassium nitrate and a desensitizing-free 35% hydrogen peroxide gel.

MATERIAL AND METHODS

Ethical approval and protocol registration

The clinical investigation was approved (protocol number 1.756.984) by the Scientific Review Committee and the Committee for the Protection of Human Participants of the State University of Ponta Grossa. It was registered in the Brazilian Clinical Trials Registry (ReBEC) under identification number RBR-4TKYS8. We prepared this article using the protocol established by the Consolidated Standards of Reporting Trials Statement (CONSORT) with extension for within-person designs [26].

Trial design, settings and locations of data collection

This study was a randomized, split-mouth, triple-blind clinical trial in which the patient, operator and evaluator were masked to each patient's group assignment. A third researcher who was not involved in the evaluation process was responsible for the randomization process. All of the participants were informed about the nature and objectives of the study. The study was performed from November 1, 2016, to March 31, 2017, in the Clinics of the School of Dentistry of the local university.

Recruitment

Participants were recruited through written advertisements placed on the university's walls. All of the volunteer participants signed an informed consent form before being enrolled in the study.

Eligibility criteria

Based on pre-established criteria, we selected 60 subjects who volunteered for this study. The participants included in the present randomized clinical trial were between 18 and 50 years old and had good general and oral health. The participants were required to have at least six maxillary anterior teeth free of caries and restorations, with canine shade A2 or

darker, as judged by comparison with a value-oriented shade guide (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Germany).

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

Sample size calculation

The primary outcome of this study was the absolute risk of tooth sensitivity. The absolute risk of tooth sensitivity (that is, the percentage of patients who reported pain at some point during dental bleaching) was reported to be 87% in an earlier study [20] for in-office bleaching with 35% hydrogen peroxide gel. Using an alpha of 0.05, 90% power and a two-sided test, the minimum sample size in this equivalence trial was 60 patients (considering 20% loss) to detect a 30% difference in the risk of tooth sensitivity between groups.

The sample size was calculated without accounting for the potential correlation between the paired treatment outcomes. This approach resulted in a larger sample size than if the correlation coefficient between treatment outcomes were not zero. We used this approach because published within-person trials do not report this correlation coefficient; thus, we opted to be conservative [26].

Randomization and allocation concealment

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

Blinding

This study was a triple-blind clinical trial in which the patient, operator and evaluator were masked to the patient's group assignment. A third researcher who was not involved in

the implementation and evaluation processes was responsible for the randomization and the delivery of and guidance on the administration of the gels.

Both the bleaching (desensitizing) and control (desensitizing-free) gels were delivered in identical syringes coded as "A" and "B." Both gels had similar consistency and color. Only the research coordinator knew the coding system.

Study intervention

Three operators with more than four years of clinical experience each performed the bleaching procedure. After placement of a lip retractor (Arcflex, FGM Dental Products, Joinville, Brazil), a light-cured gingival barrier (Top Dam, FGM Dental Products, Joinville, Brazil) was placed on the gingival tissue of the teeth to be bleached (from the 2nd left premolar to the 2nd right premolar). The gingival barrier was then light-cured according to the manufacturer's recommendations (Radii-Cal, SDI, Bayswater, Australia).

Both arches were bleached with a 35% hydrogen peroxide gel. In the desensitizing-free group, the commercial product Whiteness HP AutoMixx (FGM, Joinville, Brazil)—a desensitizing-free agent—was used. In the desensitizing group, the same bleaching agent was modified by adding 5% potassium nitrate, while keeping the hydrogen peroxide concentration at 35%. The potassium nitrate was incorporated by the manufacturer of Whiteness HP AutoMixx under the same rigorous control as the commercial product. No differences between the desensitizing-free and desensitizing gels were visible during manipulation and application. Table 4.2-1 depicts details about the compositions of the bleaching materials.

The right and left quadrants were separated with a metallic matrix inserted between the central incisors to avoid mixture of the bleaching gels. Both arches were bleached, each with its respective product, in a single 50-minute application. After this period, the gel was removed with saliva ejector and gauze, and the oral cavity was rinsed with water to remove residual gel. Two bleaching sessions were performed at a one-week interval.

Outcomes

Tooth sensitivity evaluation

The patients were instructed to fill out a form to record their tooth sensitivity during bleaching and up to 1 h, 24 h, and 48 h post-bleaching for both bleaching sessions. The patients were explained how to perform the procedure in detail. Before the bleaching began, each patient received a paper form with a mouth drawn on it containing the teeth of the upper arch and the two pain scales (described below). Each patient received an explanation on how

to fill out the form, with emphasis on the researchers being interested in differences between the two upper maxillary arches. They were not instructed to point out the painful teeth in the present study, although they were able to do so if requested. They were told to fill out the form every time they felt pain. We also explained to the patients that if they did not feel any tooth sensitivity, their intensity would be zero. These forms were returned to the researchers during the patients' next appointment (1 week later).

For the 5-point Numeric Rating Scale (NRS), the patient was asked to indicate the degree of sensitivity for each of the periods above, with 0 meaning no sensitivity, 1 meaning mild tooth sensitivity, 2 meaning moderate tooth sensitivity, 3 meaning considerable tooth sensitivity, and 4 meaning severe tooth sensitivity. In addition, the participants were also instructed to record the pain intensity using the Visual Analog Scale (VAS). This scale is a 10-centimeter horizontal line with scores of 0 and 10 at their ends, with 0 meaning no sensitivity and 10 meaning severe tooth sensitivity. The patient marked the intensity of their tooth sensitivity with a vertical line across the horizontal line of the scale. Then, the distance in millimeters from the zero end was measured with the aid of a millimeter ruler.

The data from both bleaching sessions were merged for statistical purposes, as they did not show any different patterns. For this purpose, the worst score (NRS scale) and the highest numerical value (VAS) from the two bleaching sessions during and up to 48 h post-bleaching were used to analyze the bleaching-induced tooth sensitivity.

If the participant scored 0 (no sensitivity) in all time assessments from both bleaching sessions, this participant was considered to be insensitive to the bleaching protocol. In all other circumstances, the participants were considered to have bleaching-induced tooth sensitivity.

Color evaluation

Two experienced and calibrated dentists (kappa statistics higher than 80% after previous calibration) who were not involved in the randomization procedures performed clinical assessments at baseline, 1 week after the first bleaching session, 1 week after the second bleaching and 1 month after the bleaching treatment. We never evaluated color immediately after each bleaching session to avoid the effects of dehydration and demineralization on the color measures. We evaluated color using the VITA Classical (VITA Classical Shade, Vita Zahnfabrik, Bad Säckingen, Germany) and VITA Bleachedguide 3D-MASTER (BG, VITA Zahnfabrik, Bad Säckingen, Germany). In addition, we performed an

objective color evaluation with a VITA Easyshade spectrophotometer (VITA Zahnfabrik, Bad Säckingen, Germany).

The Vita Classical scale is arranged in 16 tabs from the highest value (B1) to the lowest (C4): B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4, C4. Although this scale is not linear in the truest sense, color changes have been considered continuous and linear in several clinical studies on tooth whitening [6,7,20,27,28]. The VITA Bleachedguide 3D-MASTER contains lighter shade tabs and is organized from the highest value (0M1) to the lowest (5M3).

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

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

Statistical methods

The analysis followed the intent-to-treat protocol and involved all of the randomly divided participants (Figure 4.2-1). The statistician was also blinded to the groups. The risk of tooth sensitivity in both groups was compared with the McNemar's exact test ($\alpha = 0.05$, test for proportion of dependent data ratio). The odds ratio and the confidence interval (CI) for the effect size were also calculated.

The tooth-sensitivity intensity data for both the VAS and NRS scales were plotted in histograms and inspected for normal distributions. As the data did not have normal distribution, the groups were compared using the Wilcoxon Signed Rank test and Student-Newman-Keuls method (NRS) and Friedman test (VAS) ($\alpha = 0.05$). We calculated the phi correlation coefficient for pairs of binary data on the risk of pain between the two groups and the Spearman correlation coefficient between the groups for the intensity of tooth sensitivity.

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

RESULTS

Characteristics of the included participants

A total of 139 participants were examined according to the inclusion and exclusion criteria (Figure 4.2-1), but only 60 participants remained for the clinical trial. Table 4.2-2 describes the baseline color of the participants and their gender distribution. No hypothesis testing was performed for the baseline features, as any differences between these features were attributed to chance alone.

Adherence to the protocol

All of the participants attended the recall visits during the bleaching protocol. Figure 4.2-1 depicts the participant flow diagram in the different phases of the study design.

Risk of tooth sensitivity

The phi correlation coefficient for pairs of binary data was moderate and significant ($r = 0.64$; $p < 0.0001$). A total of 56 patients presented pain in the desensitizing-free group; among them, only two patients reported pain exclusively in the desensitizing-free group. Fifty-five patients reported pain in the desensitizing-containing group; among them, only one experienced pain exclusively in the desensitizing-containing group. In comparative terms, the odds ratio for pain (Table 4.2-3; OR = 0.5; 95% CI 0.0 to 9.6) was 50% lower for the desensitizing-containing gel. However, as the 95% confidence interval does not exclude benefit or harm (it crosses the null value of 1), no significant differences between the groups were detected (Table 4.2-3; $p = 1.0$).

Intensity of tooth sensitivity

Pain was positively correlated in both groups, with strong and significant correlations for the NRS ($r = 0.88$; $p < 0.0001$) and VAS scales ($r = 0.70$, $p < 0.0001$). The NRS scale was unable to detect significant differences between groups at the different time assessments (Table 4.2-4; $p > 0.21$); however, the VAS scale detected differences (Table 4.2-5). Lower pain intensity was observed for the desensitizing-containgin gel compared to the desensitizing-free gel during bleaching ($p = 0.003$), up to 1 h ($p = 0.002$) and 24 h ($p = 0.01$) after bleaching. The mean differences of 1.2 (0.3 to 2.1) during the bleaching, 1.6 (0.6 to 2.6) at 1 h after bleaching and 1.2 (0.0 to 2.47) at 24 h after bleaching are clinically relevant.

Color change

Significant whitening was detected with the three different tools (Table 4.2-6). Bleaching of approximately 8 units of color in the Vita Classical scale, 9 units in the Vita Bleachedguide and 13 units in the ΔE^* was observed (Table 4.2-6). No significant difference of color change was observed between the groups (Table 4.2-6; $p > 0.32$).

DISCUSSION

We opted for a within-paired design, also known as a split-mouth design, to evaluate our research question. This study design is attractive because it removes the inter-individual variability from the estimates of the treatment effect [29] and also increases the study power without the need for a high sample size.

Another methodological aspect that deserves some discussion is the type of teeth selected for the color change evaluation. In this study, color changes were evaluated in the canines rather than in the incisors. This was previously done in earlier studies [30-32]. Wetter et al. in 2009 [31], showed that the selection of the teeth does not have any impact on the findings. Hasegawa et al., in 2000 [33], indicated that bleaching procedures homogenize the whiteness of teeth and therefore the bleaching effect is higher in darker teeth, which makes them suitable for bleaching studies. Thus, using canines instead of incisors made patient recruitment easier and increased the sensitivity of finding subtle differences between bleaching protocols due to the higher bleaching level of the canines.

Hydrogen peroxide has a very low molecular weight and thus can easily penetrate enamel and dentin and reach the dental pulp within a few minutes [34-37]. Hydrogen peroxide causes an inflammatory reaction in the pulp tissue [12,38] as well as oxidative stress and cell damage, leading to the release of adenosine triphosphate, prostaglandins and other inflammatory mediators [8,9,15] which stimulate nociceptors.

This side effect has been shown to affect between 55% to 90% of the patients who undergo in-office dental bleaching [5,6,15,21,22,39]. As mentioned in the introduction, the previous application of potassium nitrate as a desensitizing agent before bleaching can minimize tooth sensitivity [18-22] but with the disadvantage of adding an extra step.

Although previous studies have focused on the inclusion of desensitizers in bleaching gels, most of the clinical trials on this topic did not use an unbiased methodology, and none of the available studies were performed in-office, as recently demonstrated in a systematic review of the literature on this topic [40]. The present study shows that the percentage of patients who reported pain at some moment during dental bleaching did not differ between groups, regardless of the bleaching gel used. Approximately 80% of complaints involved both sides of the mouth, similar to another clinical trial that employed 35% hydrogen peroxide [41-44]. However, when tooth sensitivity was analyzed at different assessment times with the VAS scale, a clinically important and statistically significant difference was observed between groups in the periods up to 24 h.

Lower intensity of tooth sensitivity was observed for the desensitizer-containing gel, probably due to the well-known mechanism of potassium nitrate in reducing dental sensitivity. Potassium nitrate prevents repolarization of the sensory nerve by increasing the concentration of potassium ions around the nerve fibers and thus reduced the excitability of the nerve, which explains the almost anesthetic effect on the nerve [21,45] and the observed reduction in the intensity of the bleaching-induced tooth sensitivity. This is in accordance with the results of a recent systematic review of the literature [8], which concluded that potassium nitrate and sodium fluoride can reduce dental sensitivity compared to placebos.

From 24 h on, the risk of pain as well as its intensity are dramatically reduced. This is in agreement with earlier studies that reported that bleaching-induced tooth sensitivity after in-office bleaching usually occurs within the first 24 h following the bleaching protocol [20,46,47]. The lack of tooth sensitivity after 48 h seems to be consistent in the literature; most of the subjects did not report any tooth sensitivity two days after the end of the bleaching [48,49].

We cannot ignore the fact that the NRS and VAS showed a lack of agreement in this study. A possible explanation may be due to the psychometric properties of each scale. Specifically, the VAS assesses pain on a continuous scale, whereas the NRS assesses pain on a discrete scale, with the smallest unit of change being 1 unit. Interestingly, the agreement between the VAS and NRS seems to vary across pain severity levels. Although both pain

scales measure the same phenomenon, the pain ratings of the pain scales were not associated [50].

According to Hjermstad et al., in 2011 [51], NRS scores basically list descriptors of pain (such as no pain, mild, moderate or severe) and may be translated into assigned numbers; this rating scale is not very sensitive but is easy to understand. In contrast, the VAS used in this study, with the anchor labels “no sensitivity” and “severe sensitivity,” is very robust, which is the reason why we are more confident in the results provided by this pain scale, besides it being the most common pain scale used in bleaching studies [7,15,21,52].

Regarding the color evaluation, no significant differences were observed between the groups, which shows that the presence of potassium nitrate does not impair the outcome of bleaching. We used three instruments to evaluate color change through visual or instrumental color analysis. A spectrophotometer provides a systematic and objective color assessment, while visual matching is affected by many factors, such as illumination and variations in human physiology, but it is the most commonly used method among clinicians [53-55]. In this study, we observed a color change of 13 units of ΔE* for both groups, as in Mena-Serrano, 2016 [30].

We also used the VITA Classical shade guide, which is frequently used in the literature [46,56,57], although it was not primarily designed for evaluating dental bleaching. Thus, we employed the Bleachedguide 3D-Master scale, too which is a shade guide scale that was specifically designed to evaluate color changes in bleached teeth. This scale was developed from studies by Paravina [54,58], who introduced a wider range of whiter colors, with better color distribution and smaller error coverage than other color guides. Despite these advantages, this scale is still not routinely used to evaluate color in dentistry; some say that the sole use of this scale would preclude comparisons with previous literature studies [14].

Finally, the limitations of this study should be reported. We only evaluated one bleaching product, but variations in the acidity of the gel and other additives may also impact the bleaching-induced tooth sensitivity. Future studies should focus on incorporating potassium nitrate into gels with different acidities and on incorporating more than one desensitizing agent into the bleaching gel.

CONCLUSION

The incorporation of potassium nitrate into an in-office bleaching gel did not reduce the risk of tooth sensitivity, but it significantly reduced the intensity of the bleaching-induced tooth sensitivity without jeopardizing the color change.

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Conflicts of interest

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

Table 4.2-1. Bleaching Gel (manufacturer, composition, groups and application method).

Manufacturer	Composition	Groups	Application Method
Hydrogen peroxide 35% (Whiteness HP AutoMixx, FGM, Joinville, SC Brazil)	Hydrogen peroxide 35%, thickening, neutralizing, consisting of calcium, glycol, dye, inorganic filler and deionized water	Desensitizing-containing: The gel contained 5% potassium nitrate (lot: 171116)	A single 50-minute application
		Desensitizing-free: The gel did not desensitizing agent (lot: 060916)	

Table 4.2-2. Baseline Characteristics of the Participants.

Baseline color (SGU; mean ± SD)*		10.1 ± 3.0
Age (years; mean ± SD)		22.1 ± 5.1
Gender (female; %)		58.3
Race	White (%)	88.3
	Black (%)	1.7
	Mulatto (%)	8.3
	Yellow (%)	1.7

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

Table 4.2-3. Matched tabulation of outcomes with the two treatments along with the odds ratio.

Upper arch		Desensitizing-free			Odds ratio (95% CI interval)*
		Positive	Negative	Total	
Desensitizing-containing	Positive	54	1	55	0.5 (0.0 to 9.6)
	Negative	2	3	5	
	Total	56	4	60	

*McNemar's test (p = 1.0). Correlation coefficient between paired data = 0.64; p < 0.0001.

Table 4.2-4. Medians and interquartile ranges of the tooth sensitivity intensity at different assessment points using the NRS scale.

Assessment times	Desensitizing-containing*	Desensitizing-free*	p-value**
During bleaching	1 (0-2) B	1 (0-2) B	0.21
Up to 1 h	2 (1-3) C	2 (1-3) C	0.43
Up to 24 h	2 (1-3) C	2 (0.2-3) C	0.81
Up to 48 h	0 (0-0) A	0 (0-0.7) A	1.00

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

Table 4.2-5. Tooth sensitivity intensity at different assessment points using the VAS scale.

Assessment times	Medians and interquartile range*		p-value**	Means and standard deviations		Difference in means (95% CI)
	Desensitizing-containing	Desensitizing-free		Desensitizing-containing	Desensitizing-free	
During bleaching	0 (0-1.6) B	1.6 (0-4.3) B	0.003	1.3 (2.1)	2.5 (2.8)	1.2 (0.3 to 2.1)
Up to 1 h	1.4 (0-5.4) C	4.2 (1.3-7.6) C	0.002	2.9 (3.2)	4.5 (3.3)	1.6 (0.6 to 2.6)
Up to 24 h	2.6 (0-5.6) C	4.5 (0.5-7.8) C	0.01	3.2 (3.3)	4.4 (3.7)	1.2 (0.0 to 2.47)
Up to 48 h	0 (0-0.6) A	0 (0-0.8) A	1.00	0.8 (1.9)	0.8 (1.8)	0.0 (-0.7 to 0.7)

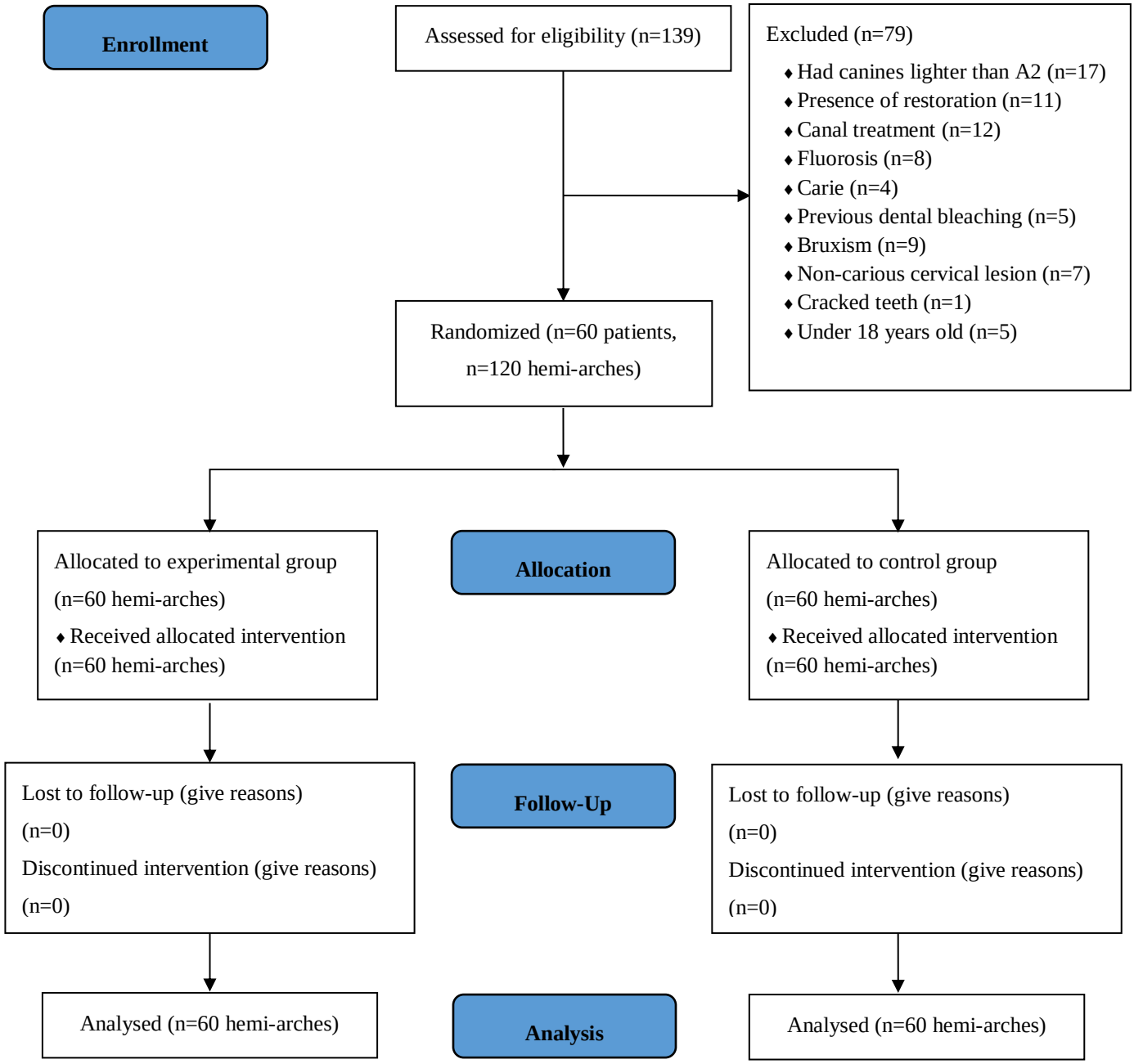
*Within each column, significant differences ($p < 0.05$) are represented distinct uppercase letters (Friedman test).
**Comparisons between groups at each assessment point was performed with the Wilcoxon Signed Rank test.

Table 4.2-6. Means and standard deviations of ΔSGU obtained with the Vita Classical and Vita Bleachedguide and ΔE* obtained by spectrophotometer between baseline vs. 1-month post-bleaching along with the p-value of the pairwise comparison, as well as, the effect size (95% confidence interval).

Color evaluation tool	Groups		Mean difference (95% CI)	p-value
	Desensitizing-containing	Desensitizing-free		
Vita Classical	7.8 ± 2.5	7.8 ± 2.6	-0.0 (-0.2 to 0.0)	0.32*
Vita Bleached	9.3 ± 2.9	9.3 ± 2.9	0.0 (0.4 to 0.0)	1.0*
ΔE*	13.2 ± 5.5	14.0 ± 5.9	0.8 (6.5 to 0.8)	0.33**

* Wilcoxon Signed Rank test.
** Paired t-test.

Figure 4.2-1. Flow diagram of study design phases, including enrollment and allocation criteria.



REFERENCES

[1] Aacd, Cosmetic dentistry state of the industry survey 2015, American Academy of Cosmetic Dentistry, (2015)
[2] G.R. Samorodnitzky-Naveh, S.B. Geiger, L. Levin, Patients' satisfaction with dental esthetics, The Journal of the American Dental Association, 138 (2007) 805-808.
[3] K. Baroudi, N. Hassan, The effect of light-activation sources on tooth bleaching, Nigerian Medical Journal, 55 (2014) 363-368.
[4] M. Kashima-Tanaka, Y. Tsujimoto, K. Kawamoto, N. Senda, K. Ito, M. Yamazaki, Generation of free radicals and/or active oxygen by light or laser irradiation of hydrogen peroxide or sodium hypochlorite, J Endod, 29 (2003) 141-143.
[5] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[6] Q. Alomari, E. El Daraa, A randomized clinical trial of in-office dental bleaching with or without light activation, J Contemp Dent Pract, 11 (2010) E017-024.
[7] E.A. De Paula, S. Kossatz, D. Fernandes, A.D. Loguercio, A. Reis, Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: A randomized tripleblind clinical trial, Oper Dent, 39 (2014) 128-135.
[8] Y. Wang, J. Gao, T. Jiang, S. Liang, Y. Zhou, B.A. Matis, Evaluation of the efficacy of potassium nitrate and sodium fluoride as desensitizing agents during tooth bleaching treatment - a systematic review and meta-analysis, J Dent, 43 (2015) 913-923.
[9] S.P. Cook, E.W. Mccleskey, Cell damage excites nociceptors through release of cytosolic atp, Pain, 95 (2002) 41-47.
[10] D.G. Soares, F.G. Basso, E.C.V. Pontes, L.D.R. Garcia, J. Hebling, C. Costa, Effective tooth-bleaching protocols capable of reducing h2o2 diffusion through enamel and dentine, J Dent, 42 (2014) 351-358.
[11] D.A. Roderjan, R. Stanislawczuk, J. Hebling, C.a.D.S. Costa, A. Reis, A.D. Loguercio, Response of human pulps to different in-office bleaching techniques: Preliminary findings, Braz Dent J, 26 (2015) 242-248.
[12] C.A. De Souza Costa, H. Riehl, J.F. Kina, N.T. Sacono, J. Hebling, Human pulp responses to in-office tooth bleaching, Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 109 (2010) e59-e64.
[13] E. Paula, S. Kossatz, D. Fernandes, A. Loguercio, A. Reis, The effect of perioperative ibuprofen use on tooth sensitivity caused by in-office bleaching, Oper Dent, 38 (2013) 601-608.
[14] M. Rezende, E. Bonafe, L. Vochikovski, P.V. Farago, A.D. Loguercio, A. Reis, et al., Pre- and postoperative dexamethasone does not reduce bleaching-induced tooth sensitivity a randomized, triple-masked clinical trial, J Am Dent Assoc, 147 (2016) 41-49.
[15] P. Charakorn, L. Cabanilla, W. Wagner, W. Foong, J. Shaheen, R. Pregitzer, et al., The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching, Oper Dent, 34 (2009) 131-135.
[16] M. Fernandes, S. Vaez, C. Lima, F. Nahsan, A. Loguércio, A. Faria-E-Silva, Preemptive use of naproxen on tooth sensitivity caused by in-office bleaching: A triple-blind, crossover, randomized clinical trial, Oper Dent, 42 (2017) 486-496.
[17] A.L. Faria-E-Silva, F.P.S. Nahsan, M.T.G. Fernandes, P.R.S. Martins-Filho, Effect of preventive use of nonsteroidal anti-inflammatory drugs on sensitivity after dental bleaching: A systematic review and meta-analysis, J Am Dent Assoc, 146 (2015) 87-93. e81.
[18] E. Bonafe, A.D. Loguercio, A. Reis, S. Kossatz, Effectiveness of a desensitizing agent before in-office tooth bleaching in restored teeth, Clin Oral Investig, 18 (2014) 839-845.
[19] A. Reis, L. Tay, D. Herrera, S. Kossatz, A. Loguercio, Clinical effects of prolonged application time of an in-office bleaching gel, Oper Dent, 36 (2011) 590-596.
[20] L.Y. Tay, C. Kose, A.D. Loguercio, A. Reis, Assessing the effect of a desensitizing agent used before in-office tooth bleaching, J Am Dent Assoc, 140 (2009) 1245-1251.

[21] D. Mehta, S. Venkata, M. Naganath, U. Lingareddy, H. Ishihata, W.J. Finger, Clinical trial of tooth desensitization prior to in-office bleaching, Eur J Oral Sci, 121 (2013) 477-481.
[22] J.K. Nanjundasetty, M. Ashrafulla, Efficacy of desensitizing agents on postoperative sensitivity following an in-office vital tooth bleaching: A randomized controlled clinical trial, J Conserv Dent, 19 (2016) 207.
[23] A. Reis, S. Kossatz, G. Martins, A. Loguercio, Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: A randomized clinical trial, Oper Dent, 38 (2013) 386-393.
[24] J.R. Gallo, J.O. Burgess, A.H. Ripps, M.J. Bell, D.E. Mercante, J.M. Davidson, Evaluation of 30% carbamide peroxide at-home bleaching gels with and without potassium nitrate—a pilot study, Quintessence Int, 40 (2009)
[25] C. Navarra, B. Reda, M. Diolosà, I. Casula, R. Di Lenarda, L. Breschi, et al., The effects of two 10% carbamide peroxide nightguard bleaching agents, with and without desensitizer, on enamel and sensitivity: An in vivo study, Int J Dent Hyg, 12 (2014) 115-120.
[26] N. Pandis, B. Chung, R.W. Scherer, D. Elbourne, D.G. Altman, Consort 2010 statement: Extension checklist for reporting within person randomised trials, BMJ, 357 (2017) j2835.
[27] J.K. Bernardon, M.V. Martins, G.B. Rauber, S.M. Junior, L.N. Baratieri, Clinical evaluation of different desensitizing agents in home-bleaching gels, The Journal of Prosthetic Dentistry, 115 (2016) 692-696.
[28] J.L. De Geus, M. De Lara, T. Hanzen, E. Fernández, A. Loguercio, S. Kossatz, et al., One-year follow-up of at-home bleaching in smokers before and after dental prophylaxis, J Dent, 43 (2015) 1346-1351.
[29] E. Lesaffre, B. Philstrom, I. Needleman, H. Worthington, The design and analysis of split-mouth studies: What statisticians and clinicians should know, Stat Med, 28 (2009) 3470-3482.
[30] A. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, 41 (2016) 455-464.
[31] N.U. Wetter, E.P. Branco, A.M. Deana, J.E. Pelino, Color differences of canines and incisors in a comparative long-term clinical trial of three bleaching systems, Lasers Med Sci, 24 (2009) 941-947.
[32] J.C. Ontiveros, R.D. Paravina, Color change of vital teeth exposed to bleaching performed with and without supplementary light, Journal of Dentistry, 37 (2009) 840-847.
[33] A. Hasegawa, A. Motonomi, I. Ikeda, S. Kawaguchi, Color of natural tooth crown in japanese people, Color Res Appl, 25 (2000) 43-48.
[34] C. Hanks, J. Fat, J.C. Wataha, J. Corcoran, Cytotoxicity and dentin permeability of carbamide peroxide and hydrogen peroxide vital bleaching materials, in vitro, J Dent Res, 72 (1993) 931-938.
[35] J.S. Cooper, T.J. Bokmeyer, W.H. Bowles, Penetration of the pulp chamber by carbamide peroxide bleaching agents, J Endod, 18 (1992) 315-317.
[36] S. Parreiras, P. Vianna, S. Kossatz, A. Loguercio, A. Reis, Effects of light activated in-office bleaching on permeability, microhardness, and mineral content of enamel, Oper Dent, 39 (2014) E225-E230.
[37] S.E.A. Camargo, M.C. Valera, C.H.R. Camargo, M.N.G. Mancini, M.M. Menezes, Penetration of 38% hydrogen peroxide into the pulp chamber in bovine and human teeth submitted to office bleach technique, J Endod, 33 (2007) 1074-1077.
[38] D.G. Soares, F.G. Basso, J. Hebling, C.A. De Souza Costa, Concentrations of and application protocols for hydrogen peroxide bleaching gels: Effects on pulp cell viability and whitening efficacy, J Dent, 42 (2014) 185-198.
[39] R.H. Leonard, L.R. Smith, D.J. Caplan, Desensitizing agent efficacy during whitening in an at-risk population, J Esthet Restor Dent, 16 (2004) 49-55.
[40] M. Rezende, F. Coppla, K. Chemin, A.C. Chibinski, A.D. Loguercio, A. Reis, Tooth sensitivity after dental bleaching with desentizing-containing and desensitizing-free bleaching gel: A sistematic review and meta-analysis, (2017) (under revision).
[41] C. Kose, A. Calixto, J. Bauer, A. Reis, A. Loguercio, Comparison of the effects of in-office bleaching times on whitening and tooth sensitivity: A single blind, randomized clinical trial, Oper Dent, 41 (2016) 138-145.

[42] A.D. Loguercio, L.Y. Tay, D.R. Herrera, J. Bauer, A. Reis, Effectiveness of nano-calcium phosphate paste on sensitivity during and after bleaching: A randomized clinical trial, Braz Dent J, 29 (2015) 1-7.
[43] F.C. Marson, L.G. Sensi, L.C.C. Vieira, E. Araujo, Clinical evaluation of in-off ice dental bleaching treatments with and without the use of light-activation sources, Oper Dent, 33 (2008) 15-22.
[44] M.a.P. Santana, F.P.S. Nahsan, A.H.D.A. Oliveira, A.D. Loguércio, A.L. Faria-E-Silva, Randomized controlled trial of sealed in-office bleaching effectiveness, Braz Dent J, 25 (2014) 207-211.
[45] D.H. Pashley, Consensus-based recommendations for the diagnosis and management of dentin hypersensitivity, Comp Contin Educ Dent, 29 (2008) 1-36.
[46] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[47] L.Y. Tay, C. Kose, D.R. Herrera, A. Reis, A.D. Loguercio, Long-term efficacy of in-office and at-home bleaching: A 2-year double-blind randomized clinical trial, Am J Dent, 25 (2012) 199-204.
[48] R.H. Leonard, L.R. Smith, G.E. Garland, K.K. Tiwana, L.A. Zaidel, G. Pugh, et al., Evaluation of side effects and patients' perceptions during tooth bleaching, J Esthet Restor Dent, 19 (2007) 355-364.
[49] R.K. Henry, S.M. Bauchmoyer, W. Moore, R.G. Rashid, The effect of light on tooth whitening: A split-mouth design, Int J Dent Hyg, 11 (2013) 151-154.
[50] M.P. Myrvik, A.L. Drendel, A.M. Brandow, K. Yan, R.G. Hoffmann, J.A. Panepinto, A comparison of pain assessment measures in pediatric sickle cell disease: Visual analog scale versus numeric rating scale, Pediatr Blood Cancer, 37 (2015) 190-194.
[51] M.J. Hjermstad, P.M. Fayers, D.F. Haugen, A. Caraceni, G.W. Hanks, J.H. Loge, et al., Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review, J Pain Symptom Manage, 41 (2011) 1073-1093.
[52] M. Pale, J.R. Mayoral, J. Llopis, M. Valles, J. Basilio, M. Roig, Evaluation of the effectiveness of an in-office bleaching system and the effect of potassium nitrate as a desensitizing agent, Odontol, 102 (2014) 203-210.
[53] R.D. Paravina, New shade guide for tooth whitening monitoring: Visual assessment, J Prosthet Dent, 99 (2008) 178-184.
[54] R.D. Paravina, W.M. Johnston, J.M. Powers, New shade guide for evaluation of tooth whitening—colorimetric study, J Esthet Restor Dent, 19 (2007) 276-283.
[55] R. Lo Giudice, G. Pantaleo, A. Lizio, U. Romeo, G. Castiello, G. Spagnuolo, et al., Clinical and spectrophotometric evaluation of led and laser activated teeth bleaching, Open Dentistry Journal, 10 (2016) 242-250.
[56] L.C.A. Almeida, H. Riehl, P.H. Dos Santos, M.L.M.M. Sundfeld, A.L.F. Briso, Clinical evaluation of the effectiveness of different bleaching therapies in vital teeth, Int J Periodontics Restorative Dent, 32 (2012)
[57] J.O. Calatayud, C.O. Calatayud, A.O. Zaccagnini, M. Box, Clinical efficacy of a bleaching system based on hydrogen peroxide with or without light activation, Eur J Esthet Dent, 5 (2010) 216-224.
[58] J.C. Ontiveros, M.S. Eldiwany, R. Paravina, Clinical effectiveness and sensitivity with overnight use of 22% carbamide peroxide gel, J Dent, 40 (2012) e17-e24.

Artigo 3

TÍTULO: IN-OFFICE DENTAL BLEACHING WITH LIGHT VS. WITHOUT LIGHT: A SYSTEMATIC REVIEW AND META-ANALYSIS

STATUS: PUBLICADO

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4.3 ARTIGO 3 – IN-OFFICE DENTAL BLEACHING WITH LIGHT VS. WITHOUT LIGHT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: A systematic review and meta-analysis were performed to answer the following research question: Does light-activated in-office vital bleaching have a greater whitening efficacy and higher tooth sensitivity (TS) in comparison with in-office vital bleaching without light when used in adults?

Data and Source: Only randomized clinical trials (RCTs) involving adults who had in-office bleaching with and without light activation were included. Controlled vocabulary and keywords were used in a comprehensive search for titles and abstracts in PubMed, and this search was adapted for Scopus, Web of Science, LILACS, BBO, Cochrane Library, and SIGLE without restrictions in May 2016 and was updated in August 2017. IADR abstracts (1990–2016), unpublished- and ongoing-trial registries, dissertations, and theses were also searched. The risk-of-bias tool of the Cochrane Collaboration was used for quality assessment. The quality of the evidence was rated using the Grading of Recommendations: Assessment, Development, and Evaluation approach. Through the use of the random effects model, a meta-analysis with a subgroup analysis (low and high hydrogen peroxide concentration) was conducted for color change (ΔE*, ΔSGU) as well as the risk and intensity of TS.

Study selection: We retrieved 6663 articles, but after removing duplicates and non-relevant articles, only 21 RCTs remained. No significant difference in ΔE*, ΔSGU, and risk and intensity of TS was observed ($p > 0.05$). For ΔE* and risk of TS, the quality of the evidence was graded as moderate whereas the evidence for ΔSGU and intensity of TS was graded as very low and low, respectively.

Conclusion: Without considering variation in the protocols, the activation of in-office bleaching gel with light does not seem to improve color change or affect tooth sensitivity, regardless of hydrogen peroxide concentration. (PROSPERO – CRD42016037630).

Clinical Relevance: Although it is commercially claimed that in-office bleaching associated with light improves and accelerates color change, this study did not confirm this belief for in-office bleaching gels with either high or low levels of hydrogen peroxide.

Keywords: Tooth bleaching. Light activation. Systematic review. Meta-analysis.

INTRODUCTION

The heightened focus on aesthetics is evidenced by the patients' increased demands to improve the appearance of their teeth. Within this context, changes in the smile play a significant role [1,2]. One of the most popular cosmetic procedures is tooth whitening, a technically easier and lower-cost procedure compared to veneers. Also, it is a very conservative method for treating dental discoloration [3,4]. Usually, dental vital bleaching is categorized as an in-office (professionally administered), an at-home (professionally dispensed) or an over-the-counter (self-administered) procedure that uses products based on hydrogen peroxide (HP) or carbamide peroxide [5-7].

Of the three bleaching techniques, the in-office one entails direct professional supervision to avoid soft-tissue exposure and gel ingestion, reduce treatment time, and yield a rapid whitening result [8-12]. There are many in-office bleaching products on the market whose manufacturers require catalytic decomposition by heat or light [2,3,8]. Different types of light-activating sources—such as lasers, light-emitting diodes (LEDs), plasma arc lamps (PAC), and halogen lamps—can be used [13]. The theoretical advantage of a light source is its ability to heat the HP, increasing the HP's decomposition rate in free radicals for the oxidization of complex organic molecules [3,8,14,15].

Despite the marketing claim of improved whitening from light-activated bleaching, this association has been questioned [2,14], as many randomized clinical trials (RCTs) have been controversial on this issue [9,12,16-20]. Additionally, some studies reported that the use of light may promote increased tooth sensitivity (TS) due to the release of more free radicals that reach the pulp [19-22].

He et al.'s earlier systematic review of the literature [23] showed that the association with light is not required for high-concentrate bleaching gels, but the same conclusion could not be reached for low-concentrate bleaching gels due to the small number of RCTs that compared light-activated systems with non-light systems. Since the publication of this previous systematic review, new RCTs comparing color change as well as the risk and intensity of TS in bleaching protocols with and without light activation have been published [9,24,25].

Therefore, the purpose of this systematic review of the literature was to update the prior systematic review and establish whether there are evidence-based differences in the bleaching efficacy and TS of bleaching protocols performed with and without light using low and high HP concentrations. To this end, the following Population, Intervention, Comparison, and Outcome (PICO) question was answered: Does light-activated in-office vital bleaching have a

greater whitening efficacy in comparison to in-office vital bleaching without light association when used in adults?

MATERIALS AND METHODS

Protocol and Registration

This study's protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO – CRD42016037630) and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement for reports [26].

Information Sources and Search Strategy

The controlled vocabulary (MeSH terms) and free keywords in the search strategy were defined based on the following PICO categories:

1. Population (P): adult patients who underwent vital tooth bleaching;

2. Intervention (I): in-office bleaching with light;

3. Comparison (C): in-office bleaching without light;

4. The outcome (O): color change in shade guide units (ΔSGU) and per a spectrophotometer (ΔE*) as well as the risk and intensity of TS taken after dental bleaching;

5. Study design (S): RCTs.

Electronic databases (MEDLINE via PubMed, Cochrane Library, Brazilian Library in Dentistry, and Latin American and Caribbean Health Sciences Literature database [LILACS]) and citation databases (Scopus and Web of Science) were searched (Table 4.3-1). The reference lists of all primary studies were manually searched for additional relevant publications. We also searched the related article links of each primary study in the PubMed database without restrictions on publication date or Latin-based languages.

Additionally, grey literature was investigated by searching the abstracts of the annual conference of the International Association for Dental Research and its regional divisions (1990–2016), the database System for Information on Grey Literature in Europe, and dissertations and theses using the ProQuest Dissertations and Theses full-text database as well as the Periódicos Capes Theses database.

To locate unpublished and ongoing trials related to the review question, clinical-trial registries were searched: Current Controlled Trials (www.controlled-trials.com), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (www.clinicaltrials.gov), ReBEC (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Eligibility Criteria

We included parallel and split-mouth RCTs that compared in-office dental bleaching with and without light in adult patients of any age group. RCTs were excluded if 1) the studies compared only different light-activated in-office bleaching treatments and 2) the studies compared in-office dental bleaching with combined bleaching (at-home bleaching with jump-start in-office bleaching).

Study Selection and Data Collection Process

Initially, the articles were selected by title and abstract in accordance with the previously described search strategy. Articles that appeared in more than one database were considered only once. Full-text articles were also obtained when the title and abstract presented insufficient information to make a clear decision. Subsequently, three reviewers classified those that met the inclusion criteria. Each eligible article received a study ID, combining the first author and year of publication.

Relevant information about the study design, participants, interventions, and outcomes was extracted independently through customized extraction forms by three authors; in cases of disagreement, a decision was reached by consensus. If there were multiple reports of the same study (i.e., reports with different follow-ups), data from all reports were extracted directly into a single data-collection form to avoid overlapping data. When data were not reported in the studies, authors were contacted by e-mail at least twice to request the missing information.

Concerning immediate color change, results from 1 week to 1 month post-bleaching, depending on what the authors reported, were extracted. Regarding TS, the data from the most immediate period were collected.

Risk of Bias in Individual Studies

Quality assessments of the selected trials were carried out by three independent reviewers using the Cochrane Collaboration tool for assessing the risk of bias in RCTs [27]. The assessment criteria contained six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. During data selection and quality assessment, any disagreements between the reviewers were solved through discussion, and if needed, consultation with a fourth reviewer (A.R.).

For each aspect of the quality assessment, the risk of bias was scored following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). Each domain level was judged as having a low, high, or unclear

risk of bias. At the study level, the study had a low risk of bias if all key domains (see below) for each outcome had a low risk of bias. If one or more key domains were judged as having unclear risk, the study as a whole had an unclear risk; if at least one key domain was considered to have a high risk of bias, the study was considered to have a high risk of bias. When a study was judged as unclear in at least one key domain, its authors were contacted to obtain more information, which allowed for a definitive judgement (yes or no).

For the patient-centered outcomes, risk and intensity of TS, the key domains were adequate for sequence generation and allocation concealment (key domains). Patient blinding was not considered a key domain, as patients could easily identify the different bleaching protocols.

For color change in ΔSGU and ΔE*, three items of the Cochrane tool were considered key domains: adequate sequence generation, allocation concealment, and examiner blinding.

Summary Measures and Synthesis of Results

Data were analyzed using Revman 5 (Review Manager Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark). Data from eligible studies were either continuous (intensity of TS, ΔSGU, and ΔE*) or dichotomous (absolute risk of TS).

Only studies classified as having low risk or unclear risk of bias in the key domains were used in the meta-analysis of each outcome. The outcomes were summarized by calculating the risk ratio, the standardized mean difference for the continuous data, and the 95% confidence interval for the dichotomous data.

The random-effects models were used. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. A subgroup analysis was performed for low- and high-concentrate bleaching gels. Studies with HP concentrations higher than 25% were classified as using high-concentrate products whereas studies with a concentration equal to or lower than 25% were considered to use low-concentrate products. Sensitivity analysis were also conducted to investigate the reasons for high heterogeneity whenever detected.

Publication bias

The funnel plot is a qualitative method for analyzing publication bias. For the continuous outcomes, the x-axis in the present analysis is the treatment effect (the overall standardized mean difference [SMD]) and the y-axis is the standard error of that treatment effect. For the dichotomous outcome, the x-axis is the risk ratio and the y-axis is the standard error of the log-risk ratio. This procedure was not done separately for each subgroup due to the reduced number of studies in the subgroup with the low concentrate HP.

Assessment of the quality of the evidence using GRADE

We graded the quality of the evidence for each outcome across the studies (body of evidence) by using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) to determine the overall strength of the evidence for each meta-analysis [28]. The GRADEpro Guideline Development Tool (available online at www.gradepro.org) was used to create a summary-of-findings table, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org).

The GRADE approach for the RCTs addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) to possibly downgrade the quality of the evidence (1 or 2 levels). Each of these topics was assessed as having "no limitations," "serious limitations," or "very serious limitations" to categorize the quality of the evidence for each outcome as high, moderate, low, or very low.

RESULTS

Study Selection

The search strategy was initially conducted May 12, 2016 and was updated August 09, 2017. After database screening and duplicate removal, 6663 studies were identified (Figure 4.3-1). After title screening, 305 studies remained, and this number was reduced to 21 after a careful examination of the abstracts.

Characteristics of Included Articles

Study design and method of color evaluation

The characteristics of the 21 selected studies are listed in Table 4.3-2. The parallel study design was predominantly used in these studies [8,12,16,18,20,22,24,25,29-33], but some studies used the split-mouth design [2,9,17,19,34-38].

For color evaluation, 16 studies used a shade guide [2,8,12,16-20,24,29,32-34,36-38]. Eleven of these 21 studies added an objective instrument (spectrophotometer or colorimeter) for color assessment [8,9,16,17,19,24,31-33,35,36]. Photography was used in seven studies [8,17,22,29,35,37,38]. One study did not evaluate the color change [25].

TS evaluation criteria

Eleven studies evaluated the intensity of TS; of these, 10 employed a 0–10 or 0–100 Visual Analog Scale (VAS) [8,9,17-19,24,25,30,31,35], and two studies employed the 0–3 or 0–4 Numerical Rating Scale (NRS) [12,24].

Nine studies evaluated the risk of TS, with six employing the VAS for pain evaluation [2,20,24,30,31,36] and four employing the NRS for pain evaluation [22,24,32,33]. Only Mena Serrano et al. [24] evaluated both the intensity and risk of TS, employing VAS and NRS. Two studies used a questionnaire to evaluate the risk of TS [37,38], and two studies did not evaluate TS [16,34].

Number of participants in the primary RCTs and gender

The patients in these studies ranged from 18 to 70 years of age. The mean age of all participants included in the examined RCTs was approximately 29.1 years, revealing a preponderance of young adults (Table 4.3-2). In all studies that reported the sample population's gender, females were prevalent [2,8,9,12,24,25,33,36]. Several studies did not report gender [16-20,22,29-32,34,35,37,38].

Bleaching protocols

The concentration of HP varied from 15% to 38% (Table 4.3-2). The application protocol of the in-office bleaching was quite variable. However, many studies applied the product in three 15-minute applications in each clinical session [2,9,13,17,18,20,24,25,31,32,35].

However, variations in this protocol were observed—with one, two, and four applications per session for different times. Most studies performed one clinical session [2,8,9,12,13,16,18,22,25,33-35,37,38], but two or three sessions with intervals between 7 and 10 days were also observed (Table 4.3-2).

Different types of light activation were used with different protocols. Four studies used halogen light [16,29,30,32,38], 10 used LEDs/lasers [2,12,17,20,24,25,29-32,35], three used only LEDs [8,12,32], five used metal-halide light [9,12,18,19,22], four used only a laser source [8,16,25,34], three used a PAC [8,33,37], and one used Nd:YAG laser [36]. In some studies, light was applied for the same amount of time as the gel; in other studies, light was applied for a few minutes with a specific interval between applications (Table 4.3-2).

Assessment of the Risk of Bias

The risk of bias in the eligible studies is presented in Figure 4.3-2. Few full-text studies reported the method of randomization, allocation concealment, and the status of whether or not the examiner was blinded during color assessment in SGU. E-mails were sent to the authors of all studies to request further information. Responses were obtained from the authors of 12 studies [2,8,13,17,20,24,25,29,30,32-35]. In sum, of the 21 studies, three were considered to have a high risk of bias [9,22,34] at the study level, so they were not used in the meta-analysis.

Meta-analysis

All meta-analysis were performed on studies classified as having low or unclear risk of bias in the key domains. From these studies, information about the outcome was reported and could be extracted. We performed a subgroup analysis based on the concentration of HP. In this phase, Kugel's 2006 study [37] was removed from the meta-analysis because the authors compared a low-concentrate HP with light vs. a high-concentrate HP without light (Figure 4.3-1). In all, 17 studies were included in the meta-analysis of the primary and secondary outcomes.

Color Change in ΔE^*

Both subgroups showed that light did not increase color change ($p = 0.90$). The SMD was 0.01 [95% CI -0.17 to 0.20]. The confidence interval includes the SMD of equality, which is equal to 0; this is further evidence of similarity between groups. We did not detect heterogeneity of the data ($p = 0.48$; $I^2 = 0\%$) (Figure 4.3-3).

Color Change in ΔSGU

Similarly, light did not benefit the color change in either group ($p = 0.15$). The overall SMD was 0.35 [95% CI -0.13 to 0.84]. The confidence interval also includes an SMD of 0 (no difference between groups). We detected high heterogeneity of the overall data ($p < 0.00001$; $I^2 = 87\%$), which could be explained by the studies that used low HP concentrations ($p < 0.00001$; $I^2 = 97\%$). The data from studies with high HP concentrations did not present heterogeneity ($p = 0.60$; $I^2 = 0\%$) (Figure 4.3-4).

Risk of Tooth Sensitivity

No significant difference was observed between subgroups of high and low HP concentrations ($p = 0.32$). The overall SMD was 0.94 [95% CI 0.77 to 1.14], showing no statistically significant differences between the groups of those bleached with light activation and those bleached without light activation ($p = 0.51$). We did not detect heterogeneity of the data ($p = 0.18$; $I^2 = 30\%$) (Figure 4.3-5).

Intensity of Tooth Sensitivity

The overall SMD was -0.12 [95% CI -0.76 to 0.53], showing no statistically significant differences between the groups ($p = 0.72$). We detected high heterogeneity of the overall data ($p < 0.00001$; $I^2 = 90\%$). This was probably due to the heterogeneity of the high-concentrate HP products ($p < 0.00001$; $I^2 = 93\%$); the low-concentrate HP products did not show the same heterogeneity ($p = 0.42$; $I^2 = 0\%$). However, this overall conclusion was primarily driven by the high number of studies included in the subgroup that had a high HP concentration. No specific

study was responsible for this higher heterogeneity (data not shown). The subgroup analysis revealed that HP in low concentrations has lower TS intensity when applied without light (p = 0.004) (Figure 4.3-6).

Publication Bias

If publication bias is not present, then the points should form a symmetrical, inverted funnel around the overall estimate of the effect, with results from smaller studies scattered more widely around the mean effect at the bottom of the graph. If, however, publication bias is present, then the graph may be asymmetrical or skewed. In our visual inspection of the funnel plots of all outcomes, we did not observe any funnel plot asymmetry (Figure 4.3-7 to 10).

Assessment of the Quality of Evidence

In the summary-of-findings table (Table 4.3-3), we show that the quality of the evidence of the color change in ΔE* and the risk of TS was rated as moderate. In these two outcomes, only the fact that most RCTs had an unclear risk of bias was responsible for downgrading the quality of the evidence by one level.

In the outcome regarding color change in ΔSGU, the quality of the evidence was graded as having very low quality due to the unclear risk of bias in most RCTs, the inconsistency of the data (unexplained heterogeneity), and the imprecision of the summary estimate. The quality of evidence for TS intensity was graded as being low, given the risk of bias of most RCTs and the imprecision of the data.

DISCUSSION

The process of randomization balances both known and unknown prognostic factors in the assignment of treatments, keeping the baseline features of the groups similar at the baseline. This is what makes an RCT the most widely accepted and powerful clinical design for assessing the true benefits of medical care [39]. Although randomization validates RCTs, the act of randomization is consistently poorly executed [40] and incompletely reported, as observed in the majority of the articles evaluated in this study.

Allocation concealment is as important as sequence generation in the randomization process. Allocation concealment has the aim of protecting the randomization process so that the treatment to be allocated is not known before the patient is enrolled in the study. Generating a random sequence but leaving it open for knowledge has no validity. Researchers cannot be allowed to know the upcoming group, as a way of preventing them from (unconsciously or otherwise) influencing which participant will enter the trial. Forty percent of the trials with inadequate or unclear concealment of the allocation sequence estimated that the groups

receiving the experimental treatments had better results than the control groups did [41]. Unfortunately, this is a very common problem in RCTs on bleaching, as was recently reported by Loguercio et al. [42].

There are many randomization methods known to effectively maintain allocation concealment; however, most are complex and expensive. Approaches such as pharmacy-controlled randomization, 24-hour central randomization offices (phone-in or web-based services), or even the use of numbered or coded containers in a placebo-controlled trial [43] require extensive infrastructure support that may exceed the resources available in single-center trials. When conducted properly, participant randomization using sequentially numbered, opaque, and sealed envelopes is the most accessible and straightforward method of maintaining allocation concealment, and it does not require the use of specialized technology [44]. Although this is a very easy process, most of the studies we reviewed did not report this information, and, of those that did, many studies had an unclear risk of bias. There is evidence that the proper implementation of these steps (sequence generation and allocation concealment) in RCTs reduces the possibility of selection bias and systematic errors [45,46].

In this study, we observed that the association of light with bleaching agents does not increase the effectiveness of bleaching. Theoretically, heat and light sources can accelerate the decomposition of HP to form oxygen and perhydroxyl free radicals, increasing the efficacy of bleaching [3,47]. However, this increase does not lead to greater whitening efficacy because of the presence of unknown rate-determining steps in the oxidizing mechanism of tooth whitening [24].

These results are in line with those of an earlier systematic review published in 2012 [23]. In the 2012 study [23], the authors revealed that both light-activated and non-light systems showed similar immediate and short-term bleaching effects when high concentrations of HP were employed.

In contrast to the present study, He et al. [23] reported that light-activated systems with low HP concentrations produced better immediate bleaching efficacy. However, this conclusion was based on only two studies, both of which had an unclear risk of bias [18,33]. This small number of studies and participants entails imprecision, which means that the quality of the evidence in the study by He et al. [23] is lower than that of our study. In the present systematic review, the studies by Tavares et al. and Ziemba et al. [18,33] were responsible for the high heterogeneity between low-concentrate products, probably due to the inclusion of patients older than the average.

As tooth color is determined mainly by the color of dentin, age is negatively correlated with whitening effect—meaning that older patients do not respond to the bleaching procedure as well as younger patients, which may be attributed to the physiological changes that occur in dental tissues over time [23,48]. In sum, the age-related decrease in protein content might be one of the reasons behind the lower bleaching efficacy in the teeth of older individuals [49]. However, low HP concentrations are not incapable of producing the same level of whitening as the other techniques studied; rather, more time may be required when using low HP concentrations.

Regarding TS, no significant difference in the risk of TS was observed for any of the comparisons. The risk of TS refers to the percentage of patients who reported pain at some moment during dental bleaching. However, the greater TS intensity was observed when bleaching was performed using products with low HP concentrations and light activation, a consistent finding in all primary studies included in this review [18,19,24]. The increased rate of the HP free radicals released by light activation can increase the number of free radicals that reach the pulp, leading to a more intense inflammatory response and pain triggering [50].

We cannot disregard the fact that the variations observed in the bleaching and light-activation protocols can also explain the similarity between light versus non-light in terms of color change and TS. As previously mentioned in the Results section, the number of bleaching sessions, the HP concentrations and brands, the light sources (lasers, LEDs, PACs, and halogen lamps), and the protocols were quite variable in the primary studies. Unfortunately, due to the small number of included studies, we could not use a meta-regression analysis to evaluate some of the parameters described above.

These factors may lead to criticism regarding the combination of different kinds of studies in a meta-analysis. Inevitably, however, studies combined in a meta-analysis differ in their characteristics. Deciding how similar studies need to be for use in a meta-analysis is based on subjective judgment, and researchers may have different opinions concerning the appropriateness of combining results. As reported by Borenstein et al. in 2009 [51] in their book *An Introduction to Meta-Analysis*, meta-analysis almost always address broader questions than individual studies; therefore, we can anticipate that effects may vary from one study to another. In this way, we can consider this as a further strength of the meta-analysis, in that it allows the formal evaluation of differences and makes attempts to investigate the reasons behind them.

Bringing this discussion to the present study, we could not answer a very specific question about the effectiveness of "a laser-LED source applied three times for a duration of 2

min each during in-office bleaching with 35% HP bleaching gel versus that of a 35% HP bleaching gel given at three 15-min applications per session without light application." Nonetheless, this meta-analysis allowed us to determine that light-activated bleaching (regardless of light source and protocol) is similar to the use of HP alone (regardless of protocol) in terms of color change. Perhaps a more specific answer could be obtained through a network meta-analysis with the aim of identifying whether there is any specific type of light or bleaching protocol that benefits from light activation. However, this network meta-analysis also has disadvantages—for it suffers from indirectness, which reduces the strength of the evidence. Our research groups are developing a network meta-analysis to address this specific question.

Data collection for the present study may allow other researchers to combine results based on their own judgment and reach other conclusions. This study also highlights the number of variables involved in the in-office bleaching protocol and may yield improvements in the clinical practice just by raising awareness of them.

It is worth mentioning that, for the color change in ΔE* and risk of TS, the quality of evidence was graded as moderate; therefore, we are moderately confident in the effect estimate—which means that the true effect is likely to be close to the estimate observed, though there is a possibility that it may be different. Caution should be taken when interpreting the color change in ΔSGU and in data about TS intensity because the quality of the evidence for these two outcomes was graded as very low and low, respectively.

Further RCTs comparing variables in the bleaching protocol, light source, and application should be performed to provide a more comprehensive evaluation of the variables involved in the bleaching techniques.

CONCLUSIONS

Neither the efficacy nor the risk of TS of in-office bleaching was influenced by the use of light, although the greater intensity of TS was observed when bleaching was performed using products with low HP concentrations. However, this should be interpreted with caution, as it represents an overall comparison without considering variations in the protocols (number of bleaching sessions, product, and kind of the light) of the bleaching techniques in the studies included.

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Marson, Gustavo Moncada, Jesus O. Calatayud, Alexandra Mena Serrano, Jo M. Goodson, Joe C. Ontiveros, Jussara K. Bernardon, Letícia C. A. G de Almeida, Patricia M. de Freitas, Rafael F. L. Mondelli, Sevil Gurgan, and Stella Kossatz. This study was partially supported by The National Council for Scientific and Technological Development (CNPq) under grants # 304105/2013-9 and 305588/2014-1 from Brazil.

Table 4.3-1. Electronic database and search strategy.

PubMed (12/May/2016 updated in 09/Aug/2017)		
#1 ((((((((((((((((((tooth discoloration[MeSH Terms]) OR dentition, permanent[MeSH Terms]) OR color[MeSH Terms]) OR color[Title/Abstract]) OR colour[Title/Abstract]) OR "tooth discoloration"[Title/Abstract]) OR "tooth discolouration"[Title/Abstract]) OR "teeth discoloration"[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 "tooth staining"[Title/Abstract]) OR "teeth staining"[Title/Abstract]) OR "dental discoloration"[Title/Abstract]) OR "dental discolouration"[Title/Abstract]) OR "stained teeth"[Title/Abstract]) OR "stained tooth"[Title/Abstract]) OR "dental staining"[Title/Abstract]	#2 ((((((((((((((((tooth bleaching[MeSH Terms]) OR peroxides[MeSH Terms]) OR tooth bleaching agents[MeSH Terms]) OR hydrogen peroxide[MeSH Terms]) OR carbamide peroxide[Supplementary Concept]) OR light[MeSH Terms]) OR lasers[MeSH Terms]) OR bleaching[Title/Abstract]) OR whitening[Title/Abstract]) OR "hydrogen peroxide"[Title/Abstract]) OR "carbamide peroxide"[Title/Abstract]) OR "in office"[Title/Abstract]) OR "light activation"[Title/Abstract]) OR heat[Title/Abstract]) OR ultraviolet[Title/Abstract]) OR lamp[Title/Abstract]) OR “light activated”[Title/Abstract]) OR LED[Title/Abstract]	#3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])
#1 AND #2 AND 3		

Table 4.3-2. Summary of the primary studies included in this systematic review.

Study ID	Study design [setting]	Number patients [drop-outs]	Subjetcs age mean ± SD [range] (years)	No. of males [%]	Baseline color/ evaluated tooth	Groups/Materials	Bleaching protocol		Light source	Color assessment [outcome]	Tooth sensitivity: Scale [Outcome]
							Gel protocol Applications x min [sessions] (interval)	Light protocol	Spectrum (nm)/ (Intensity, mW/cm^2) [power output (W)]		
Almeida, 2012 [29] and Almeida 2012 [30]*	Parallel [n.r.]	40 [0]	n.r. ± n.r. [18 - 28]	n.r. [n.r.]	n.r./n.r.	I: AH 10% CP[a] II: IO 35% HP[b] III: IO 35% HP[b] + light[A] IV: IO 35% HP[b] + light[B]	I: 4h/daily (21 days) II-IV: 3 x 10 min [3] (7 days)	III: 20 s IV: 3 x 3 min	III: 450-500 (400) [0.2] IV: 470-808 (120) [0.2]	Vita Classical[o]; Photography [ΔSGU]	VAS 0-10 [Risk and intensity of TS]
Alomari, 2010 [12]	Parallel [n.r.]	40 [n.r.]	27.8 ± n.r. [18 - 40]	12 [30]	A3/Anterior teeth	I: IO 35% HP[c] II: IO 35% HP[c] + light[B] III: IO 35% HP[c] + light[C] IV: IO 35% HP[c] + light[D]	I-IV: 3 x 20 min [1]	II-IV: 3 x 20 min	n.r./ (n.r.)/ [n.r.]	Vita Classical[o] [ΔSGU]	NRS 0-3 [Intensity of TS]
Bernardon, 2010 [17]	Split-mouth [n.r.]	90 [1]	n.r. ± n.r. [n.r.- n.r.]	n.r. [n.r.]	A2/Anterior teeth	I: AH 10% CP[a] *vs.* IO 35% HP[b] + light[B] II: IO 35% HP[b] *vs.* IO 35% HP[b] + light[B] III: AH 10% CP[a] *vs.* IO 35% HP[b] + light[B] [1 session] and AH 10% CP[a]	AH: 8h/daily (14 days) IO: 3 x 15 min [2] (15 days)	4 min	n.r. (n.r.) [n.r.]	Vita Classical[o]; Spectrophotometer[p] Photography [ΔSGU and ΔE*]	VAS 0-10 [Intensity of TS]
Bortolatto, 2013 [31]	Parallel [n.r.]	40 [8]	n.r. ± n.r. [18 - 25]	n.r. [n.r.]	n.r./n.r.	I: IO 35% HP[d] II: IO 35% HP[d] + light[B]	I: 3 x 15 min [3] (7 days) II: 3 x 8 min [3] (7 days)	3 x 4 min	425-480/810 (300) [1.8/0.6]	Spectrophotometer[p] [ΔE*]	VAS 0-100 [Risk and intensity of TS]
Calatayud, 2010 [34]	Split-mouth [n.r.]	21 [0]	n.r. ± n.r. [18 - 38]	n.r. [n.r.]	A2/Anterior teeth	I: IO 35% HP[e] + light[E] II: IO 35% HP[e]	I and II: 2 x 10 min [1]	2 x 10 min	380-530 (n.r.) [n.r.]	Vita Classical[o] [ΔSGU]	n.r. [n.r.]
Freitas, 2016 [2]	Split mouth [University]	22 [0]	20.5 ± n.r. [18 - 25]	10 [45]	A2/Anterior teeth	I: IO 35% HP[d] II: IO 35% HP[d] + light[B]	I: 3 x 15 min [1] II: 3 x 8 min [1]	3 x 1 min (interspersing 1 min)	470/810 (35—400) [0.2]	Vita Classical[o] [ΔSGU]	VAS 0-10 [Risk of TS]
Gurgan, 2010 [8]	Parallel [n.r.]	40 [0]	27.3 ± n.r. [18 - 30]	11 [27.5]	A3/Anterior teeth	I: IO 38% HP[c] II: IO 37% HP[f] + light[E] III: IO 35% HP[g] + light[F] IV: IO 38% HP[h] + light[C]	I: 2 x 15 min [1] II: 3 x 8 min [1] III: 3 x 20 min [1] IV: 2 x 20 min [1]	II: 2 x 105 s III: 2 x 10 min (interspersing 30 s) IV: 2 x 20 min	II: 815 (n.r.) [10] III: 400-490 (2800) [n.r] IV: 400-500 (n.r.) [n.r.]	Vita Classical[o] Spectrophotometer[p] Photography [ΔSGU and ΔE*]	VAS 0-10 [Intensity of TS]
Henry, 2013 [9]	Split-mouth [n.r.]	49 [0]	38.4 ± 13.6 [n.r.- n.r.]	24 [49]	A3/Anterior teeth	I: IO 25% HP[i] + light[D] II: IO 25% HP[i]	I and II: 3 x 15 min [1]	3 x 15 min	n.r. (n.r.) [n.r.]	Spectrophotometer[p] [ΔE*]	VAS 0-10 [Intensity of TS]
Kossatz, 2011 [20]	Parallel [University]	30 [0]	n.r. ± n.r. [n.r - n.r.]	n.r. [n.r.]	C2/Upper Incisor	I: IO 35% HP[b] + light[B] II: IO 35% HP[b]	I and II: 3 x 15 min [2] (7 days)	3 x 5 min (interspersing 2 min)	470/830 (200) [n.r.]	Vita Classical[o] [ΔSGU]	VAS 0-10 [Risk]

Kugel, 2006 [37]	Split-mouth [n.r.]	10 [0]	n.r. ± n.r. [n.r - n.r.]	n.r. [n.r.]	A3/Anterior teeth	I: IO 15% HP[j] + light[F] II: IO 38% HP[c]	I and II: 3 x 20 min [1]	3 x 20 min	n.r. (n.r.) [n.r.]	Vita Classical[o] Photography [ΔSGU and ΔE*]	Questionnaire [Risk of TS]
Kugel, 2009 [22]	Parallel [University]	33 [3]	30.9 ± n.r. [22 - 48]	n.r. [n.r.]	A2/Anterior teeth	I: IO 25% HP[k] + light[D] II: IO 25% HP[k] III: only light[D]	I-III: 3 x 20 min [1]	20 min	n.r. (n.r.) [n.r.]	Photography [ΔE*]	NRS 0-3 [Risk of TS]
Marson, 2008 [32]	Parallel [n.r.]	40 [0]	n.r. ± n.r. [18-28]	n.r. [n.r.]	n.r./Anterior teeth	I: IO 35% HP[b] II: IO 35% HP[b] + light[A] III: IO 35% HP[b] + light[C] IV: IO 35% HP[b] + light[B]	I-IV: 3 x 15 min [2] (7 days)	3 x 15 min	I: 400-500 (n.r.) [n.r.] II: 450-500 (n.r.) [n.r.] III: 470 (n.r.) [n.r.]	Vita Classical[o] Spectrophotometer[p] [ΔSGU and ΔE*]	NRS 0-4 [Risk of TS]
Mena Serrano, 2016 [24]	Parallel [University]	77 [0]	22.5 ± 3.8 [18 - 27]	27 [35]	A3/Upper Canine	I: IO 20% HP[b] II: IO 20% HP[b] + light[B] III: IO 35% HP[b] IV: IO 35% HP[b] + light[B]	I-IV: 3 x 15 min [2] (7 days)	5 x 1 min (interspersing 2 min)	470/830 (200) [n.r.]	Vita Classical[o] Spectrophotometer[p] [ΔSGU and ΔE*]	VAS 0-100 and NRS 0-4 [Risk and intensity of TS]
Moncada, 2013 [25]	Parallel [University]	87 [26]	23.2 ± 3.7 [18 - 37]	23 [26.4]	n.r./n.r.	I: IO 15% HP + light[B] II: IO 35% HP + light[E] III: IO 35% HP[l]	I: 3 x 15 min [1] II: 3 x 10 min [1] III: 1 x 45 min [1]	I: 5 x 1 min and 30 s II: 3 x 6 min	I: 470/830 (450) [n.r.] II: n.r. (n.r.) [n.r.]	n.r. [n.r.]	VAS 0-100 [Intensity of TS]
Mondelli, 2012 [35]	Split-mouth [n.r.]	48 [19]	n.r. ± n.r. [n.r - n.r.]	n.r. [n.r.]	A3/Anterior teeth	I: IO 35% HP[d] + light[B] II: IO 35% HP[d] III: IO 38% HP[c] + light[B] IV: IO 38% HP[c] V: AH 15% CP[m]	I and III: 3 x 11 min [1] II and IV: 3 x 15 min [1] V: 2h/daily (10 days)	3 x 3 min (interspersing 1 min)	470/810 (350/200) [n.r.]	Spectrophotometer[p]Photography [ΔE*]	VAS 0-10 [Intensity of TS]
Ontiveros, 2009 [19]	Split-mouth [n.r.]	20 [0]	n.r. ± n.r. [18 – 30]	n.r. [n.r.]	A2/Anterior teeth	I: IO 25% HP[i] + light[D] II: IO 25% HP[i]	I and II: 3 x 15 min [1]	3 x 15 min	350-600 (n.r.) [n.r.]	Vita Classical[o] Spectrophotometer[p] Vita Bleachedguide 3D-Master[q] [ΔSGU and ΔE*]	VAS 0-10 [Intensity of TS]
Papathanasiou, 2002 [38]	Split-mouth [University]	20 [0]	n.r. ± n.r. [n.r.- n.r.]	n.r. [n.r.]	A3/Anterior teeth	I: IO 35% HP[c] +light[A] II: IO 35% HP[c]	I and II: 1 x 20 min [1]	20 min	n.r. (n.r.) [n.r.]	Vita Classical[o] Photography [ΔSGU]	Questionnaire [Risk of TS]
Polydorou, 2013 [16]	Parallel [n.r.]	60 [0]	27.6 ± 5.0 [18 - 70]	n.r. [n.r.]	C1/Upper Canine	I: IO 38% HP[c] II: IO 38% HP[c] + light[A] III: IO 38% HP[c] + light[E]	I-III: 4 x 15 min [1]	II: 4 x 8 min III: 4 x 30 s	II: 480-520 (n.r.) [150] III: 980 (n.r.) [6]	Vita Classical[o] Spectrophotometer[p]	n.r. [n.r.]

										[ΔSGU and ΔE*]	
Strobl, 2010 [36]	Split-mouth [n.r.]	20 [0]	n.r. ± n.r. [n.r. - n.r.]	7 [35]	A1/n.r.	I: IO 35% HP[n] + light[G] II: IO 35% HP[n]	I and II: 2 x 1 min and 45 sec and [2] (7 days)	3 x 10 s	1064 µm (n.r.) [4]	Vita Classical[o] Chromatometer ShadeEye NCC[r] [ΔSGU and ΔE*]	VAS 0-10 [Risk of TS]
Tavares, 2003 [33]	Parallel [n.r.]	87 [0]	44.0 ± n.r. [20 - 67]	38 [44]	D4/Upper Incisor	I: IO 15% HP + light[F] II: IO 15% HP III: IO placebo gel + light[F]	I-III: 3 x 20 min [1]	60 min	400-505 (130-160) [n.r.]	Vita Classical[o] CR-321 Chromameter[s] [ΔSGU and ΔE*]	NRS 0-3 [Risk of TS]
Ziemba, 2005 [18]	Parallel [n.r.]	50 [1]	n.r. ± n.r. [18 - 70]	[n.r.]	A3/Anterior teeth	I: IO 25% HP[i] + light[D] II: IO 25% HP[i]	I and II: 3 x 15 min [1]	3 x 15 min	365-500 (n.r.) [n.r.]	Vita Classical[o] [ΔSGU]	VAS 0-10 [Intensity of TS]

Abbreviations: ID–identification; SD–standard deviation; n.r.–not reported in the study; AH–At-Home bleaching; CP–Carbamide Peroxide; IO–In-Office bleaching; HP–Hydrogen Peroxide; ΔSGU–shade guide units; ΔE*–color difference measured with a spectrophotometer; VAS–Visual Analog Scale; TS–Tooth Sensitivity; NRS–Numeric Rating Scale.
*Two reports of the same study, that are complementary.
a Whiteness Perfect (FGM, Joinville, Brazil);
b Whiteness HP Maxx (FGM, Joinville, Brazil);
c Opalescence Xtra Boost (Ultradent Inc., South Jordan, UT, USA);
d Lase Peroxide Sensy (DMC, São Carlos, Brazil);
e QuickWhite (DMDS House, Canterbury, UK);
f LaserWhite 10 (Biolase Technology Inc., San Clemente, CA, USA);
g Remewhite (Remedent, Deurle, Belgium);
h By White (Biowhite, Ensodent, Italy);
i Zoom 2 (Discus Dental, Inc., Culver City, CA, USA);
j BriteSmile (Walnut Creek, CA, USA);
k ZOOM Chairside Whitening System (Discus Dental, Inc., Culver City, CA, USA);
l White Gold Office (Dentsply, 38West Clarke Ave., Milford, USA);
m Opalescence PF (Ultradent, South Jordan UT, USA);
n Fotona (Fotona d.d., Ljubljana, Slovenia);
o Vita Classical Shade (Vita Zahnfabrik, Bad Säckingen, Germany);
p Spectrophotometer (Vita Easyshade, Vident, Brea, CA, USA);
q Vita Bleachedguide 3D-Master (Vita Zahnfabrik, Bad Säckingen, Germany);
r Chromatometer ShadeEye NCC (Shofu Dental GmbH, Ratingen, Germany);
s CR-321 Chromameter (Minolta, Ramsey, N.J.).
A Halogen light;
B LED/laser;
C LED
D Metal halide light;
E Laser;
F Plasma arc lamp;
G Nd:YAG laser;

Table 4.3-3. Summary of finding table and quality of the evidence.

Patient or population: dental bleaching in adults

Intervention: in-office bleaching without light activation

Comparison: in-office bleaching with light activation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	With light activation	Without light activation			
Color change in Delta E assessed with: spectrophotometer/colorimeter follow up: mean 1 months	-	SMD 0.01 SD higher (0.17 lower to 0.2 higher)	-	483 (11 RCTs)	⊕⊕⊕◯ MODERATE [a]
Color change in Delta SGU assessed with: shade guide units follow up: mean 1 months	-	SMD 0.35 SD higher (0.13 lower to 0.84 higher)	-	659 (15 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
Risk of tooth sensitivity assessed with: VAS pain scale follow up: immediately after bleaching	972 per 1000	914 per 1000 (749 to 1000)	RR 0.94 (0.77 to 1.14)	269 (9 RCTs)	⊕⊕⊕◯ MODERATE [a]
Intensity of tooth sensitivity assessed with: VAS pain scale follow up: immediately after bleaching	-	SMD 0.12 SD lower (0.76 lower to 0.53 higher)	-	461 (10 RCTs)	⊕⊕◯◯ LOW [a,c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **SMD:** Standardised mean difference; **RR:** Risk ratio
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effectt
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Most RCTs are at unclear risk of bias
b. Inconsistency in the data due to high and non-explained heterogeneity
c. High confidence interval that does not exclude great benefit or great harm

Figure 4.3-1. Flow diagram of study identification.

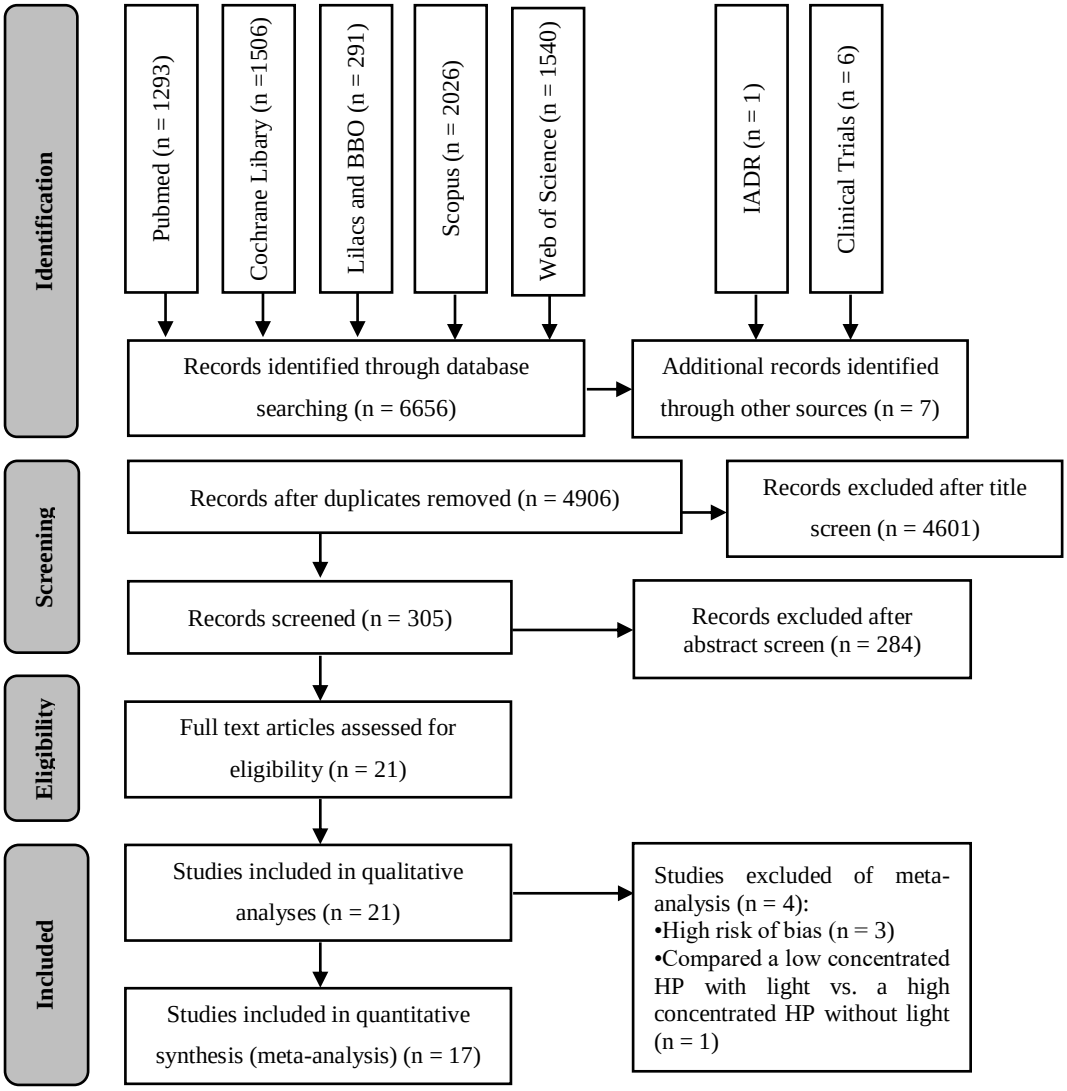


Figure 4.3-2. Summary of the risk-of-bias assessment, according to the Cochrane Collaboration tool. The underlined authors provided extra information by e-mail to allow an assessment of the risk of bias.

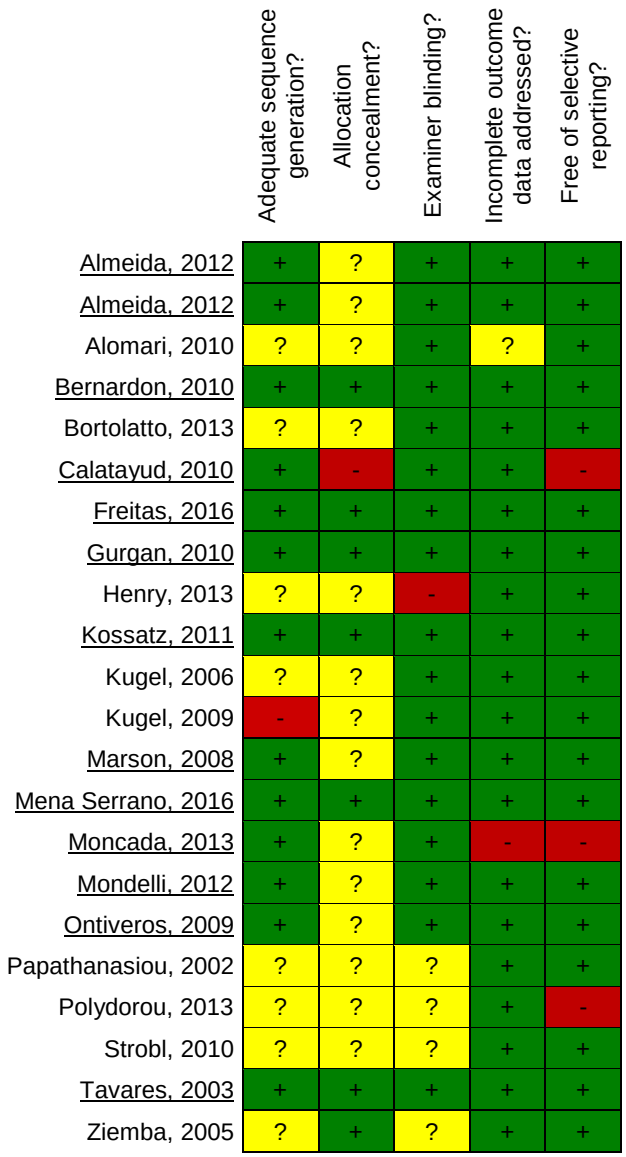


Figure 4.3-3. Forest plot of the color change in ΔE* for in-office bleaching with light (Bleach+light) vs. without light (Bleach).

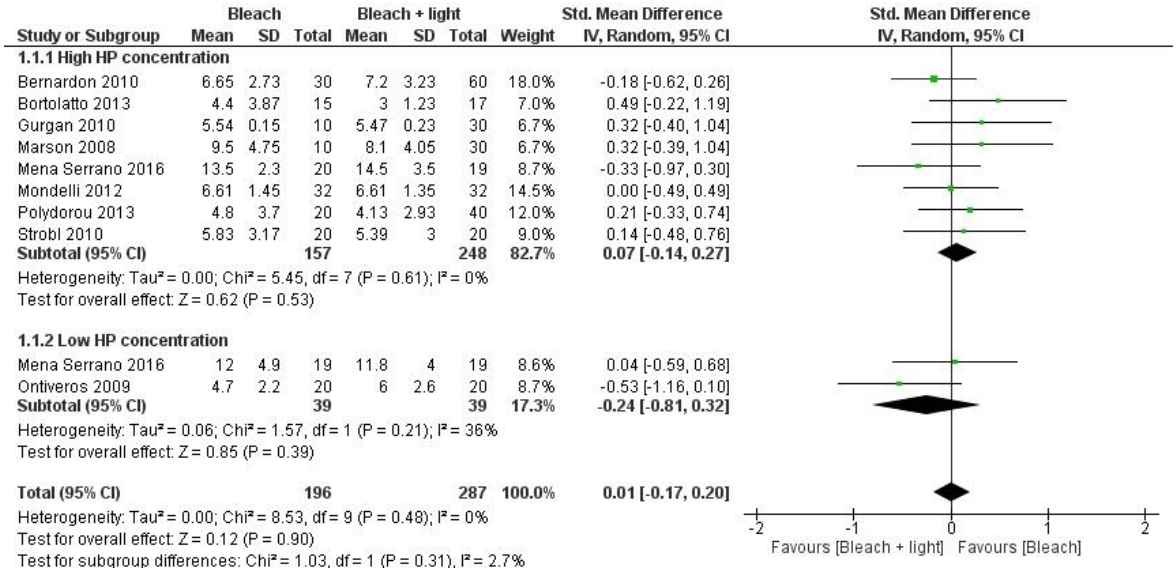


Figure 4.3-4. Forest plot of the color change in ΔSGU for in-office bleaching with light (Bleach+light) vs. without light (Bleach).

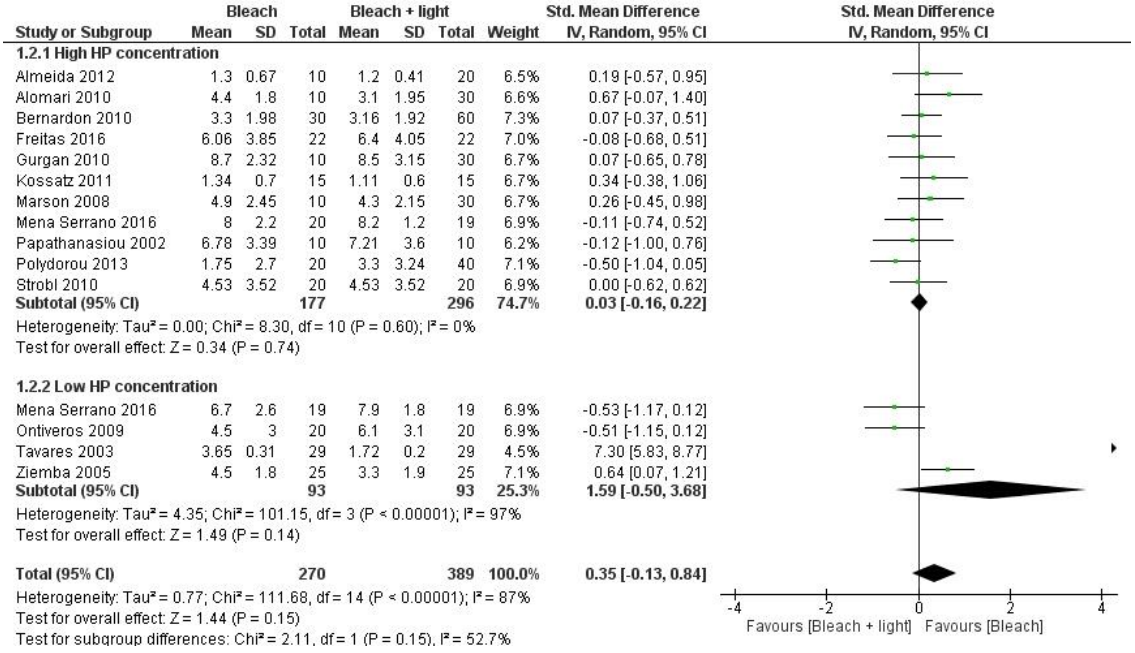


Figure 4.3-5. Forest plot of the risk of TS for in-office bleaching with light (Bleach+light) vs. without light (Bleach).

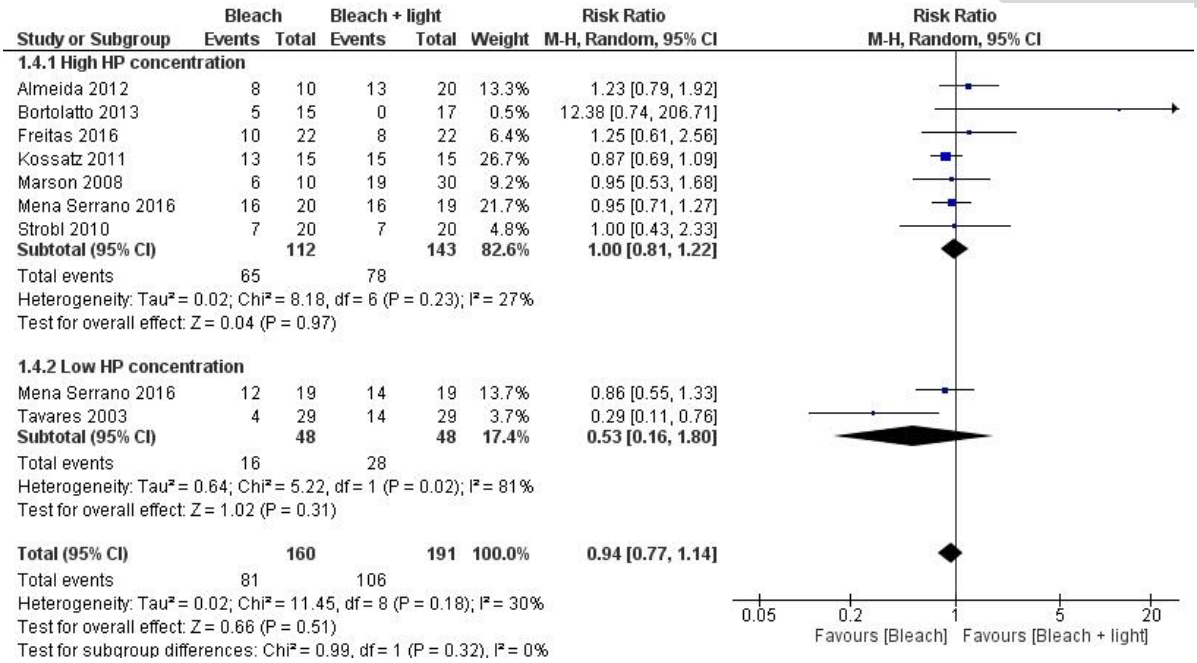


Figure 4.3-6. Forest plot of the intensity of TS for in-office bleaching with light (Bleach+light) vs. without light (Bleach).

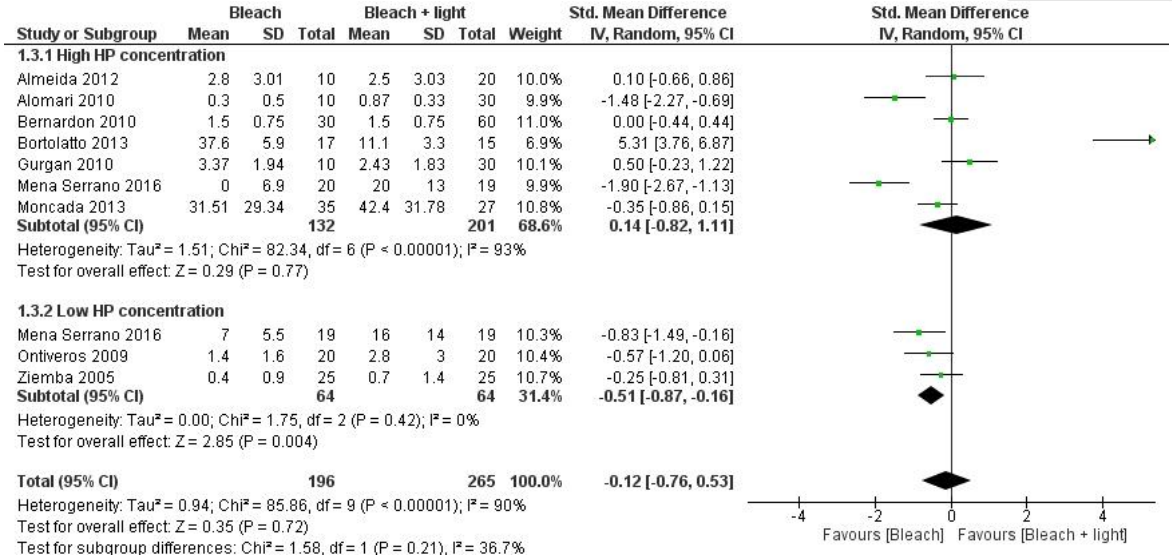


Figure 4.3-7. Funnel plot of the color change in ΔE* for in-office bleaching with low and high HP concentrations.

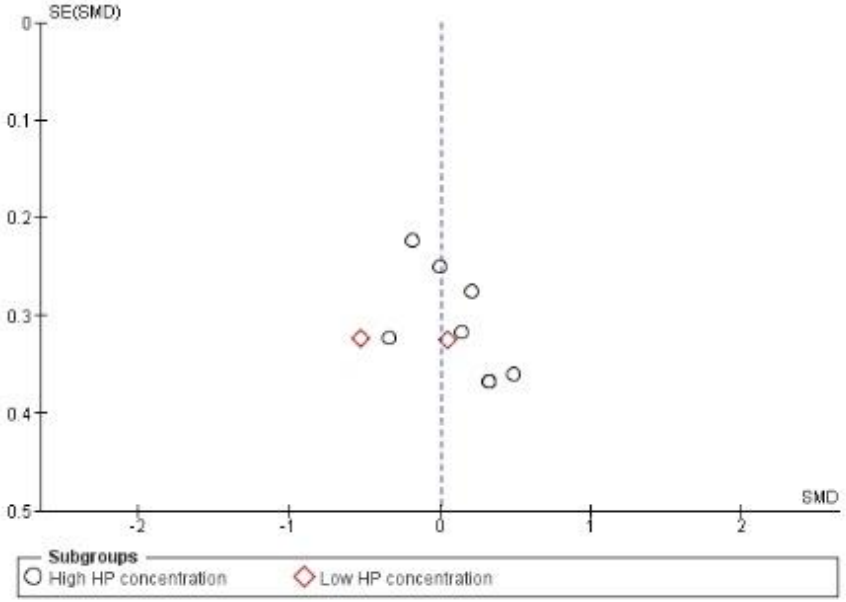


Figure 4.3-8. Funnel plot of the color change in ΔSGU for in-office bleaching with low and high HP concentrations.

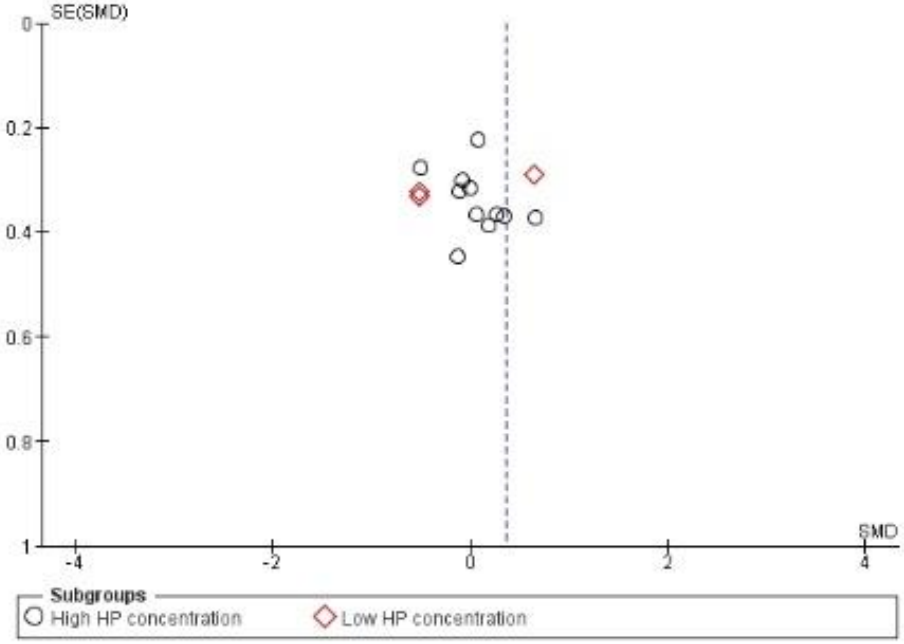


Figure 4.3-9. Funnel plot of the risk of TS for in-office bleaching with low and high HP concentrations.

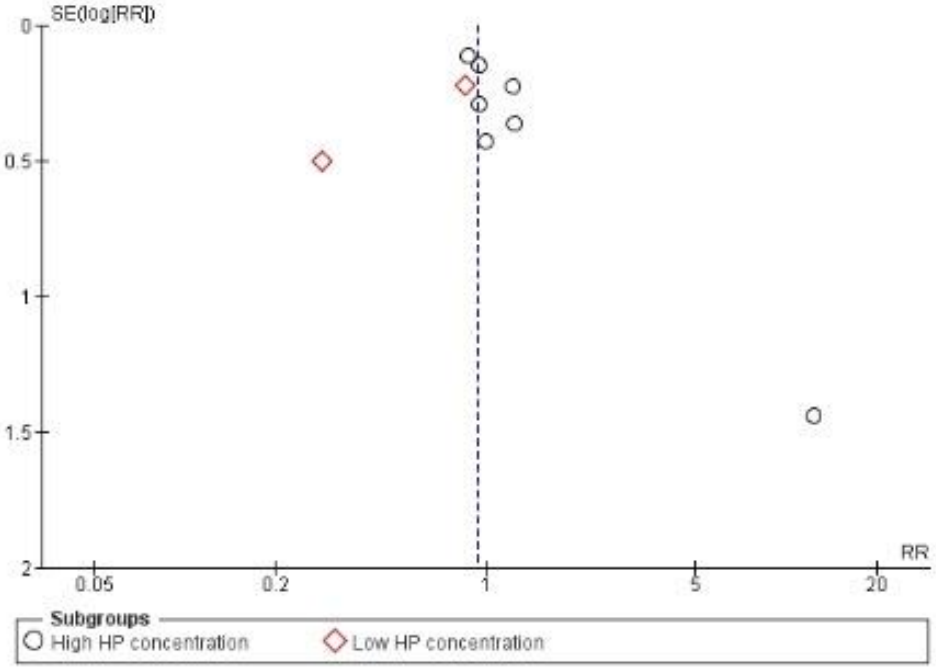
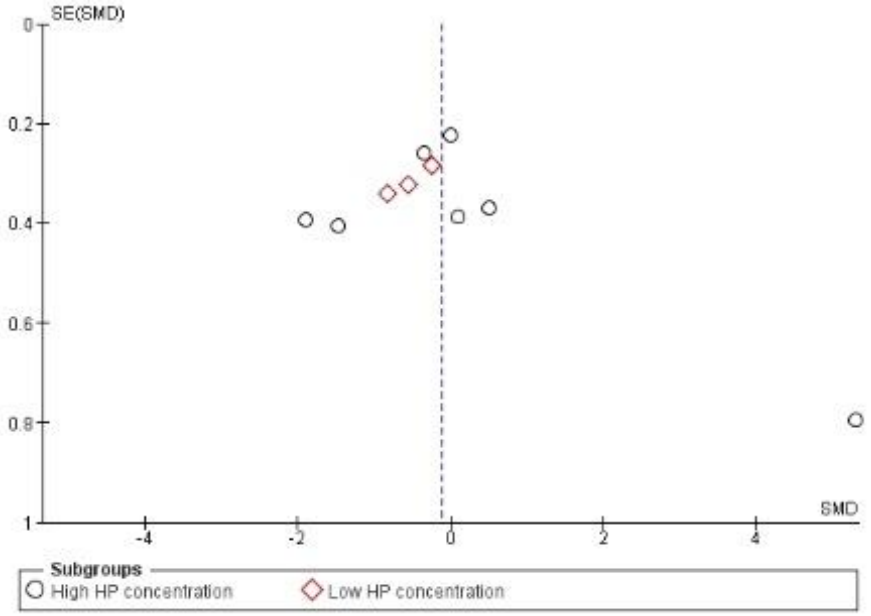


Figure 4.3-10. Funnel plot of the intensity of TS for in-office bleaching with low and high HP concentrations.



REFERENCES

[1] B.J. Nutter, M.O. Sharif, A.B. Smith, P.A. Brunton, A clinical study comparing the efficacy of light activated in-surgery whitening versus in-surgery whitening without light activation, J Dent, 41 Suppl 5 (2013) e3-7.
[2] P.M. De Freitas, A.N. Menezes, A.C. Da Mota, A. Simoes, F.M. Mendes, A.D. Lago, et al., Does the hybrid light source (led/laser) influence temperature variation on the enamel surface during 35% hydrogen peroxide bleaching? A randomized clinical trial, Quintessence Int, 47 (2016) 61-73.
[3] A. Joiner, The bleaching of teeth: A review of the literature, J Dent, 34 (2006) 412-419.
[4] D.C. Sarrett, Tooth whitening today, J Am Dent Assoc, 133 (2002) 1535-1538.
[5] R. Hayward, Y. Osman, S.R. Grobler, A clinical study of the effectiveness of a light emitting diode system on tooth bleaching, Open Dent J, 6 (2012) 143-147.
[6] J.L. De Geus, L.M. Wambier, S. Kossatz, A.D. Loguercio, A. Reis, At-home vs in-office bleaching: A systematic review and meta-analysis, Oper Dent, 41 (2016) 341-356.
[7] J. Dahl, U. Pallesen, Tooth bleaching—a critical review of the biological aspects, Crit Rev Oral Biol Med, 14 (2003) 292-304.
[8] S. Gurgan, F.Y. Cakir, E. Yazici, Different light-activated in-office bleaching systems: A clinical evaluation, Lasers Med Sci, 25 (2010) 817-822.
[9] R.K. Henry, S.M. Bauchmoyer, W. Moore, R.G. Rashid, The effect of light on tooth whitening: A split-mouth design, Int J Dent Hyg, 11 (2013) 151-154.
[10] A.D. Loguercio, L.Y. Tay, D.R. Herrera, J. Bauer, A. Reis, Effectiveness of nano-calcium phosphate paste on sensitivity during and after bleaching: A randomized clinical trial, Braz Oral Res, 29 (2015) 1-7.
[11] L.Y. Tay, C. Kose, A.D. Loguercio, A. Reis, Assessing the effect of a desensitizing agent used before in-office tooth bleaching, J Am Dent Assoc, 140 (2009) 1245-1251.
[12] Q. Alomari, E. El Daraa, A randomized clinical trial of in-office dental bleaching with or without light activation, J Contemp Dent Pract, 11 (2010) E017-024.
[13] J.C. Ontiveros, In-office vital bleaching with adjunct light, Dent Clin North Am, 55 (2011) 241-253.
[14] M. Sulieman, E. Macdonald, J.S. Rees, M. Addy, Comparison of three in-office bleaching systems based on 35% hydrogen peroxide with different light activators, Am J Dent, 18 (2005) 194-197.
[15] C.R.G. Torres, D.C. Barcellos, G.R. Batista, A.B. Borges, K.V. Cassiano, C.R. Pucci, Assessment of the effectiveness of light-emitting diode and diode laser hybrid light sources to intensify dental bleaching treatment, Acta Odontol Scand, 69 (2011) 176-181.
[16] O. Polydorou, M. Wirsching, M. Wokewitz, P. Hahn, Three-month evaluation of vital tooth bleaching using light units-a randomized clinical study, Oper Dent, 38 (2013) 21-32.
[17] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[18] S.L. Ziemba, H. Felix, J. Macdonald, M. Ward, Clinical evaluation of a novel dental whitening lamp and light-catalyzed peroxide gel, J Clin Dent, 16 (2005) 123-127.
[19] J.C. Ontiveros, R.D. Paravina, Color change of vital teeth exposed to bleaching performed with and without supplementary light, J Dent, 37 (2009) 840-847.
[20] S. Kossatz, A.P. Dalanhol, T. Cunha, A. Loguercio, A. Reis, Effect of light activation on tooth sensitivity after in-office bleaching, Oper Dent, 36 (2011) 251-257.
[21] F.Z. Trindade, A.P. Ribeiro, N.T. Sacono, C.F. Oliveira, F.C. Lessa, J. Hebling, et al., Trans-enamel and trans-dentinal cytotoxic effects of a 35% h2o2 bleaching gel on cultured odontoblast cell lines after consecutive applications, Int Endod J, 42 (2009) 516-524.
[22] G. Kugel, S. Ferreira, S. Sharma, M.L. Barker, R.W. Gerlach, Clinical trial assessing light enhancement of in-office tooth whitening, J Esthet Restor Dent, 21 (2009) 336-347.
[23] L.B. He, M.Y. Shao, K. Tan, X. Xu, J.Y. Li, The effects of light on bleaching and tooth sensitivity during in-office vital bleaching: A systematic review and meta-analysis, J Dent, 40 (2012) 644-653.
[24] A. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, 41 (2016) 455-464.

[25] G. Moncada, D. Sepulveda, K. Elphick, M. Contente, J. Estay, V. Bahamondes, et al., Effects of light activation, agent concentration, and tooth thickness on dental sensitivity after bleaching, Oper Dent, 38 (2013) 467-476.
[26] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: The prisma statement, Int J Surg, 8 (2010) 336-341.
[27] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, et al., The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ, 343 (2011) d5928.
[28] G. Guyatt, A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, et al., Grade guidelines: 1. Introduction—grade evidence profiles and summary of findings tables, J Clin Epidemiol, 64 (2011) 383-394.
[29] L.C.A. Almeida, H. Riehl, P.H. Dos Santos, M.L.M.M. Sundfeld, A.L.F. Briso, Clinical evaluation of the effectiveness of different bleaching therapies in vital teeth, Int J Periodontics Restorative Dent, 32 (2012)
[30] L.C.a.G. Almeida, H. Riehl, P.H. Santos, M.L.M.M. Sundfeld, B.a.L. F., Occurrence of sensitivity during at-home and in-office tooth bleaching therapies with or without use of light sources, Acta Odontol Latinoam, 25 (2012) 3-8.
[31] J.F. Bortolatto, H. Pretel, C.S. Neto, M.F. Andrade, G. Moncada, O.B.O. Junior, Effects of led–laser hybrid light on bleaching effectiveness and tooth sensitivity: A randomized clinical study, Laser Phys Lett, 10 (2013) 085601.
[32] F.C. Marson, L.G. Sensi, L.C. Vieira, E. Araujo, Clinical evaluation of in-office dental bleaching treatments with and without the use of light-activation sources, Oper Dent, 33 (2008) 15-22.
[33] M. Tavares, J. Stultz, M. Newman, V. Smith, R. Kent, E. Carpino, et al., Light augments tooth whitening with peroxide, J Am Dent Assoc, 134 (2003) 167-175.
[34] J.O. Calatayud, C.O. Calatayud, A.O. Zaccagnini, M. Box, Clinical efficacy of a bleaching system based on hydrogen peroxide with or without light activation, Eur J Esthet Dent, 5 (2010) 216-224.
[35] R.F. Mondelli, J.F. Azevedo, A.C. Francisconi, C.M. Almeida, S.K. Ishikiriama, Comparative clinical study of the effectiveness of different dental bleaching methods - two year follow-up, J Appl Oral Sci, 20 (2012) 435-443.
[36] A. Strobl, N. Gutknecht, R. Franzen, R.D. Hilgers, F. Lampert, J. Meister, Laser-assisted in-office bleaching using a neodymium:Yttrium-aluminum-garnet laser: An in vivo study, Lasers Med Sci, 25 (2010) 503-509.
[37] G. Kugel, A. Papathanasiou, A.J. Williams, C. Anderson, S. Ferreira, Clinical evaluation of chemical and light-activated tooth whitening systems, Compend Contin Educ Dent Suppl, 27 (2006) 54-62.
[38] A. Papathanasiou, S. Kastali, R.D. Perry, G. Kugel, Clinical evaluation of a 35% hydrogen peroxide in-office whitening system, Compend Contin Educ Dent Suppl, 23 (2002) 335-338.
[39] C. Begg, M. Cho, S. Eastwood, Et Al., Improving the quality of reporting of randomized controlled trials: The consort statement, JAMA, 276 (1996) 637-639.
[40] K.F. Schulz, Subverting randomization in controlled trials, JAMA, 274 (1995) 1456-1458.
[41] P. Jüni, D.G. Altman, M. Egger, Assessing the quality of controlled clinical trials, BMJ, 323 (2001) 42-46.
[42] A.D. Loguercio, B.M. Maran, T.A. Hanzen, A.M.D. Paula, J. Perdigão, A. Reis, Randomized clinical trials of dental bleaching – compliance with the consort statement: A systematic review, Braz Oral Res, 31 (2017)
[43] K.F. Schulz, D.A. Grimes, Allocation concealment in randomised trials: Defending against deciphering, Lancet, 359 (2002) 614-618.
[44] D.G. Altman, K.F. Schulz, Concealing treatment allocation in randomised trials, BMJ, 323 (2001) 446-447.
[45] G. Enderlein, Pocock, sj: Clinical trials—a practical approach. John wiley & sons, chichester—new york—brisbane—toronto—singapore 1983, 265 s.,£ 16.95, Biom J, (1985)
[46] K.F. Schulz, I. Chalmers, D.A. Grimes, D.G. Altman, Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals, JAMA, 272 (1994) 125-128.

[47] M. Kashima-Tanaka, Y. Tsujimoto, K. Kawamoto, N. Senda, K. Ito, M. Yamazaki, Generation of free radicals and/or active oxygen by light or laser irradiation of hydrogen peroxide or sodium hypochlorite, J Endod, 29 (2003) 141-143.
[48] H. Fujikawa, K. Matsuyama, A. Uchiyama, S. Nakashima, T. Ujiie, Influence of salivary macromolecules and fluoride on enamel lesion remineralization in vitro, Caries Res, 42 (2008) 37-45.
[49] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[50] L. Markovic, K. Fotouhi, H. Lorenz, R.A. Jordan, P. Gaengler, S. Zimmer, Effects of bleaching agents on human enamel light reflectance, Oper Dent, 35 (2010) 405-411.
[51] M. Borenstein, L.V. Hedges, J. Higgins, H.R. Rothstein, Meta-regression: Introduction to meta-analysis, Introduction to Meta-analysis, (2009) 187-203.

Artigo 4

TÍTULO: DIFFERENT LIGHT ACTIVATION TO DENTAL BLEACHING: A SYSTEMATIC REVIEW AND A MIXED TREATMENT COMPARISON META-ANALYSIS

STATUS: PROCESSO SUBMISSÃO

REVISTA: ---

4.4 ARTIGO 4 – DIFFERENT LIGHT ACTIVATION TO DENTAL BLEACHING: A SYSTEMATIC REVIEW AND A MIXED TREATMENT COMPARISON META-ANALYSIS

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ABSTRACT

Objective: A systematic review and a mixed treatment comparison (MTC) meta-analysis were performed to answer the following research question: Is there any light-activation protocol capable of improving color change efficacy when associated to an in-office bleaching gel in adults?

Methods: Search was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library and SIGLE, without restrictions in April 28, 2017 (updated on March 30, 2018). IADR abstracts (1990–2018), unpublished and ongoing trials registries, dissertations and theses were also searched. Only randomized clinical trials conducted in adults that included at least one group treated with in-office dental bleaching with light-activation were included. The risk of bias (RoB) was evaluated used Cochrane Collaboration tool. A random-effects Bayesian MTC model was used to combine light-activated vs. light-free in-office bleaching with direct light-free comparison trials. Meta-analysis with independly analysis (high- and low-concentrate hydrogen peroxide [HP]) was conducted for color change (ΔE*, ΔSGU).

Results: After removal of duplicates, title and abstract screening, 28 studies remained. Nine studies were considered to be at low RoB, five were at high RoB and the remaining were at an unclear RoB. The MTC analysis showed no significant difference in color change (ΔE* and ΔSGU) between light-activation protocols and light-free in-office bleaching, regardless of the HP concentration in the efficacy of the bleaching.

Conclusion: No type of light-activated in-office bleaching was superior to light-free in-office bleaching for both high- and low-concentrate HP in-office bleaching gels. PROSPERO CRD42017078743

Clinical Relevance: Although many times the dental professionals, use the "laser whitening" as a form of marketing, this study confirm that no type of light activation for in-office bleaching can improve the bleaching efficacy.

Keywords: Tooth Bleaching. Tooth discoloration. Light activation. Mixed-treatment comparison.

INTRODUCTION

Vital dental bleaching is a technique that produces quick results and improves the patient's appearance and self-esteem. A study conducted with questionnaires by Poznan and Poland, reported that 85% of the patients submitted to dental bleaching was satisfied with their final appearance [1]. Similar findings were observed in the city of Santiago, Chile, where the authors reported that most of the patients were highly satisfied after a bleaching treatment [2]. Basically, there are two types of dentist-supervised dental bleaching: the at-home and in-office bleaching protocols. Although at-home bleaching is the most used technique, some patients require faster results and thus in-office, rather than at-home bleaching, is a more suitable procedure [3,4]. As at-home bleaching, in-office protocol produces satisfactory whitening results [5-9].

In-office bleaching systems employs high concentrate hydrogen peroxide that are sometimes activated with heat and/or light sources [10-12]. The rationale behind the use of light with in-office bleaching is to accelerate the bleaching process. By increasing the temperature of hydrogen peroxide applied to the dental surface, one can increase the hydrogen peroxide decomposition rate in free radicals for oxidization of complex organic molecules [13,14]. This association is usually named as “power” or “jump-start” bleaching”. There are many types of light-activating sources such as halogen lamps, laser, Light-Emitting Diodes (LEDs), metal halide and Plasma Arc Lamps (PAC) [5,15-19].

The benefits of this association has been questioned, since many randomized clinical trials (RCTs) have found controversial findings [16,20-23]. A recent systematic review [24] comparing the efficacy of a control group (bleaching without light activation) versus the combined effect of light-activated bleaching systems showed that light activation does not seem to improve color change, however in this systematic review, all types of light-activated systems were merged and not evaluated separately. Perhaps, differences in the light activated protocols may play a role on the performance of the light activated bleaching.

A systematic review of the literature with mixed treatment comparisons allow the comparison of different types of treatment, in which the gold standard is unknown. Such approach combines the extracted data in a series of mixed treatment meta-analysis, which incorporated evidence from trials indirectly, comparing protocols with a common comparator (such as bleaching without light) as well as evidence from direct comparisons of protocols (that is, head-to-head trials) [25].

Application of this approach enables treatments to be ranked in terms of the probability of each protocol being the first or most effective for each outcome measure, when difference between protocols are observed. Therefore, the purpose of this systematic review is to establish if there are evidence-based differences in the bleaching efficacy of light-free and the different types of light-activated bleaching protocols using high- and low-concentrate HP with three analytic approaches: direct comparison meta-analysis, indirect comparison meta-analysis, and mixed treatment comparisons, in order to include simultaneously all available data in the literature. To this end, the following PICO question (Population, Intervention, Comparison, and Outcome) was answered: Is there any light-activation protocol capable of improving color change efficacy when associated to an in-office bleaching gel in adults?

MATERIAL AND METHODS

Protocol and Registration

This study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO – CRD42017078743) and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for reports [26].

Information Sources and Search Strategy

The controlled vocabulary (MeSH terms) and free keyword in the search strategy were defined based on the aspects of population (adult patients who underwent vital tooth bleaching) and intervention (light activated in-office bleaching). The outcomes color change in ΔE* (CIEL*a*b* color scale system) and in shade guide units (ΔSGU) after dental bleaching were evaluated.

Electronic databases (MEDLINE via PubMed, Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature database (LILACS) and citation databases, Scopus, and Web of Science) were searched (Table 4.4-1). The reference lists of all primary studies were hand searched for additional relevant publications. We also searched the related article links of each primary study in the PubMed database without restrictions on publication date or languages.

Additionally, grey literature was investigated by searching the abstracts of the annual conference of the International Association for Dental Research and its regional divisions (1990-2018), the database System for Information on Grey Literature in Europe and dissertations and theses using the ProQuest Dissertations and Theses Full text database as well as the Periódicos Capes Theses database.

To locate unpublished and ongoing trials related to the review question, the clinical trial registries were searched: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (www.clinicaltrials.gov), ReBEC (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Eligibility Criteria

We included parallel and split-mouth RCTs that compared in-office dental bleaching with and without light activation in adult patients of any age group. RCTs were excluded if studies compared in-office dental bleaching with combined bleaching (in-office bleaching with jump-start at-home bleaching).

Study Selection and Data Collection Process

Initially, the articles were selected by title and abstract according to the previously described search strategy. Articles that appeared in more than one database were considered only once. Full-text articles were also obtained when the title and abstract presented insufficient information to make a clear decision. Subsequently, three reviewers classified those that met the inclusion criteria.

Each eligible article received a study ID, combining first author and year of publication. Relevant information about the study design, participants, interventions, and outcomes were extracted independently using customized extraction forms by three authors; in cases of disagreement, a decision was reached by consensus.

Concerning color change, results from 1-week post-bleaching were extracted. As some studies did not report this period, the most immediately post-bleaching period were extracted up to 1-month post-bleaching, depending on what authors reported.

Risk of Bias in Individual Studies

Quality assessments of the selected trials were carried out by three independent reviewers using the Cochrane Collaboration tool for assessing risk of bias in RCTs [27]. The assessment criteria contain six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data and selective outcome reporting, and other possible sources of bias. No extra source of bias was evaluated in the present investigation. During data selection and quality assessment, any disagreements between the reviewers were solved through discussion, and if needed, by consulting a fourth reviewer (A.R.).

For each aspect of the quality assessment, the risk of bias was scored following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0

(http://handbook.cochrane.org). Each domain level was judged as low, high, or unclear risk of bias. At the study level, the study was at low risk of bias if all key domains (see below) for each outcome were at low risk of bias. If one or more key domains were judged as at unclear risk, the study as a whole, was at unclear risk; if at least one key domain was considered at high risk of bias, the study was considered at high risk of bias. When a study was judged as unclear in at least one key domain, its authors were contacted to obtain more information to allow for a definitive judgement (yes or no). Three items of the Cochrane tool were considered key domains: adequate sequence generation, allocation concealment and examiner blinding.

Summary Measures and Statistical Analysis

Only studies classified as at low or unclear risk bias in the key domains were used in the meta-analysis of each outcome. Subgroup analysis was performed for high- and low-concentrate HP bleaching gels. Studies with HP concentrations higher than 25% were classified as high concentrate products; while studies with a concentration equal to or lower than 25% were considered low concentrate products.

The MTC methodology was chosen for the statistical analysis in order to simultaneously evaluate the effects of the different treatments. The compilation of evidence was made through a Mixed Treatment Comparison (MTC), which combines direct and indirect comparisons concomitantly. The direct evidence was computed with random effects model meta-analysis of head-to-head color change comparisons. This model is supported by the Markov Chain Monte Carlo (MCMC) hierarchy and is extremely versatile, allowing data of more than two heterogeneous arms and variability between trials. The analyzes were implemented using the R statistical software (https://cran.r-project.org) and Bayesian inference was performed using JAGS (http://mcmc-jags.sourceforge.net).

In this study, the common comparator was the light-free bleaching treatment, in which two analyzes were done. Firstly, a traditional meta-analysis of the direct evidence, from the studies comparing different therapeutic methods were conducted, deriving a mean difference and a confidence interval (CI) of 95%. Heterogeneity was assessed using the Cochran Q test and statistics.

Subsequently the network meta-analysis was performed, the common comparator was the groups that did not use light, and the light treatment groups were treated as different groups. The most appropriate model adjustment was made: fixed or random effect verified by the Deviance Information Criterion (DIC), in which the non-informative priors were evaluated for accuracy and effect sizes, such as convergence, correlation and quality of fit.

MTC models assumes that there is consistency between direct and indirect evidence, that is, information of both sources of evidence are similar enough in order to be combined. We checked the consistency assumption using the posterior plots and the Bayesian p-values produced the node-splitting method by Dias et al., 2010 [28]. In this approach, each node in the network of evidence has its direct, indirect and MTC components analyzed. Consistency is observed if the p value of the analysis is greater than the significance level (set to be 0.01 in the analysis, since the same data are used in multiple comparisons).

In case of differences between treatments, a Bayesian approach using probability values will be summarized as Surface Under the Cumulative Ranking Curve (SUCRA) to evaluate the probability of the most effective or safer treatment. The higher the value of SUCRA, the better the degree of intervention.

RESULTS

Study Selection

The search strategy was conducted initially on April 28, 2017 and was updated on March 30, 2018. After database screening and duplicate removal, 4906 studies were identified (Figure 4.4-1). After title screening, 136 studies remained, and this number was reduced to 28 after careful examination of the abstracts.

Characteristics of Included Articles

Study design and method of color evaluation

The characteristics of the 28 selected studies are listed in Table 4.4-2. The study design was balanced, 14 studies used parallel design [5,11,16,19,22,29-37], and 14 studies used the split-mouth design [15,17,18,20,21,23,38-45].

For color evaluation, 22 studies used a shade guide [5,11,15,16,18,19,21,23,30,32-38,40-45]. Fifteen out of these 28 studies used an objective instrument (spectrophotometer or colorimeter) for color assessment [11,17,19,20,22,29,32,33,35,36,38-41,45]. Photography was used in nine studies [5,11,18,20,31,38,39,42,43].

Number or participants in the primary RCTs and gender

The number of patients per group included in these studies ranged from 18 to 78 years old. The mean age of all participants included in the RCTs that reported this information was approximately 30 years, showing a predominance of young adults (Table 4.4-2). In all studies that reported the sample population gender, females were prevalent [11,16,17,19,21,22,35,41,44,45]. Several studies did not report this characteristic [5,15,18,20,23,29-34,36-40,42,43].

Bleaching protocols

The concentration of HP varied from 6% to 38% (Table 4.4-2). The application protocol of the in-office bleaching was quite variable, although a high number of studies applied the product for three 15-minutes applications in each clinical session [11,17,21,29,30,32-35,37-40,43].

Variations in this protocol were observed, with one, two and four applications per session, for different periods of times. Most studies performed one single clinical session [11,16-21,23,31,32,34,36,37,39,42,44,46], but two or three sessions with intervals between 7 and 14 days were also observed (Table 4.4-2).

Different types of light activation were used. Six studies used halogen lamp [5,16,33,36,42,43], thirteen used LED/Laser [5,15,21,22,29,30,33-35,38,39,43,45], seven used only LED [11,15,16,23,32,33,43], eight used metal-halide light [16-18,20,31,37,44,46], four used only a laser source [11,32,36,41], and two used PAC [11,19] with different protocols. In some studies, light was applied for the same time of the gel; in other studies, light was applied for few minutes with a specific time interval between applications (Table 4.4-2).

Assessment of the Risk of Bias

The risk of bias of the eligible studies is presented in Figure 4.4-2. Few full-text studies reported the method of randomization, allocation concealment, and whether or not the examiner was blinded during color assessment in shade guide units, being usually classified as at unclear risk of bias. However, four out of the 28 studies were considered to be at high risk of bias at the study level [17,23,31,43], so they were not used in the meta-analysis.

Evidence network

All meta-analysis was performed on studies classified as at low or unclear risk of bias in the key domains. We performed independly analysis based on the concentration of HP. In this phase, other studies were removed from the meta-analysis. The study by Bortolatto 2016 [22], Kugel 2006 [18], Martin 2015 [34] and Martín 2015 [45] were removed because the authors compared a low-concentrate HP vs. a high-concentrate HP, the study by Posso Moreno 2010 [20] was removed because the data could not be extracted and the study by Ward 2012 [44] was removed because the authors did not have a comparator group in the study (Figure 4.4-1). In summary, 18 studies were included in the meta-analysis of color change outcome. At this point it is worth mentioning that each study may have more than one comparison and therefore more than 18 pairs could have been included in each one of the meta-analysis described below.

Figure 4.4-3 shows the evidence network of light activation comparisons, where each node represents an intervention, the line thickness the number of searches included in the study. From the evidence network is possible to observe that some pairwise comparisons have only direct evidence that comes from head-to-head studies (light-free vs. LED, for example; Figure 4.4-3A), some have only indirect evidence (for example, metal halide light vs. LED/laser; Figure 4.4-3B), other comparisons only have indirect evidence coming from the trials comparing light-free vs. metal halide light and light-free vs. LED/laser and other pairs have both direct and indirect evidence (Figure 4.4-3).

For high-concentrate HP gel, color change of six types of light activation were compared in ΔE* (Figure 4.4-3A), including 21 pairs of comparisons and totalizing 641 patients. Seven types of light activation were compared in ΔSGU (Figure 4.4-3B), including 31 pairs of comparisons and totalizing 835 patients. For low-concentrate HP products, color change of three types of light activation were compared in ΔE* (Figure 4.4-3C), including 2 pairs of comparisons and totalizing 78 patients and four types of light activation were compared in ΔSGU (Figure 4.4-3D), including 4 pairs of comparison and totalizing 186 patients.

Mixed-treatment comparison

Table 4.4-3 summarizes the results of the MTC meta-analysis of the effect of different types of light activation on the mean difference (MD) of the color change in ΔE* and ΔSGU for high- and low-concentrate HP gels, and with the comparisons available, no type of light activation was superior to any other in ΔE* and in ΔSGU, regardless of the HP concentration. In face of that we have not performed the SUCRA analysis described in the methods section.

Consistency of analysis

No evidence of inconsistency between direct and indirect evidence was detected. The smallest Bayesian p-value found was equal to 0.11 for the LED light versus LED/Laser treatment comparison for ΔSGU (Figure 4.4-4 and 5).

DISCUSSION

For the research question under evaluation in this study, multiple types of light activation devices are present in the market and they vary significantly in light spectrum, intensity and power output. Although previous systematic reviews of literature have already focused in this research question, they merged the same outcome of all types of light activation devices to compare them against a control group of in-office bleaching without light activation [24,47]. The combination of different kinds of studies in a meta-analysis has been one of the criticisms to this methodology as such process is based on subjective judgment, and researchers

may have different opinions concerning the appropriateness of combining results. Additionally, there is often an interest among clinicians to identify the most effective treatment or to rank the treatments among a range of clinical available alternatives, such as the type of light activation device used in conjunction with in-office bleaching.

Recently, mixed treatment comparisons (MTC) have been presented as an extension of traditional meta-analysis, which includes only studies that compare the same or alike interventions with the same control group, by allowing the inclusion of multiple pairwise comparisons. In such approach, direct head-to-head comparisons and indirect comparison of two interventions is made through a common comparator. This method has become increasingly common in the medical literature [48-51]; however in dental literature there are few studies that used this methodology [52-54]. Indirect comparisons can increase the validity of comparisons obtained with direct comparisons [55] and may also provide valuable clinical information in the absence of direct comparative data [56].

Differently from the two previous traditional systematic reviews of the literature [24,47], the present study evaluated the impact of the different types of light activation on the bleaching efficacy through a Bayesian MTC approach. We could confirm previous findings that light activation, irrespective of their source, does not affect the efficacy of bleaching in terms of color change, which indeed confirm the results of the traditional meta-analysis presented in the earlier systematic review [16,33,36].

The rationale behind the lack of efficacy of light activation was previously mentioned in an earlier publication [24]. From chemical theories, we know that heat and light sources can accelerate the decomposition of HP to form oxygen and perhydroxyl free radicals, but this does not necessarily mean that under a clinical scenario, greater whitening efficacy will be observed, as shown in the present systematic review. It is very likely that there are unknown rate-determining steps in the oxidizing mechanism of tooth whitening [24], which may play a more significant role on the color change.

For instance, the mean age of the participants included in the primary studies of this systematic review are under 30 years old (Table 4.4-2). It was demonstrated that for every increase of 1 year in the participant's age we observed a decrease of the final whitening degree of 0.69 for the ΔE, suggesting that the whitening degree is negatively affected by the participant's age years [57]. In other words, as most of the RCTs evaluated color change in young patients in which color change occurs easier, we may not extend the conclusions of this systematic review to elderly patients. This is one of the limitation of the present and earlier

systematic reviews of the literature [24,58,59]. The results described in these systematic reviews appraise and summarizes the evidence of the primary studies but also carry on their limitations. Perhaps the use of light-activation in-office bleaching may be effective in more challenging clinical scenarios, such as elderly patients and RCTs with such population sample are encouraged.

In agreement with the systematic review of Maran et al. [24], we did not observe differences in color change between high and low concentrate bleaching gels. However, in the latter comparison, there are still few well-conducted RCTs, which reduces the precision of the color change outcome. Perhaps well-conducted RCTs should be conducted with lower HP concentrations and varied types of light sources to increase the precision of the estimates herein presented or to change our view in this aspect.

Although the main goal of tooth bleaching is to whiten teeth, tooth sensitivity is the main adverse effect of this cosmetic treatment. There is a wide belief that light activation may lead to higher risk and/or intensity of bleaching-induced tooth sensitivity. This finding was indeed demonstrated for low concentrate products in an earlier systematic review [59], but the quality of the evidence was not high because of the data imprecision of the estimate due to the low number of included studies. Adding indirect information to this outcome through mixed treatment comparisons may increase the reliability of this estimate. Bleaching-induced tooth sensitivity were not evaluated in this study; but it is under investigation through another mixed treatment comparison analysis and their results will be soon published in the literature.

Another important factor evaluated in this study that deserves attention from the research community was the risk of bias of the studies included in this review. From the 28 studies, only 6 were classified as at low risk of bias in all domains. Additionally, the majority of the studies did not report adequately the key domains randomization and allocation concealment. Randomization is the most important tool that only RCTs can employ. It provides comparative groups at baseline for both known and unknown baseline features. However, randomization alone is not complete and may be broken if the random sequence is not kept secret until implementation.

The process of protecting random sequence is called allocation concealment [60,61] and the adequate management of random sequence and allocation concealment keep the study free of selection bias. In the newer version of the Cochrane Collaboration tool for assessing the risk of bias of RCTs (RoB 2.0 version), randomization and allocation concealment were merged in a single domain as the both focus on preventing selection bias.[62] Future RCTs on this topic

should pay more attention to these aspects during design and execution to increase the quality of the evidence produced in the dental field.

Finally, this systematic review has other limitations apart from the ones already addressed. The analysis did not take into account the differences in the protocols of each light activation device, but it seems that for high concentrate in-office gels, the use of light activation may be useless for a young population. And some comparisons take into account only one pair analyzed. Future RCTs with low concentrate gels are still require increasing the precision of the findings herein reported.

CONCLUSIONS

The efficacy of in-office bleaching not was influenced by light-activation regardless of the type of device used for such purpose. The same findings were observed for high- and low-concentrate in-office bleaching gels, although for the latter there is still a limited number of published articles.

Conflict of interest

There was no conflict of interest present during the undertaking of this study. The study did not receive any internal or external funding.

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Table 4.4-1. Electronic database and search strategy conducted initially in 28 April 2017 and was updated in 30th March 2018.

PubMed		
#1 ((((((((((((((((((tooth discoloration[MeSH Terms]) OR dentition, permanent[MeSH Terms]) OR color[MeSH Terms]) OR color[Title/Abstract]) OR colour[Title/Abstract]) OR "tooth discoloration"[Title/Abstract]) OR "tooth discolouration"[Title/Abstract]) OR "teeth discoloration"[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 "tooth staining"[Title/Abstract]) OR "teeth staining"[Title/Abstract]) OR "dental discoloration"[Title/Abstract]) OR "dental discolouration"[Title/Abstract]) OR "stained teeth"[Title/Abstract]) OR "stained tooth"[Title/Abstract]) OR "dental staining"[Title/Abstract] #1 AND #2 AND 3	#2 ((((((((((((((((tooth bleaching[MeSH Terms]) OR peroxides[MeSH Terms]) OR tooth bleaching agents[MeSH Terms]) OR hydrogen peroxide[MeSH Terms]) OR carbamide peroxide[Supplementary Concept]) OR light[MeSH Terms]) OR lasers[MeSH Terms]) OR bleaching[Title/Abstract]) OR whitening[Title/Abstract]) OR "hydrogen peroxide"[Title/Abstract]) OR "carbamide peroxide"[Title/Abstract]) OR "in office"[Title/Abstract]) OR "light activation"[Title/Abstract]) OR heat[Title/Abstract]) OR ultraviolet[Title/Abstract]) OR lamp[Title/Abstract]) OR "light activated"[Title/Abstract]) OR LED[Title/Abstract]	#3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])
Cochrane		
#1 MeSH descriptor: [Tooth Discoloration] explode all trees #2 MeSH descriptor: [Dentition, Permanent] explode all trees #3 MeSH descriptor: [Color] explode all trees #4 t*th next discoloration:ti,ab,kw or discolored next t*th:ti,ab,kw or t*th next staining:ti,ab,kw or dental next discoloration:ti,ab,kw or stained next t*th:ti,ab,kw (Word variations have been searched) #5 dental next staining:ti,ab,kw or color:ti,ab,kw (Word variations have been searched) #6 #1 or #2 or #3 or #4 or #5 #7 MeSH descriptor: [Tooth Bleaching] explode all trees #8 MeSH descriptor: [Peroxides] explode all trees #6 AND #15	#9 MeSH descriptor: [Tooth Bleaching Agents] explode all trees #10 MeSH descriptor: [Hydrogen Peroxide] explode all trees #11 MeSH descriptor: [Light] explode all trees #12 MeSH descriptor: [Lasers] explode all trees #13 "carbamide peroxide":ti,ab,kw or bleaching:ti,ab,kw or whitening:ti,ab,kw or "hydrogen peroxide":ti,ab,kw or "in office":ti,ab,kw (Word variations have been searched) #14 light next activat*:ti,ab,kw or heat:ti,ab,kw or ultraviolet:ti,ab,kw or lamp:ti,ab,kw or LED:ti,ab,kw (Word variations have been searched) #15 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	
LILACS/BBO		
#1 (MH:"tooth discoloration" OR MH:"dentition permanent" OR MH:color OR color OR cor OR colour OR "tooth discolouration" OR "descoloração de dente" OR "decoloración de lo diente" OR "teeth discoloration" OR "decoloración de los dientes" OR "descoloração dos dentes" OR "teeth discolouration" OR "discolored tooth" OR "diente descolorido" OR "dente descolorido" OR "discolored teeth" OR "dientes descoloridos" OR "dentes descoloridos" OR "discoloured tooth" OR "discoloured teeth" OR "tooth staining" OR "manchas en los	#2 (MH:"tooth bleaching" OR MH:peroxides OR MH:"tooth bleaching agents" OR MH:"hydrogen peroxide" OR MH:light OR MH:lasers OR "peroxide carbamide" OR "peróxido de carbamida" OR bleaching OR blanqueo OR branqueamento OR whitening OR blanqueamiento OR "in office" OR "en el consultorio" OR "em consultório" OR "light activation" OR "activación de la luz" OR fotoativação OR heat OR calor OR ultraviolet OR ultravioleta OR lamp OR lámpara OR lâmpada OR "light activated" OR "activado por la luz" OR "ativado por luz" OR LED)	

Artigo 4

dientes" OR "manchamento dental" OR "dental discoloration" OR "decoloración dental" OR "descoloração dental" OR "dental discolouration" OR "stained teeth" OR "dientes manchados" OR "dentes manchados" OR "stained tooth" OR "diente manchado" OR "dente manchado" OR "dental staining" OR "mancha en los dientes" OR "mancha nos dentes") #1 AND #2	
Scopus	
#1 (TITLE-ABS-KEY ("permanent dentition") OR TITLE-ABS-KEY ("t??th discoloration") OR TITLE-ABS-KEY (colo*r) OR TITLE-ABS-KEY ("t??th discolouration") OR TITLE-ABS-KEY ("discoloured t??th") OR TITLE-ABS-KEY ("discolored t??th") OR TITLE-ABS-KEY ("t??th staining") OR TITLE-ABS-KEY ("dental discolo*ration") OR TITLE-ABS-KEY ("stained t??th") OR TITLE-ABS-KEY ("dental staining")) #1 AND #2	#2 TITLE-ABS-KEY ("t??th bleaching") OR TITLE-ABS-KEY (peroxides) OR TITLE-ABS-KEY ("t??th bleaching agents") OR TITLE-ABS-KEY ("hydrogen peroxide") OR TITLE-ABS-KEY (light) OR TITLE-ABS-KEY (lasers) OR TITLE-ABS-KEY (bleaching) OR TITLE-ABS-KEY (whitening) OR TITLE-ABS-KEY ("carbamide peroxide") OR TITLE-ABS-KEY ("in office") OR TITLE-ABS-KEY ("light activat*") OR TITLE-ABS-KEY (heat) OR TITLE-ABS-KEY (ultraviolet) OR TITLE-ABS-KEY (lamp) OR TITLE-ABS-KEY (led)
Web of science	
#1 Tópico: ("permanent dentition") OR Tópico: (“t*th discolo*ration”) OR Tópico: (colo$r) OR Tópico: (“discolo*red t*th”) OR Tópico: (“t*th staining") OR Tópico: (“dental discolo*ration”) OR Tópico: ("stained t*th") OR Tópico: ("dental staining") #1 AND #2	#2 Tópico: ("t*th bleaching") OR Tópico: (peroxides) OR Tópico: (“tooth bleaching agents”) OR Tópico: (“hydrogen peroxide”) OR Tópico: (light) OR Tópico: (lasers) OR Tópico: (bleaching) OR Tópico: (whitening) OR Tópico: ("carbamide peroxide") OR Tópico: ("in office") OR Tópico: ("light activat*") OR Tópico: (heat) OR Tópico: (ultraviolet) OR Tópico: (lamp) OR Tópico: (LED)

Table 4.4-2. Summary of the primary studies included in this systematic review.

Study ID	Study design [setting]	No. patients [drop-outs]	Subjetcs age in means ± SD [range] (yr)	No. of subjetcs [%] (male)	Baseline color/ evaluated tooth	Groups/Materials	Bleaching protocol		Light source	Color assessment [outcome]
							Gel protocol Applications x min [sessions] (interval)	Light protocol	Spectrum (nm)/Intensity (mW/cm^2)/power output (W)	
Almeida, 2012[5]	Parallel [n.r.]	40 [0]	n.r. ± n.r. [18-28]	n.r. [n.r.]	n.r./n.r.	I: AH 10% CP[a] II: IO 35% HP[bA] III: IO 35% HP[b] + light[B] IV: IO 35% HP[b] + light[C]	I: 4h/daily (21 days) II-IV: 3 x 10 min [3] (7 days)	III: 3 x 20 sec IV: 3 x 3 min	III: 450-500 / 400 / 0.2 IV: 470 and 808 / 120 and n.r. / 0.2	Vita Classical[o] Photography [ΔSGU]
Almeida Farhat, 2014[15]	Split-mouth [n.r.]	16 [0]	n.r ± n.r. [18-30]	n.r. [n.r.]	C2/Anterior teeth	I: IO 35% HP[c] + light[D] II: IO 35% HP[c] + light[C]	3 x 10 min [2] (7 days)	3 x 1 min (2-min interval)	I: n.r. / n.r. / n.r. II: 425-480 and 810 / 300 and 200 / 0.2	Vita Classical[o] [ΔSGU]
Alomari, 2010[16]	Parallel [n.r.]	40 [n.r.]	27.8 ± n.r. [18-40]	12 [30]	A3/Anterior teeth	I: IO 35% HP[dA] II: IO 35% HP[d] + light[B] III: IO 35% HP[d] + light[D] IV: IO 35% HP[d] + light[E]	I-IV: 3 x 20 min [1]	II-IV: 3 x 20 min	n.r./ n.r. / n.r.	Vita Classical[o] [ΔSGU]
Bernardon, 2010[38]	Split-mouth [n.r.]	90 [1]	n.r. ± n.r. [n.r.-n.r.]	n.r. [n.r.]	A2/Anterior teeth	I: AH 10% CP[a] vs. IO 35% HP[b] + light[C] II: IO 35% HP[bA] vs. IO 35% HP[b] + light[C] III: AH 10% CP[a] vs. IO 35% HP[b] + light[C] [1 session] and AH 10% CP[a]	AH: 8h/daily (14 days) IO: 3 x 15 min [2] (15 days)	1 x 4 min	n.r./ n.r. / n.r.	Vita Classical[o] Spectrophotometer[p] Photography [ΔSGU and ΔE*]
Bortolatto, 2013[29]	Parallel [n.r.]	40 [8]	n.r. ± n.r. [18-25]	n.r. [n.r.]	n.r./n.r.	I: IO 35% HP[cA] II: IO 35% HP[c] + light[C]	I: 3 x 15 min [3] (7 days) II: 3 x 8 min [3] (7 days)	4 x 1 min	425-480 and 810 / 300 and n.r. / 1.8	Spectrophotometer[p] [ΔE*]
Bortolatto, 2016[22]	Parallel [University]	48 [0]	24.2 ± 3.9 [18-25]	24 [50]	n.r./n.r.	I: IO 6% HP[c] + light[C] II: IO 35% HP[e] + light[C]	2 x 12 min [2] (7 days)	6 x 1 min (1-min interval	455-485 and 810 / 300 and 200 / 1.8	Spectrophotometer[p] [ΔE*]
Calatayud, 2010[23]	Split-mouth [n.r.]	21 [0]	n.r. ± n.r. [18-38]	n.r. [n.r.]	A2/Anterior teeth	I: IO 35% HP[f] + light[D] II: IO 35% HP[fA]	2 x 10 min [1]	2 x 10 min	380-530 / n.r. / n.r.	Vita Classical[o] [ΔSGU]
Freitas, 2016[21]	Split mouth [University]	22 [0]	20.5 ± n.r. [18-25]	10 [45]	A2/Anterior teeth	I: IO 35% HP[cA] II: IO 35% HP[c] + light[C]	I: 3 x 15 min [1] II: 3 x 8 min [1]	3 x 1 min	470 and 810 / 350 and n.r. / 0.2	Vita Classical[o] [ΔSGU]
Gomes, 2008[43]	Split-mouth [n.r.]	24 [0]	n.r. ± n.r. [20-30]	n.r. [n.r.]	n.r./n.r.	I: IO 35% HP[b] + light[D] vs. IO 35% HP[b] + light[B] II: IO 35% HP[b] + light[C] vs. IO 35% Hp[bA]	3 x 15 min [2] (7 days)	I: 3 x 30 sec II: 3 x 3 min	I: 440-480 vs. n.r. / 1400 vs. n.r. / n.r. vs. n.r. II: 470 and 830 / 63 and 500. / n.r.	Vita Classical[o] Photography [ΔSGU]
Gurgan, 2010[11]	Parallel [n.r.]	40 [0]	27.3 ± n.r. [18-30]	11 [27.5]	A3/Anterior teeth	I: IO 38% HP[dA] II: IO 37% HP[g] + light[F] III: IO 35% HP[h] + light[G] IV: IO 38% HP[i] + light[D]	I: 2 x 15 min [1] II: 3 x 8 min [1] III: 3 x 20 min [1] IV: 2 x 20 min [1]	II: 2 x 105 sec III: 3 x 10 min (30-sec	II: 815 / n.r. / 10 III: 400-490 / 2800 / n.r	Vita Classical[o] Spectrophotometer[p] Photography [ΔSGU and ΔE*]

								interval) IV: 2 x 20 min	IV: 400-500 / n.r. / n.r.	
Henry, 2013[17]	Split-mouth [n.r.]	49 [0]	38.4 ± 13.6 [n.r.-n.r.]	24 [49]	A3/Anterior teeth	I: IO 25% HP[j] + light[E] II: IO 25% HP[jA]	3 x 15 min [1]	3 x 15 min	n.r. / n.r. / n.r.	Spectrophotometer[p] [ΔE*]
Kossatz, 2011[30]	Parallel [University]	30 [0]	n.r. ± n.r. [n.r-n.r.]	n.r. [n.r.]	C2/Upper central incisor	I: IO 35% HP[b] + light[C] II: IO 35% HP[bA]	3 x 15 min [2] (7 days)	3 x 5 min (2-min interval)	470 and 830 / 200 and n.r. / n.r.	Vita Classical[o] [ΔSGU]
Kugel, 2006[18]	Split-mouth [n.r.]	10 [0]	n.r. ± n.r. [n.r.]	n.r. [n.r.]	A3/Anterior teeth	I: IO 15% HP[k] + light[E] II: IO 38% HP[dA]	3 x 20 min [1]	3 x 20 min	n.r. / n.r. / n.r.	Vita Classical[o] Photography [ΔSGU and ΔE*]
Kugel, 2009[31]	Parallel [University]	33 [3]	30.9 ± n.r. [22-48]	n.r. [n.r.]	A2/Anterior teeth	I: IO 25% HP[l] + light[E] II: IO 25% HP[lA] III: only light[E]	3 x 20 min [1]	3 x 20 min	n.r. / n.r. / n.r.	Photography [ΔE*]
Lo Giudice, 2016[32]	Parallel [n.r.]	18 [0]	n.r. ± n.r. [n.r-n.r.]	n.r. [n.r.]	n.r./n.r.	I: IO 35% HP[d] + light[D] II: IO 35% HP[d] + light[F]	3 x 15 min [1]	3 x 15 min	I: 495 / 30000 / 0.6 II: n.r. / n.r. / n.r.	Vita Classical[o] Spectrophotometer[p] [ΔE*]
Marson, 2008[33]	Parallel [n.r.]	40 [0]	n.r. ± n.r. [18-28]	n.r. [n.r.]	n.r./Anterior teeth	I: IO 35% HP[bA] II: IO 35% HP[b] + light[B] III: IO 35% HP[b] + light[D] IV: IO 35% HP[b] + light[C]	3 x 15 min [2] (7 days)	3 x 15 min	I: 400-500 / n.r./ n.r. II: 450-500 / n.r. / n.r. III: 470 / n.r / n.r.	Vita Classical[o] Spectrophotometer[p] [ΔSGU and ΔE*]
Martin, 2015[34]	Parallel [University]	70 [45]	23.6 ± 4.0 [18-37]	n.r. [n.r.]	n.r./n.r.	I: IO 15% HP[c] + light[C] II: IO 35% HP[c] + light[C]	I: 3 x 15 min [1] II: 3 x 12 min [1]	I: 3 x 15 min II: 3 x 12 min	450 and 808 / 400 and 100 / n.r..	Vita Classical[o] [ΔSGU]
Martín, 2015[45]	Split-mouth [University]	30 [1]	24.1 ± 5.0 [18-44]	17 [63.3]	A2/Central incisors	I: IO 6% HP[c] + light[C] II: IO 35% HP[c] + light[C]	2 x 12 min [3] (7 days	2 x 12 min	n.r and n.r. / n.r. and n.r. / 1.5	Vita Classical[o]; Vita Bleachedguide[q]; Spectrophotometer[p] [ΔSGU; ΔE*]
Mena Serrano, 2016[35]	Parallel [University]	77 [0]	22.5 ± 3.8 [18-27]	27 [35]	A3/Upper Canine	I: IO 20% HP[bA] II: IO 20% HP[b] + light[C] III: IO 35% HP[bA] IV: IO 35% HP[b] + light[C]	3 x 15 min [2] (7 days)	5 x 1 min (2-min interval)	470 and 830 / n.r. and 200 / n.r.	Vita Classical[o] Spectrophotometer[p] [ΔSGU and ΔE*]
Mondelli, 2012[39]	Split-mouth [n.r.]	48 [19]	n.r. ± n.r. [n.r.]	n.r. [n.r.]	A3/Anterior teeth	I: IO 35% HP[c] + light[C] II: IO 35% HP[cA] III: IO 38% HP[d] + light[C] IV: IO 38% HP[dA] V: AH 15% CP[m]	I and III: 3 x 11 min [1] II and IV: 3 x 15 min [1] V: 2h/daily (10 days)	3 x 3 min (1-min interval)	470 and 810 / 350 and 200 / n.r.	Spectrophotometer[p] Photography [ΔE*]
Ontiveros, 2009[40]	Split-mouth [n.r.]	20 [0]	n.r. ± n.r. [18-30]	n.r. [n.r.]	A2/Anterior teeth	I: IO 25% HP[j] + light[E] II: IO 25% HP[jA]	3 x 15 min [1]	3 x 15 min	350-600 / n.r. / 0.2	Vita Classical[o] Spectrophotometer[p] Vita Bleachedguide 3D-Master[q] [ΔSGU and ΔE*]
Papathanasiou, 2002[42]	Split-mouth [University]	20 [0]	n.r. ± n.r. [n.r.-n.r.]	n.r. [n.r.]	A3/Anterior teeth	I: IO 35% HP[d] + light[B] II: IO 35% HP[dA]	1 x 20 min [1]	1 x 20 min	n.r. / n.r. / n.r.	Vita Classical[o] Photography [ΔSGU]

Polydorou, 2013[36]	Parallel [n.r.]	60 [0]	27.6 ± 5.0 [18-70]	n.r. [n.r.]	C1/Upper Canine	I: IO 38% HP[dA] II: IO 38% HP[d] + light[B] III: IO 38% HP[d] + light[E]	4 x 15 min [1]	II: 4 x 8 min III: 4 x 30 sec	II: 480-520 / n.r. / 150 III: 980 / n.r. / 6	Vita Classical[o] Spectrophotometer[p] [ΔSGU and ΔE*]
Posso Moreno, 2010[20]	Split-mouth [n.r.]	10 [0]	n.r. ± n.r. [18-28]	n.r. [n.r.]	n.r./n.r.	I: IO 25% HP[l] + light[E] II: IO 25% HP[lA]	2 x 20 min [1]	2 x 20 min	n.r. / n.r. / n.r.	Spectrophotometer[p] Photography [ΔE*]
Strobl, 2010[41]	Split-mouth [n.r.]	20 [0]	n.r. ± n.r. [n.r-n.r.]	7 [35]	A1/n.r.	I: IO 35% HP[n] + light[F] II: IO 35% HP[nA]	2 x 1 min and 45 sec [2] (7 days)	3 x 10 sec	1064 µm / 1.4 J/cm^2 / 4	Vita Classical[o] Chromatometer ShadeEye NCC[r] [ΔSGU and ΔE*]
Tavares, 2003[19]	Parallel [n.r.]	87 [0]	44 ± n.r. [17-64]	38 [44]	D4/Upper Incisor	I: IO 15% HP + light[G] II: IO 15% HP[A] III: IO placebo gel + light[G]	3 x 20 min [1]	3 x 20 min	400-505 / 130-160 / n.r.	Vita Classical[o] CR-321 Chromameter[s] [ΔSGU and ΔE*]
Ward, 2012[44]	Split-mouth [n.r.]	15 [0]	37 ± n.r. [18-78]	12 [80]	A3/Anterior teeth	I: 15% HP[l] + light[E] II: 25% HP[l] + light[E]	3 x 20 min [1]	3 x 20 min	400-505 / n.r. / n.r.	Vita Classical[o] [ΔSGU]
Ziemba, 2005[37]	Parallel [n.r.]	50 [1]	n.r. ± n.r. [18-70]	[n.r.]	A3/Anterior teeth	I: IO 25% HP[j] + light[E] II IO 25% HP[jA]	3 x 15 min [1]	3 x 15 min	365-500 / n.r. / n.r.	Vita Classical[o] [ΔSGU]

Abbreviations: ID–identification; SD–standard deviation; n.r.–not reported in the study; AH–At-Home bleaching; CP–Carbamide Peroxide; IO–In-Office bleaching; HP–Hidrogen Peroxide; ΔSGU–shade guide units; ΔE*–color difference measured with a spectrophotometer.
a Whiteness Perfect (FGM, Joinville, Brazil)
b Whiteness HP Maxx (FGM, Joinville, Brazil)
c Lase Peroxide Sensy (DMC, São Carlos, Brazil)
d Opalescence Xtra Boost (Ultradent Inc., South Jordan, UT, USA)
e Total Blanc (Nova DFL, Rio de Janeiro, RJ, Brazil)
f QuickWhite (DMDS House, Canterbury, UK)
g LaserWhite 10 (Biolase Technology Inc., San Clemente, CA, USA)
h Remewhite (Remedent, Deurle, Belgium)
i By White (Biowhite, Ensodent, Italy)
j Zoom 2 (Discus Dental, Inc., Culver City, CA, USA)
k BriteSmile (Walnut Creek, CA, USA)
l ZOOM Chairside Whitening System (Discus Dental, Inc., Culver City, CA, USA)
m Opalescence PF (Ultradent, South Jordan UT, USA)
n Fotona (Fotona d.d., Ljubljana, Slovenia)
o Vita Classical Shade (Vita Zahnfabrik, Bad Säckingen, Germany)
p Spectrophotometer (Vita Easyshade, Vident, Brea, CA, USA)
q Vita Bleachedguide 3D-Master (Vita Zahnfabrik, Bad Säckingen, Germany)
r Chromatometer ShadeEye NCC (Shofu Dental GmbH, Ratingen, Germany)
s CR-321 Chromameter (Minolta, Ramsey, N.J.)
A Light-free
B Halogen Lamp
C LED/Laser
D LED
E Metal halide light
F Laser
G PAC

Table 4.4-3. Mixed-treatment comparison (MTC) analysis of the effect of color change with different kind of light activation. (A) MTC of the effect of color change in ΔE* (on the underside) and ΔSGU (on the top side) for high-concentrate HP on the median of the mean difference (MD). Results are MD [(95% confidence interval (CI)] in the column-defining light activation compared with the row-light activation on the top side. (B) MTC of the effect of color change in ΔE* (on the underside) and ΔSGU (on the top side) for low-concentrate HP on the median of the mean difference (MD). Results are MD [(95% confidence interval (CI)] in the column-defining light activation compared with the row-light activation on the top side.

A

Light-free	0.15 (−0.43, 0.70)	−0.13 (−0.53, 0.32)	0.15 (−0.69, 1.10)	−0.15 (−1.50, 1.40)	0.97 (−0.12, 2.30)	0.03 (−2.10, 2.30)
0.10 (−1.80, 1.80)	**Halogen lamp**	−0.27 (−0.74, 0.42)	−0.03 (−0.87, 0.99)	−0.20 (−1.70, 1.30)	0.82 (−0.27, 2.00)	−0.13 (−2.30, 2.20)
0.49 (−0.38, 1.60)	0.46 (−1.40, 2.60)	**LED/Laser**	0.28 (−0.55, 1.20)	−0.05 (−1.50, 1.50)	1.10 (−0.10, 2.20)	0.12 (−2.10, 2.50)
−0.25 (−1.70, 0.83)	−0.38 (−2.40, 1.60)	−0.77 (−2.70, 0.64)	**LED**	−0.25 (−1.80, 1.30)	0.80 (−0.58, 2.10)	−0.18 (−2.40, 2.20)
--	--	--	--	**Metal halide light**	1.00 (−0.81, 2.80)	0.10 (−2.40, 2.80)
−0.25 (−1.60, 0.59)	−0.34 (−2.30, 1.40)	−0.75 (−2.50, 0.40)	0.08 (−1.50, 1.30)	--	**Laser**	0.91 (−1.40, 3.20)
−0.40 (−2.10, 0.89)	−0.56 (−2.70, 1.70)	−0.90 (−2.90, 0.60)	−0.15 (−1.70, 1.40)	--	−0.24 (−1.50, 1.40)	**PAC**

B

Light-free	--	1.20 (−1.90, 4.20)	--	−0.09 (−2.10, 2.20)	--	−1.90 (−4.60, 0.85)
--	**Halogen lamp**	--	--	−1.30 (−4.90, 2.60)	--	--
−0.13 (−3.4, 3.1)	--	**LED/Laser**	--	--	--	−3.10 (−7.00, 1.10)
--	--	--	**LED**	--	--	−1.80 (−5.50, 1.50)
1.3 (−0.78, 3.5)	--	1.5 (−2.5, 5.4)	--	**Metal halide light**	--	--
--	--	--	--	--	**Laser**	--
--	--	--	--	--	--	**PAC**

Figure 4.4-1. Flow diagram of study identification**.**

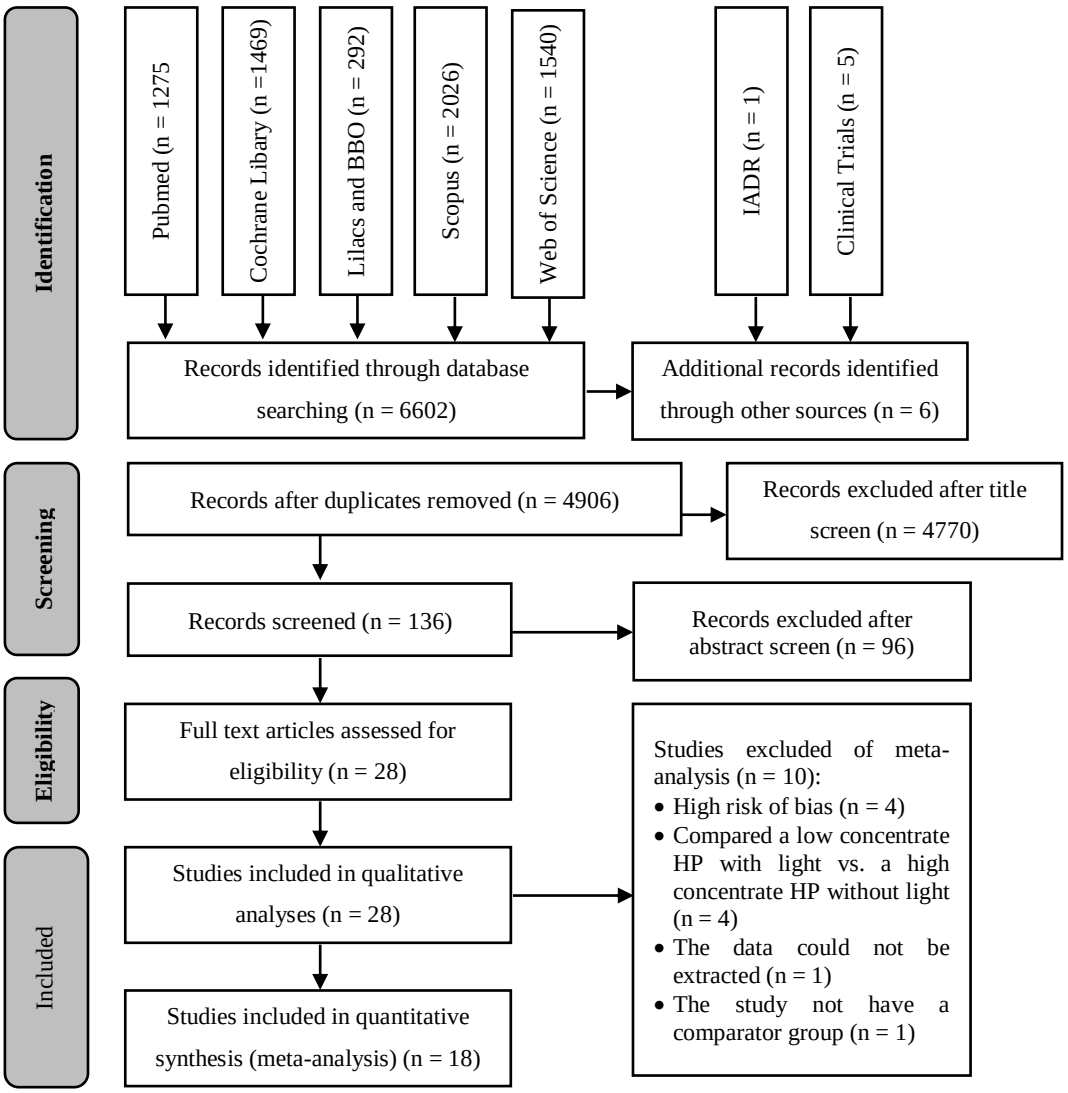


Figure 4.4-2. Summary of the risk of bias assessment, according to the Cochrane Collaboration tool.

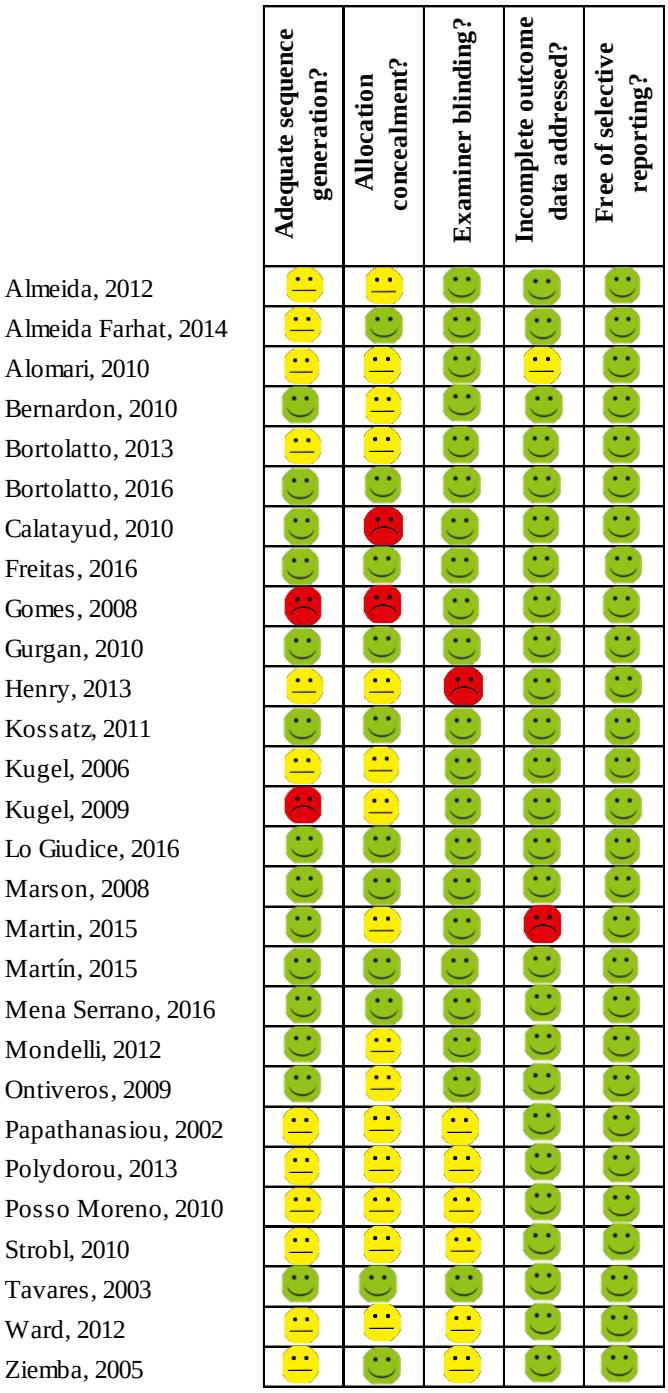


Figure 4.4-3. Mixed treatment comparison of eligible comparisons for the mixed-treatment comparison meta-analysis to color change (A) ΔE* for high-concentrate HP; (B) ΔSGU for high-concentrate HP; (C) ΔE* for low-concentrate HP; (D) ΔSGU for low-concentrate HP. (n = number of patients for the pairs).

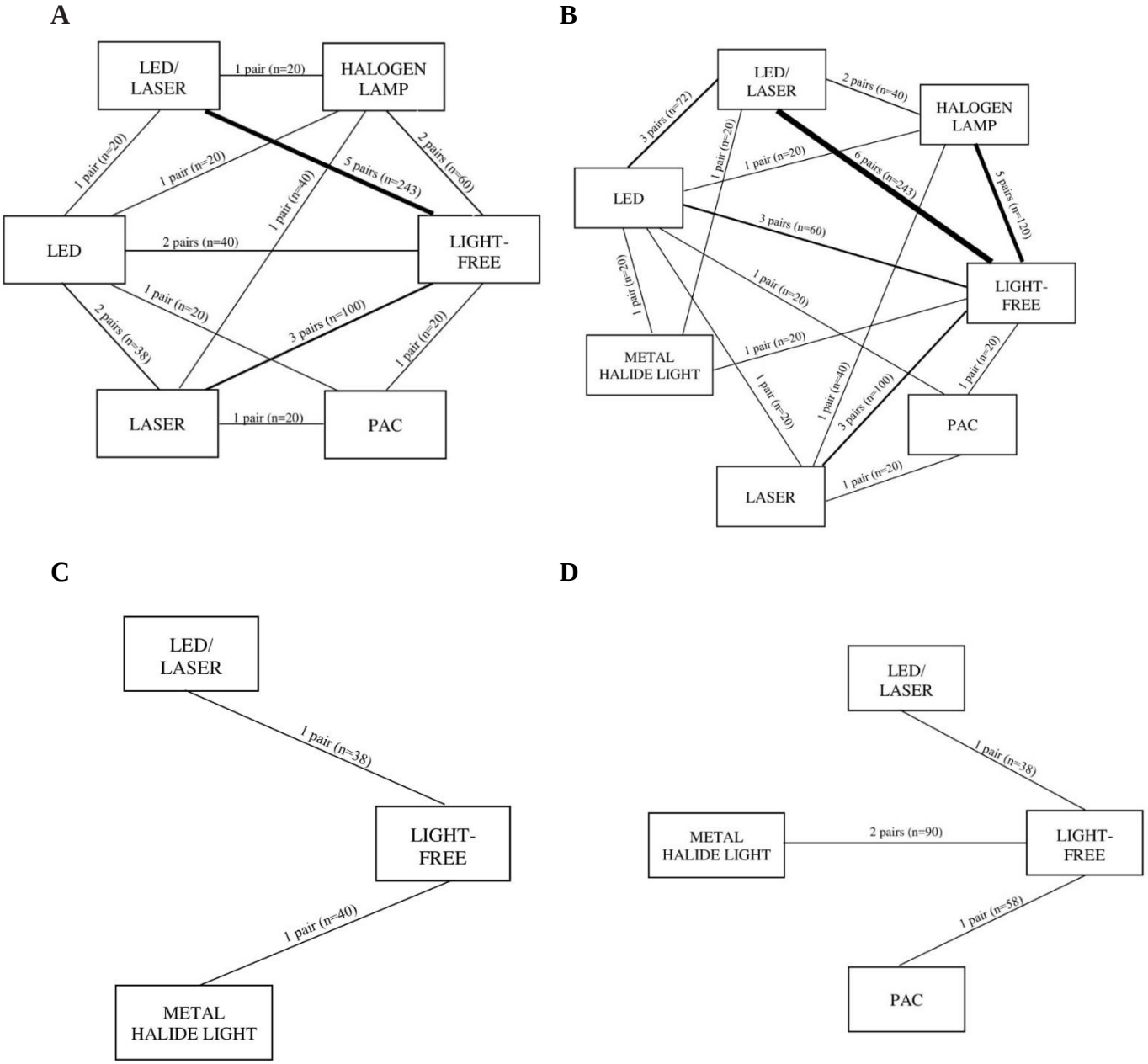


Figure 4.4-4. Forest plot of evaluation of the inconsistency assumption between direct and indirect evidence used in the mixed treatment comparison (MTC) meta-analysis to effect of color change in ΔE* for high-concentrate HP with different kind of light activation on the median of the mean difference (MD) ($p < 0.05$ indicates inconsistency of the pairs).

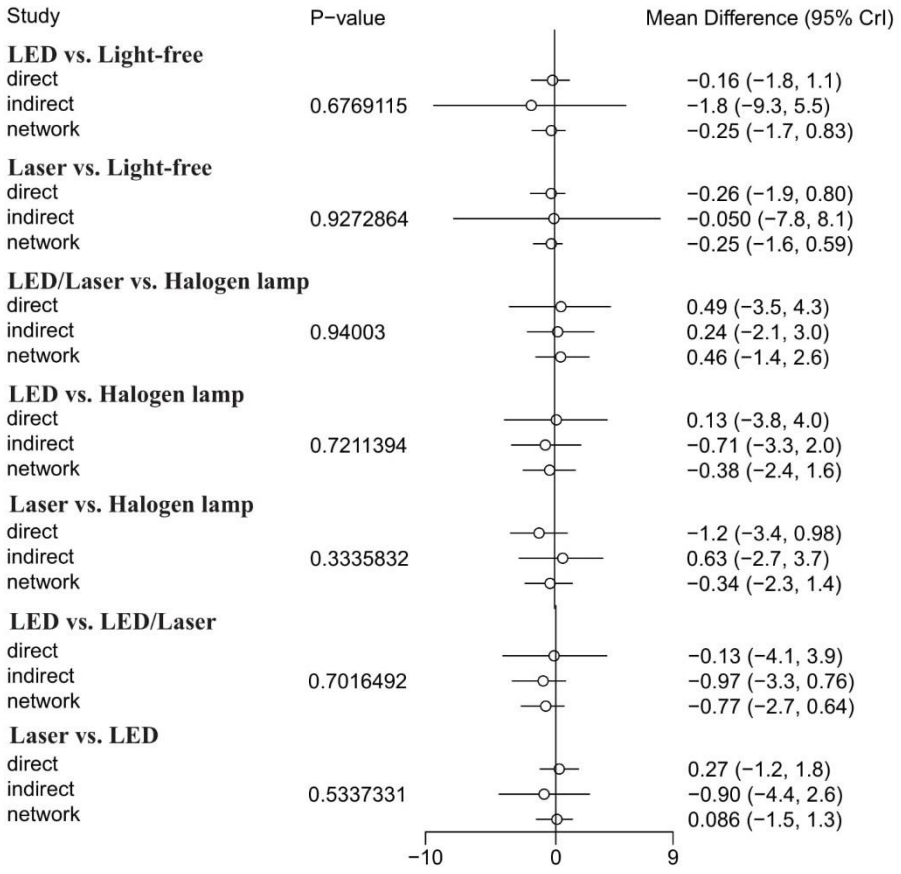
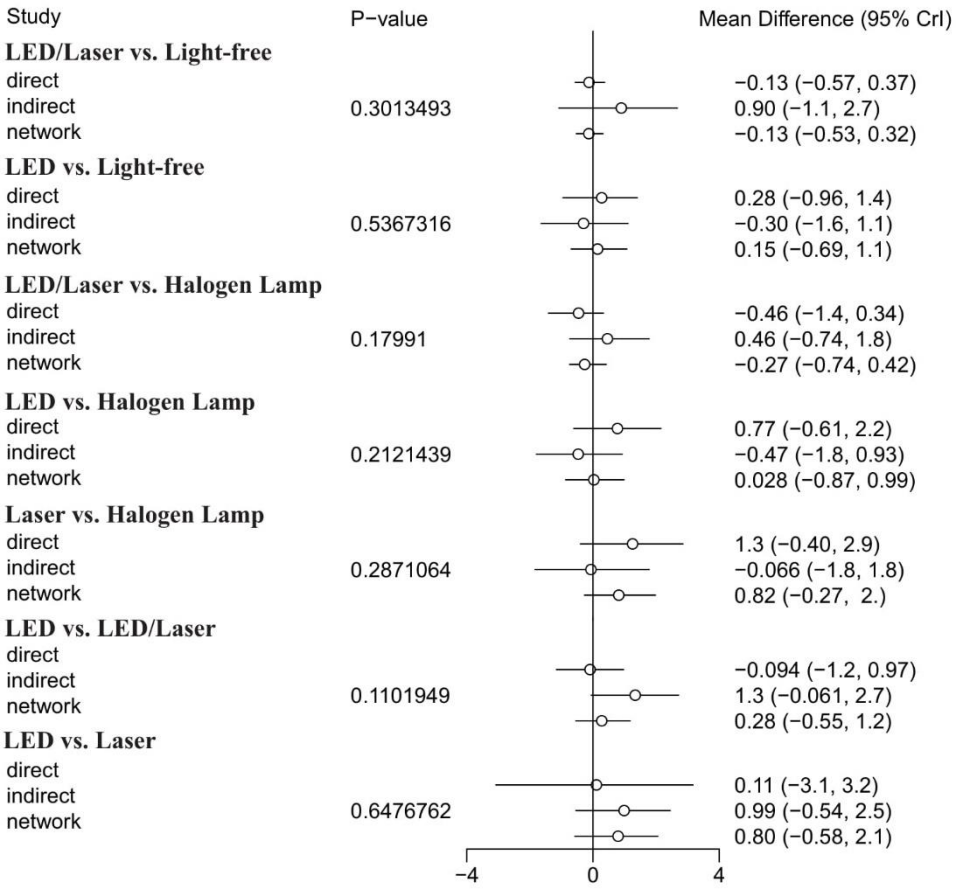


Figure 4.4-5. Forest plot of evaluation of the inconsistency assumption between direct and indirect evidence used in the mixed treatment comparison (MTC) meta-analysis to effect of color change in ΔSGU for high-concentrate HP with different kind of light activation on the median of the mean difference (MD) ($p < 0.05$ indicates inconsistency of the pairs).



REFERENCES

[1] M. Katarzyna, M.-S. Zofia, S. Tomasz, M. Barbara, P. Agnieszka, L. Jarosław, et al., Temperament and perception of tooth bleaching results, Family Medicine & Primary Care Review, (2016) 294-297.
[2] J. Martin, V. Rivas, P. Vildósola, L. Moncada, O.B. Oliveira Junior, J.R.C. Saad, et al., Personality style in patients looking for tooth bleaching and its correlation with treatment satisfaction, Braz Dent J, 27 (2016) 60-65.
[3] J.E. Dahl, U. Pallesen, Tooth bleaching - a critical review of the biological aspects, Critical Reviews in Oral Biology & Medicine, 14 (2003) 292-304.
[4] J.L. De Geus, L.M. Wambier, S. Kossatz, A.D. Loguercio, A. Reis, At-home vs in-office bleaching: A systematic review and meta-analysis, Oper Dent, 41 (2016) 341-356.
[5] L.C.A. Almeida, H. Riehl, P.H. Dos Santos, M.L.M.M. Sundfeld, A.L.F. Briso, Clinical evaluation of the effectiveness of different bleaching therapies in vital teeth, Int J Periodontics Restorative Dent, 32 (2012)
[6] P. Charakorn, L. Cabanilla, W. Wagner, W. Foong, J. Shaheen, R. Pregitzer, et al., The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching, Oper Dent, 34 (2009) 131-135.
[7] A. Gallagher, B. Maggio, J. Bowman, L. Borden, S. Mason, H. Felix, Clinical study to compare two in-office (chairside) whitening systems, J Clin Dent, 13 (2002) 219-224.
[8] L. Giachetti, F. Bertini, C. Bambi, M. Nieri, D.S. Russo, A randomized clinical trial comparing at-home and in-office tooth whitening techniques a nine-month follow-up, Journal of the American Dental Association, 141 (2010) 1357-1364.
[9] L.Y. Tay, C. Kose, D.R. Herrera, A. Reis, A.D. Loguercio, Long-term efficacy of in-office and at-home bleaching: A 2-year double-blind randomized clinical trial, Am J Dent, 25 (2012) 199-204.
[10] A. Joiner, The bleaching of teeth: A review of the literature, J Dent, 34 (2006) 412-419.
[11] S. Gurgan, F.Y. Cakir, E. Yazici, Different light-activated in-office bleaching systems: A clinical evaluation, Lasers Med Sci, 25 (2010) 817-822.
[12] M. Sulieman, E. Macdonald, J. Rees, M. Addy, Comparison of three in-office bleaching systems based on 35% hydrogen peroxide with different light activators, American Journal of Dentistry, 18 (2005) 194-197.
[13] M. Kashima-Tanaka, Y. Tsujimoto, K. Kawamoto, N. Senda, K. Ito, M. Yamazaki, Generation of free radicals and/or active oxygen by light or laser irradiation of hydrogen peroxide or sodium hypochlorite, J Endod, 29 (2003) 141-143.
[14] W. Buchalla, T. Attin, External bleaching therapy with activation by heat, light or laser - a systematic review, Dental Materials, 23 (2007) 586-596.
[15] P.B. De Almeida Farhat, F.A. Santos, J.C. Gomes, O.M. Gomes, Evaluation of the efficacy of led-laser treatment and control of tooth sensitivity during in-office bleaching procedures, Photomed Laser Surg, 32 (2014) 422-426.
[16] Q. Alomari, E. El Daraa, A randomized clinical trial of in-office dental bleaching with or without light activation, J Contemp Dent Pract, 11 (2010) E017-024.
[17] R.K. Henry, S.M. Bauchmoyer, W. Moore, R.G. Rashid, The effect of light on tooth whitening: A split-mouth design, Int J Dent Hyg, 11 (2013) 151-154.
[18] G. Kugel, A. Papathanasiou, A.J. Williams, C. Anderson, S. Ferreira, Clinical evaluation of chemical and light-activated tooth whitening systems, Compend Contin Educ Dent Suppl, 27 (2006) 54-62.
[19] M. Tavares, J. Stultz, M. Newman, V. Smith, R. Kent, E. Carpino, et al., Light augments tooth whitening with peroxide, J Am Dent Assoc, 134 (2003) 167-175.
[20] S.L. Posso Moreno, D.X. Ramírez Ramírez, J.A. Rosas Jaimes, E.H. Güiza Cristancho, Comparación del blanqueamiento dental con peróxido de hidrógeno al 25 percent en consultorio, utilizando o no activación con lámpara de luz halógena, Univ odontol, 29 (2010) 19-25.
[21] P.M. De Freitas, A.N. Menezes, A.C. Da Mota, A. Simoes, F.M. Mendes, A.D. Lago, et al., Does the hybrid light source (led/laser) influence temperature variation on the enamel surface during 35% hydrogen peroxide bleaching? A randomized clinical trial, Quintessence Int, 47 (2016) 61-73.
[22] J.F. Bortolatto, T.C. Trevisan, P.S.I. Bernardi, E. Fernandez, L.N. Dovigo, A.D. Loguercio, et al. A novel approach for in-office tooth bleaching with 6 % h<inf>2</inf>o<inf>2</inf>/tio_n and led/laser

system-a controlled, triple-blinded, randomized clinical trial. Lasers in medical science; 2016. p. 437-444.
[23] J.O. Calatayud, C.O. Calatayud, A.O. Zaccagnini, M. Box, Clinical efficacy of a bleaching system based on hydrogen peroxide with or without light activation, Eur J Esthet Dent, 5 (2010) 216-224.
[24] B.M. Maran, A. Burey, T. De Paris Matos, A.D. Loguercio, A. Reis, In-office dental bleaching with light vs. Without light: A systematic review and meta-analysis, J Dent, (2017)
[25] G. Lu, A. Ades, Combination of direct and indirect evidence in mixed treatment comparisons, Statistics in medicine, 23 (2004) 3105-3124.
[26] B. Hutton, G. Salanti, D.M. Caldwell, A. Chaimani, C.H. Schmid, C. Cameron, et al., The prisma extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanationsprisma extension for network meta-analysis, Annals of internal medicine, 162 (2015) 777-784.
[27] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ, 343 (2011) d5928.
[28] S. Dias, N. Welton, D. Caldwell, A. Ades, Checking consistency in mixed treatment comparison meta-analysis, Statistics in medicine, 29 (2010) 932-944.
[29] J.F. Bortolatto, H. Pretel, C.S. Neto, M.F. Andrade, G. Moncada, O.B.O. Junior, Effects of led–laser hybrid light on bleaching effectiveness and tooth sensitivity: A randomized clinical study, Laser Phys Lett, 10 (2013) 085601.
[30] S. Kossatz, A.P. Dalanhol, T. Cunha, A. Loguercio, A. Reis, Effect of light activation on tooth sensitivity after in-office bleaching, Oper Dent, 36 (2011) 251-257.
[31] G. Kugel, S. Ferreira, S. Sharma, M.L. Barker, R.W. Gerlach, Clinical trial assessing light enhancement of in-office tooth whitening: Masters of esthetic dentistry, Journal of Esthetic and Restorative Dentistry, 21 (2009) 336-347.
[32] R. Lo Giudice, G. Pantaleo, A. Lizio, U. Romeo, G. Castiello, G. Spagnuolo, et al., Clinical and spectrophotometric evaluation of led and laser activated teeth bleaching, Open Dentistry Journal, 10 (2016) 242-250.
[33] F.C. Marson, L.G. Sensi, L.C.C. Vieira, E. Araujo, Clinical evaluation of in-off ice dental bleaching treatments with and without the use of light-activation sources, Oper Dent, 33 (2008) 15-22.
[34] J. Martín, N. Ovies, P. Cisternas, E. Fernández, O.O. Junior, M. De Andrade, et al., Can an led-laser hybrid light help to decrease hydrogen peroxide concentration while maintaining effectiveness in teeth bleaching?, Laser Physics, 25 (2015) 025608.
[35] A. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, 41 (2016) 455-464.
[36] O. Polydorou, M. Wirsching, M. Wokewitz, P. Hahn. Three-month evaluation of vital tooth bleaching using light units-a randomized clinical study. Oper Dent; 2013. p. 21-32.
[37] S.L. Ziemba, H. Felix, J. Macdonald, M. Ward, Clinical evaluation of a novel dental whitening lamp and light-catalyzed peroxide gel, J Clin Dent, 16 (2005) 123-127.
[38] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[39] R.F.L. Mondelli, J.F.D.G. De Azevedo, A.C. Francisconi, C.M. De Almeida, S.K. Ishikiriama, Comparative clinical study of the effectiveness of different dental bleaching methods - two year follow-up, J Appl Oral Sci, 20 (2012) 435-443.
[40] J.C. Ontiveros, R.D. Paravina, Color change of vital teeth exposed to bleaching performed with and without supplementary light, J Dent, 37 (2009) 840-847.
[41] A. Strobl, N. Gutknecht, R. Franzen, R.D. Hilgers, F. Lampert, J. Meister, Laser-assisted in-office bleaching using a neodymium:Yttrium-aluminum-garnet laser: An in vivo study, Lasers Med Sci, 25 (2010) 503-509.
[42] A. Papathanasiou, S. Kastali, R.D. Perry, G. Kugel, Clinical evaluation of a 35% hydrogen peroxide in-office whitening system, Compend Contin Educ Dent Suppl, 23 (2002) 335-338.
[43] R.S. Gomes, F.B.D. Souza, C.M. Lacerda, C.F.F. Brambilla, R.C. Pascotto, Avaliação clínica da eficiência do uso do sistema led-laser, led e luz halógena na ativação do agente clareador em dentes vitalizados, Rev dental press estét, 5 (2008) 62-77.

[44] M. Ward, H. Felix. A clinical evaluation comparing two h2o2 concentrations used with a light-assisted chairside tooth whitening system. Compendium of continuing education in dentistry; 2012. p. 286-291.
[45] J. Martin, P. Vildosola, C. Bersezio, A. Herrera, J. Bortolatto, J.R. Saad, et al., Effectiveness of 6% hydrogen peroxide concentration for tooth bleaching-a double-blind, randomized clinical trial, J Dent, 43 (2015) 965-972.
[46] J.C. Ontiveros, In-office vital bleaching with adjunct light, Dent Clin North Am, 55 (2011) 241-253.
[47] L.B. He, M.Y. Shao, K. Tan, X. Xu, J.Y. Li, The effects of light on bleaching and tooth sensitivity during in-office vital bleaching: A systematic review and meta-analysis, J Dent, 40 (2012) 644-653.
[48] L. Sekine, V.D. Morais, K.M. Lima, T.G. Onsten, P.K. Ziegelmann, R.A. Ribeiro, Conventional and high-dose daunorubicin and idarubicin in acute myeloid leukaemia remission induction treatment: A mixed treatment comparison meta-analysis of 7258 patients, Hematol Oncol, 33 (2015) 212-219.
[49] J. Rheinheimer, P.K. Ziegelmann, R. Carlessi, L.R. Reck, A.C. Bauer, C.B. Leitao, et al., Different digestion enzymes used for human pancreatic islet isolation: A mixed treatment comparison (mtc) meta-analysis, Islets, 6 (2014) e977118.
[50] R.A. Ribeiro, P.K. Ziegelmann, B.B. Duncan, S.F. Stella, J.L. Da Costa Vieira, L.M.F. Restelatto, et al., Impact of statin dose on major cardiovascular events: A mixed treatment comparison meta-analysis involving more than 175,000 patients, International journal of cardiology, 166 (2013) 431-439.
[51] S. Bangalore, B. Toklu, N. Amoroso, M. Fusaro, S. Kumar, E.L. Hannan, et al., Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: Mixed treatment comparison meta-analysis, BMJ, 347 (2013) f6625.
[52] C.M. Faggion, Jr., L. Chambrone, S. Listl, Y.K. Tu, Network meta-analysis for evaluating interventions in implant dentistry: The case of peri-implantitis treatment, Clin Implant Dent Relat Res, 15 (2013) 576-588.
[53] C.W. Pires, D. Pedrotti, T.L. Lenzi, F.Z.M. Soares, P.K. Ziegelmann, R.O. Rocha, Is there a best conventional material for restoring posterior primary teeth? A network meta-analysis,
[54] S.J.a.-O.H.O.O. Pulikkotil, V.a.-O.H.O.O. Nagendrababu, S.K. Veettil, P. Jinatongthai, F.C.a.-O.H.O.O. Setzer, Effect of oral premedication on the anaesthetic efficacy of inferior alveolar nerve block in patients with irreversible pulpitis - a systematic review and network meta-analysis of randomized controlled trials. Lid - 10.1111/iej.12912 [doi],
[55] A. Joseph, R. Ayyagari, M. Xie, S. Cai, J. Xie, M. Huss, et al., Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: A mixed treatment comparison, Eur Child Adolesc Psychiatry, 26 (2017) 875-897.
[56] J.P. Jansen, B. Crawford, G. Bergman, W. Stam, Bayesian meta-analysis of multiple treatment comparisons: An introduction to mixed treatment comparisons, Value in Health, 11 (2008) 956-964.
[57] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[58] M. Rezende, F. Coppla, K. Chemin, A.C. Chibinski, A.D. Loguercio, A. Reis, Tooth sensitivity after dental bleaching with a desensitizing-containing and a desensitizing-free bleaching gel: A systematic review and meta-analysis, Oper Dent, (2018)
[59] J.L. De Geus, L.M. Wambier, T.F. Boing, A.D. Loguercio, A. Reis, At-home bleaching with 10% vs. More concentrated carbamide peroxide gels: A systematic review and meta-analysis., Oper Dent, (2018)
[60] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, et al., The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ, 343 (2011) d5928.
[61] P. Jüni, D.G. Altman, M. Egger, Assessing the quality of controlled clinical trials, BMJ, 323 (2001) 42-46.
[62] J. Higgins, J. Sterne, J. Savović, M. Page, A. Hróbjartsson, I. Boutron, et al. A revised tool for assessing risk of bias in randomized trials. Cochrane Methods Cochrane Database of Systematic Reviews. Chandler J, McKenzie J, Boutron I, Welch V ed; 2016.

Artigo 5

TÍTULO: ARE COMBINED BLEACHING TECHNIQUES BETTER THAN AT-HOME OR IN-OFFICE BLEACHING? A SYSTEMATIC REVIEW AND META-ANALYSIS

STATUS: PROCESSO SUBMISSÃO

REVISTA: ---

4.5 ARTIGO 5 – ARE COMBINED BLEACHING TECHNIQUES BETTER THAN AT-HOME OR IN-OFFICE BLEACHING? A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: A systematic review and meta-analysis were performed to answer the following focused question: "Does combined in-office and at-home bleaching produce improved color change and lower tooth sensitivity than the sole use of at-home (AH) or in-office bleaching (IO) techniques in adults?".

Methods: Search was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library and SIGLE, without restrictions in Augustu 28, 2017 (updated on April 25, 2018). IADR abstracts (1990–2018), unpublished and ongoing trials registries, dissertations and theses were also searched. Only randomized clinical trials in adults that compared combined vs sole AH or sole IO bleaching were included. The risk of bias (RoB) was evaluated used Cochrane Collaboration tool. Meta-analysis were conducted for color change (ΔE*, ΔSGU), risk and intensity of TS, using random effects model. Heterogeneity was assessed with Cochran Q test and I^2 statistics. GRADE assessed the quality of the evidence.

Results: After removal of duplicates, title and abstract screening, 11 studies remained. Only one was considered to be at low RoB; the remaining were at an unclear RoB. For combined vs. IO bleaching no significant difference was observed for ΔE* and ΔSGU. Data were not available to meta-analysis the risk and intensity of TS for this comparison. For combined vs. AH bleaching no significant difference was observed for ΔE*, ΔSGU and risk of TS, but lower TS intensity was detected for the AH bleaching (SMD 0.86 95% CI 0.31 to 1.41). Quality of evidence was moderate for color change in ΔE*, and low and very low for the other outcomes due to unclear RoB, the inconsistency and imprecision of the estimates.

Conclusion: Lower intensity of TS was observed for the sole AH group without jeopardizing color change. However, more studies are still encouraged due to the low quality of evidence for most of the outcomes. PROSPERO CRD42016036555.

Keywords: Tooth Bleaching. Tooth discoloration. Tooth sensitivity. Systematic review. Meta-analysis.

Clinical Relevance: If clinicians are to choose between combined bleaching and sole AH bleaching, the latter may be preferable as combined bleaching may potentiate the risk of TS without any additional benefit in terms of color change. For the comparison between combined bleaching and the sole IO bleaching, no difference in color change was detected; however, there was TS could not be compared due to lack of data and further studies should be conducted to allow clinical recommendations.

INTRODUCTION

Dental bleaching is the most popular cosmetic procedures because it is a conservative method for treating dental discoloration [1,2] and it meets the needs of an increasing number of patients that requests treatment for esthetic discoloration [3-5]. Furthermore, dental bleaching is technically easier and lower-cost when compared to any other type of cosmetic treatment, as for instance, veneers.

Dentist-supervised dental bleaching can be performed in-office by the dentist using high concentrate hydrogen peroxide (HP) or it can be done at-home, by the patient, using low concentrate carbamide peroxide (CP) or low concentrate HP [6]. Although at-home bleaching is frequently used, some patients do not adapt to the daily use of a tray for several weeks; so they request a tray-free and faster bleaching option [7,8]. In-office bleaching is a good alternative for such patients. It can performed in one to four clinical appointments with applications lasting from 15 to 60 min [9-11]. This technique, however, has the disadvantage of producing a higher intensity of tooth sensitivity (TS) during and after bleaching due to the inflammatory reaction produced by HP and free radicals when they achieve the dental pulp [12-15].

A common clinical practice is to combine both at-home and in-office bleaching techniques [16-18] to obtain faster bleaching effect [18], improved color stability [17,19] and reduced levels of TS. Within this context, a single in-office bleaching session is usually performed firstly to provide an initial “jump-start” bleaching effect [20,21]. Then, the patient continues the protocol at-home with a custom-made bleaching tray using low concentrate products until the desired shade is obtained [17,18,22].

Some randomized clinical trials (RCTs) have already compared combined bleaching technique with the sole use of at-home or in-office protocols [17,20,23,24]; however conflicting results in terms of risk and intensity of tooth sensitivity [25] and color change and stability [17,18,20,22] have been reported.

Perhaps such differences are attributed to differences in protocols and deserves a deeper systematic revision to reach more reliable conclusions and allow for clinical recommendations. Therefore, the aim of the present systematic review of the literature was to evaluate if there are evidence-based differences in color change, risk and intensity of tooth sensitivity of combined bleaching versus the sole use of at-home or in-office bleaching protocols. To this end, we aimed to answer the following focused question based on the PICO strategy (P - participant, I - intervention, C - comparator and O - outcome): Does combined in-office and at-home bleaching

produce improved color change and lower tooth sensitivity than the sole use of at-home or in-office bleaching techniques in adults?

MATERIALS AND METHODS

Protocol and Registration

This systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42016036555. The present study was reported following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [26].

Information Sources and Search Strategy

The search strategy was firstly defined for the database MEDLINE via PubMed based using controlled vocabulary (MeSH terms) and free keywords for each concept of the PICO question described at the end of the introduction section. The outcomes to be evaluated was color change in units of ΔE* (CIEL*a*b* system) [27] and in shade guide units (ΔSGU), as well as the risk and intensity of TS.

The MEDLINE search strategy was adapted to other electronic databases (Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature database (LILACS) and citation databases (Scopus, and Web of Science) (Table 4.5-1). Additionally, grey literature was investigated by searching the abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (1990-2018), the database System for Information on Grey Literature in Europe and dissertations and theses using the ProQuest Dissertations and Theses full-text database as well as the Periódicos Capes Theses database.

Ongoing studies were searched in the following clinical trial registries: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (http://www.clinicaltrials.gov), ReBEC (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). Additionally, we hand-searched the reference lists of all primary and eligible studies of this systematic review for additional relevant publications. The two first pages of the related articles link of each primary study in the PubMed database was also searched. In the whole search process, we did not restrict studies based on publication date and/or language.

Eligibility Criteria

We included parallel and split-mouth randomized clinical trials (RCTs) conducted in adult patients of any age group that answered the PICO question described in the end of the

introduction section. RCTs were excluded if the studies compared only different combined bleaching treatments.

Study Selection and Data Collection Process

The articles retrieved by the literature search were revised in three phases. All studies were initially scanned for relevance by title, and the abstracts of those that were not excluded at this stage were appraised. The next step included the abstract reading and the studies that could not be excluded according to our eligibility criteria in the abstract review had their full text retrieved for further evaluation. The full-texts were then read by three reviewers to check if they met the inclusion criteria. Finally, the eligible articles received a study identification (ID), combining first author and year of publication.

Two reviewers independently abstracted data from included articles, such as study design, participants, interventions, and outcomes. In cases of disagreement, a decision was reached by consulting a third reviewer. If there were multiple reports of the same study (i.e., reports with different follow-ups), data from all reports were extracted directly into a single data-collection form to avoid overlapping data.

We collected data from color change after the end of the bleaching treatment with periods ranging from one week to two weeks post-bleaching. This variation was due to the differences in the assessment period reported in the studies. When more than one post-bleaching period was reported in the same period, we opted to collected the data close to 1-week post-bleaching period. Regarding TS, the worst mean value of TS reported for the group was collected.

Risk of Bias in Individual Studies

Quality assessments of the selected trials were carried out by three independent reviewers using the Cochrane Collaboration tool for assessing the risk of bias in RCTs [28]. The assessment criteria contain six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Disagreements between the reviewers were solved through discussion, and if needed, by consulting a fourth reviewer (A.R.).

For each aspect of the quality assessment, the risk of bias was scored following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.02 (http://handbook.cochrane.org). Each domain level was judged as having low, high, or unclear risk of bias. At the study level, the study was at low risk of bias if all key domains (see below) for each outcome were at low risk of bias. If one or more key domains were judged as having

unclear risk, the study was at unclear risk, and if at least one key domain was considered at high risk of bias, the study was considered at high risk of bias.

For the patient-centered outcomes such as the risk and intensity of TS, the key domains were adequate sequence generation and allocation concealment. Patient blinding was not considered a key domain as patients could easily identify the different bleaching protocols. For color change in ΔSGU, three items of the Cochrane tool were considered key domains: adequate sequence generation, allocation concealment, and examiner blinding. However, for ΔE*, examiner blinding was not considered a key domain, because the previous knowledge of the treatment would not affect the results produced by an objective tool for color assessment such as spectrophotometers or colorimeters.

Summary Measures and Synthesis of Results

Data were analyzed using Revman 5.3 (Review Manager Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis were performed in studies classified as at low or at unclear risk of bias. Studies judged to be at high risk of bias were not included in the meta-analysis. Data from eligible studies were summarized by calculating the risk ratio (risk of TS) and the standardized mean difference (intensity of TS and ΔE*). For the ΔSGU, mean difference was calculated when studies used the same shade guide or we used the standardized mean difference when at least one study used a different shade guide tool.

For all meta-analysis, we used the random-effects models. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. Sensitivity analysis were also conducted to investigate the reasons for high heterogeneity, whenever detected. We performed individual meta-analysis for studies that compared combined bleaching vs. in-office bleaching and those that compared combined bleaching vs. at-home bleaching as both type of comparisons was identified in the systematic review.

Assessment of the quality of the evidence using GRADE

We graded the quality of the evidence for each outcome across the studies (body of evidence) by using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) to determine the overall strength of the evidence for each meta-analysis[29]. The GRADE pro Guideline Development Tool (available online at www.gradepro.org) was used to create a summary-of-findings table, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions 5.2.0 (http://handbook.cochrane.org).

The GRADE approach for RCTs addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) to possibly downgrade the quality of the evidence (1 or 2 levels). Each of these topics was assessed as having "no limitations", "serious limitations," or "very serious limitations" to categorize the quality of the evidence into high, moderate, low, and very low.

RESULTS

Study Selection

The search strategy was conducted initially on 28th August 2017 and was updated on 25th April 2018. After database screening and duplicate removal, 624 studies were identified (Figure 4.5-1). After title screening, 304 studies remained, and this number was reduced to 11 after careful examination of the abstracts.

Characteristics of Included Articles

Eight studies have already been published [10,11,16,18,21,30-32], two studies were abstracts of the IADR [33,34] and one study was in a thesis format, which had not been submitted to publication yet [35].

Study design

The characteristics of the eleven eligible studies are listed in Table 4.5-2. Eight studies used the parallel design [10,11,16,30,31,33-35], and three studies used the split-mouth design [18,21,32] (Table 4.5-2).

Color evaluation criteria

Eight studies used the Vita Classical Shade guide (Vita Zahnfabrik, BadSäckingen, Germany) [10,11,16,18,21,31,32,35] and two studies used the Vita Bleached guide 3D-Mastershade guide (Vita Zahnfabrik, Bad Säckingen, Germany) [33,35]. Six studies used an objective instrument for color assessment (spectrophotometer or colorimeter) [10,18,21,32,34,35]. Photography was used in four studies [18,21,31,33]. One study did not evaluated color change [30] (Table 4.5-2).

TS evaluation criteria

The intensity of TS was evaluated using VAS [16,18,21,32,35]. This outcome was not evaluated in four studies [30,31,33,34]. Three studies evaluated the risk of TS (Table 4.5-2).

Number of participants in the primary RCTs and gender

The number of patients per group ranged from 18 to 78 years of age. The mean age of all participants that reported this information was approximately 30.9 years (Table 4.5-2). In the studies that reported the gender of the sample, females were more prevalent [10,18,32,35].

Bleaching protocols

Three studies evaluated combined bleaching (in-office plus at-home bleaching) vs. sole in-office bleaching, [11,18,31] while four studies evaluated combined bleaching (in-office plus at-home bleaching) vs. sole at-home bleaching [10,16,32,35]. Four studies included both comparisons [21,30,33,34]. For this reason, individual meta-analysis for each one of these comparisons were performed as it would not be reasonable to merge these data.

Sole in-office bleaching. The product employed was high concentrate hydrogen peroxide (35% or 37%). In each clinical session, the product remained in contact with the dental structure from 15 to 60 minutes and, in total, one to four clinical appointments were performed with a time interval of6to 15 days. (Table 4.5-2).

Sole at-home bleaching. Carbamide peroxide (10% or 16%) or hydrogen peroxide (4% HP) were employed. The bleaching trays were used from 7 to 21 days with a daily use that varied from1 h to 8h (Table 4.5-2).

Combined bleaching. For in-office bleaching, the HP concentration varied from 9% to 38%. In each clinical session, the product remained in contact with the dental structure from 15 to 60 minutes. In some studies, the bleaching product was applied only once at the beginning of the treatment, while in others, more than one in-office bleaching was applied with at-home session in-between. For the at-home bleaching, CP (10% or 16%) or HP (4% or 6%) was used in bleaching trays for 5 to 28 days with daily use of 1 to 8h (Table 4.5-2).

Assessment of the Risk of Bias

The risk of bias of the eligible studies is presented in Figure 4.5-2. Few full-text studies reported the method of randomization, allocation concealment, and whether or not the examiner was blinded during color assessment in shade guide units (SGU). In summary, from the 11 studies, only one was considered to be at low risk of bias [35] and the remaining were considered to be at an unclear risk of bias.

Meta-analysis

Meta-analysis were performed on all studies from which information about the outcome was reported and could be extracted (Figure 4.5-1). One study [30] was not included in the meta-analysis because the main objective of the study was to evaluate the buccal microbiota after bleaching and therefore the outcomes of color change and TS were not reported.

Three studies did not report the standard deviation (SD) of TS intensity [21,32,36] and one study did not report the SD of color change in ΔE* and ΔSGU outcomes [32]. When more than half of the included studies in the meta-analysis reported the SD, the missing data of the

other studies with missing information was imputed based on the average of the coefficient of variance of the remaining articles.

*Color Change in ΔE**

Combined vs. in-office bleaching. Three studies were included in this meta-analysis [18,21,34]. The overall standardized mean difference (SMD) was 1.76 [95% CI -0.48 to 4.00] with no significant difference between groups (p = 0.12). Data were heterogeneous (p <0.00001; I^2 = 97%) (Figure 4.5-3A).The Wetter's 2009 study [10] was not included in this meta-analysis because they did not report color change in ΔE*,but as change in chroma.

Combined vs. at-home bleaching. Four studies were included in this meta-analysis [21,32,34,35]. The overall standardized mean difference (SMD) was 0.09 [95% CI -0.18 to 0.37] with no significant difference between groups (p = 0.50). Data was not heterogeneous (p = 0.35; I^2 = 8%) (Figure 4.5-3B). Imputation of the SD was done in the Machado's 2016 study [32].

Color Change in ΔSGU

Combined vs. in-office bleaching. Four studies were included in this meta-analysis [11,18,21,31]. The overall mean difference (MD) was 1.27 [95% CI -1.05 to 3.59] and no significant difference was observed between groups (p = 0.28). Data were heterogeneous (p <0.00001; I^2 = 99%) (Figure 4.5-4A).

Combined vs. at-home bleaching. Five studies were included in this meta-analysis [16,21,32,33,35]. The standardized mean difference (SMD) was -0.18 [95% CI -0.54 to 0.18] and it was not statistically different (p = 0.32). We detected heterogeneity of the data (p = 0.13; I^2 = 44%) (Figure 4.5-4B). Imputation of the SD was done for the Machado's 2016 study [32].

Risk of Tooth Sensitivity

Combined vs. in-office bleaching. Studies that performed this comparison did not report the risk of tooth sensitivity.

Combined vs. at-home bleaching. Only two studies were included in this meta-analysis [10,35]. The risk ratio was 1.36 [95% CI 0.84 to 2.19], showing no significant differences between the groups (p = 0.21). We did not detect heterogeneity of the data (p = 0.68; I^2 = 0%) (Figure 4.5-5).

Intensity of Tooth Sensitivity

Combined vs. in-office bleaching. Only two studies could be included in this meta-analysis [18,21]; however both did not report the standard deviation of the TS intensity and therefore, this meta-analysis was not run.

Combined vs. at-home bleaching. Four studies were included in this meta-analysis [16,21,32,35]. The overall standardized mean difference (SMD) was 0.86 [95% CI 0.31 to 1.41] and it was significant different ($p = 0.002$). We detected high heterogeneity of the data ($p < 0.01$; $I^2 = 73\%$) (Figure 4.5-6). Imputation of the SD was performed in the study of Bernardon's 2010 [21] and Machado's 2016 [32].

Sensitivity analysis

In studies that did not report the SD, we have imputed a SD that was based on the average of the coefficient of variation of the other studies that reported the same finding [37]. More extreme imputations (such as a value that corresponded to the lowest coefficient of variation of the primary studies and a value that was as high as the reported mean) was evaluated and no differences in the results herein reported could be detected.

Combined vs. in-office bleaching. The heterogeneity observed in the data; from ΔE* was caused by the Matis' 2009 study [18] and from ΔSGU were caused by the Kugel's 1997 and Matis' 2009 studies.

Combined vs. at-home bleaching. The heterogeneity observed in data from ΔSGU was caused by the Vochikovski's 2018 study [35] and from intensity of TS was caused by the Dawson's 2011 study [38].

Assessment of the Quality of Evidence

The body of evidence produced by color change in ΔE* of combined vs. at-home bleaching was graded as moderate. The other outcomes were graded as low or very low, due to the unclear risk of bias in most RCTs, the inconsistency of the data and the imprecision of the summary estimate (Table 4.5-3).

DISCUSSION

Systematic reviews and meta-analysis are important in resolving the problem of controversies between clinical trials. Additionally, systematic reviews and meta-analysis can provide a critical evaluation of the body of evidence and summarize it for development of recommendations for clinical implementation [39].

The search strategy of any systematic usually have high sensitivity (number of relevant reports divided by the total number of existing reports). In a search with high sensitivity, the accuracy of the search (number of relevant documents divided by the total number or articles retrieved) is reduced, explaining why we obtain a huge number of retrieved articles end up with only a few articles on the subject of research [39,40].

Among the factors that affect the risk of bias of the primary studies, correct randomization is essential in a RCT. It ensures that the chances of a patient being allocated in the test or control group are the same for all participants, which means that known and unknown prognostic factors are balanced among groups [28]. However, the random sequence should be protected until implementation [28] in a process called as allocation concealment. Most of the eligible studies from this systematic review were classified as at unclear risk of bias. This judgement was based on the lack of clear description of the randomization and allocation concealment process. This is accordance to what was recently published by Loguercio et al.2017 [41], who reported that more than 50% of RCT about bleaching had a high or unclear risk of bias for randomization and allocation concealment. Unfortunately, effect sizes from studies with inappropriate random sequence and/or allocation concealment favor the experimental group [42], producing biased conclusions.

The combined bleaching technique was suggested to potentiate the bleaching effect and improve the color stability [17]. However, in none of the two comparisons performed in this study (combined bleaching vs. sole in-office bleaching and combined bleaching vs. sole at-home bleaching), a higher degree of color change was observed in one to two weeks after the end of the bleaching protocol. This belief is probably the result of earlier studies that used to compare a single in-office bleaching vs. a 2- or 3-week at-home protocol [36,43-46]. A single in-office bleaching session is usually not enough to achieve the same degree of whitening that an extended at-home bleaching protocol.

This probably explains the high heterogeneity of the meta-analysis of ΔE* for combined bleaching vs. in-office bleaching. In this meta-analysis, the study of Matis et al. 2009 [36] compared one in-office bleaching session vs. a combined bleaching that consisted of a one in-office bleaching session plus one-week of at-home protocol. In such study, a high effect size was observed in favor of the combined bleaching; a finding not observed in the other studies that performed two [21] or three [34] in-office bleaching sessions.

In a similar trend, the color change in ΔSGU for the same comparison (combined vs. in-office bleaching) resulted in a high heterogeneity. Again the study of Matis et al., 2009 [36] performed just a single in-office bleaching while Kugel et al., 1997 [31] left the gel in contact with the dental structure for a very short period of only 15 minutes in two clinical sessions. A previous RCT reported that a single 15-min application per session, even when applied in two clinical sessions, does not allow the same color change than two or three 15-min applications per clinical appointment [47] as it yields a lower whitening degree after two bleaching sessions.

For the other comparison (combined vs at-home bleaching), no difference in color change in in ΔE* was observed. The at-home protocol of all studies included in this meta-analysis consisted of a 14-day or 21-day regimen and the combined bleaching consisted of a single 30-min or 45-min application plus a 14-day or 21-day regimen of at-home bleaching. As shown by Kihn et al., 2000 [48] the difference of color change is not noticeable until the full two-week regimen was completed. Thus, a 14-day or 21-day regimen should be accomplished for an effective tooth bleaching with the at-home protocol without the need of an in-office bleaching session [49-51]. Additionally, it is important to emphasis that in this analysis we did not detect heterogeneity and the quality of evidence was graded as moderate.

In regard to color change in ΔSGU for this comparison (combined vs. at-home bleaching), heterogeneity was observed as differently to the other primary studies in this comparison, Vochikovski 2018 reported higher whitening efficacy for the combined bleaching group. This was the single study that used a low HP concentration (4%) compared to other studies that used 10% to 16% carbamide peroxide. An earlier systematic review of the literature that compared at-home bleaching with carbamide peroxide or low concentrate HP showed that bleaching with carbamide peroxide yields to higher bleaching efficacy in terms of color change [52]. While both carbamide peroxide and HP are used for whitening, their properties are quite different, and this may play a role on the difference herein observed. HP-based products are very unstable and release all of its active hydrogen peroxide in 30 to 60 min [53,54] while HP-release from carbamide peroxide gels is slower than in HP-based products with a release of about 50 % in the first 2 to 4 h, then the remainder over the next 2 to 6 h [53,55].

The other outcome evaluated in this study was tooth sensitivity, considered a side effect commonly reported after vital tooth bleaching [7,56]. TS probably arises from the diffusion of HP into the dental structure until pulp chamber. In the pulp, HP induces the release of cell-derived factors such as adenosine triphosphate (ATP) and prostaglandins, which can excite or sensitize nociceptors [57,58].

One of the factors that affect the intensity of TS is the concentration of the bleaching agent. In-office bleaching were associated with a high intensity of TS than at-home bleaching [59]. This is the reason of why we observed a high intensity of TS for the combined bleaching in the comparison combined vs. at-home bleaching. This was expected, due to the use of bleaching agents in concentrations much higher in the combined bleaching than that used in the sole at-home protocol [60-62].

The meta-analysis described above was heterogeneous probably due to the study of Dawson et al., 2011. Differently from the other studies, these authors combined the at-home protocol with a low concentrate HP concentrate (9% and 27%) and therefore they did not detect significant differences between combined and at-home protocols. Additionally, this was the single study that performed at-home bleaching before the in-office protocol. Perhaps such approach prepared the pulp tissue with the presence/or even faster release of catalases to decompose hydrogen peroxide into water and oxygen.

In the present study, the risk of TS, that is, the percentage of patients who reported pain at some point during dental bleaching was not different in the comparison combined vs. at-home bleaching. Indeed, this was observed in an earlier study that merged the results of several RCTs about at-home and in-office bleaching [59]. Unfortunately, we could not compare the TS risk and intensity of combined bleaching vs. sole in-office bleaching due to the lack of data availability. This should encourage further studies for this comparison.

Some decisions had to be made during data collection and deserves some discussion. The choice to collect the worst TS mean value presented in the study was to produce a fair comparison between the protocols. As TS is lower in the at-home bleaching, if we collected data were collected only at the end of each treatment (after in-office, or after at-home bleaching or after combined bleaching), the TS of the combined group would be similar to the at-home protocol, as at-home protocol was usually performed after the in-office jump start. Apart from that, the peak of pain varies among techniques. For in-office bleaching it was reported to start within one hour after the beginning of the treatment, with a pain peak within one and six hours post-treatment[63]. For at-home bleaching, most patients usually report TS on the first days of gel application and tend to disappear after four days for most patients [64]

Finally, the limitations of this study should be reported. As few studies remained in this systematic review, more randomized clinical trials with low risk of bias should be conducted to compare both techniques and allow for a more comprehensive evaluation of protocols. Additionally, these results should be interpreted with caution as it represents an overall comparison without taking into consideration variations in the protocols (daily usage time, number of bleaching sessions, product concentration and days of home-use) of the bleaching techniques.

CONCLUSIONS

When compared to at-home bleaching, the combined technique produced a higher intensity of TS without any additional benefit in terms of color change. When compared to in-

office bleaching, combined bleaching yielded similar color change, but we still lack information about TS between these two bleaching approaches. A moderate quality of evidence was only observed in the outcome color change in ΔE* for the combination combined vs. at home bleaching; all others were graded as low or very low, which emphases the need for well-conducted RCTs on this issue.

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Table 4.5-1. Electronic database and search strategyconducted initially in 28 August 2017 and was updated in 25 April 2018.

Pubmed		
#1 ((((((((((((((((((toothdiscoloration[MeSHTerms]) OR dentition, permanent[MeSHTerms]) OR color[MeSHTerms]) OR "toothdiscoloration"[Title/Abstract]) OR "toothdiscolouration"[Title/Abstract]) OR "teethdiscoloration"[Title/Abstract]) OR "teethdiscolouration"[Title/Abstract]) OR "permanentdention"[Title/Abstract]) OR color[Title/Abstract]) OR colour[Title/Abstract]) OR "discoloredtooth"[Title/Abstract]) OR "discolouredtooth"[Title/Abstract]) OR "discoloredteeth"[Title/Abstract]) OR "discolouredteeth"[Title/Abstract]) OR "dental discoloration"[Title/Abstract]) OR "dental discolouration"[Title/Abstract]) OR "toothstaining"[Title/Abstract]) OR "teethstaining"[Title/Abstract]) OR "stainedtooth"[Title/Abstract]) OR "stainedteeth"[Title/Abstract]) OR "dental staining"[Title/Abstract])	#2((((((((((((((((toothbleaching[MeSHTerms]) OR toothbleachingagents[MeSHTerms]) OR peroxides[MeSHTerms]) OR hydrogen peroxide[MeSHTerms]) OR carbamide peroxide[SupplementaryConcept]) OR dental offices[MeSHTerms]) OR bleaching[Title/Abstract]) OR whitening[Title/Abstract]) OR peroxides[Title/Abstract]) OR "hydrogen peroxide"[Title/Abstract]) OR "carbamide peroxide"[Title/Abstract]) OR "dental offices"[Title/Abstract]) OR "dental office"[Title/Abstract]) OR "in-office"[Title/Abstract]) OR "at-home"[Title/Abstract]) OR "home-use"[Title/Abstract]) OR "home-care"[Title/Abstract]) OR "jump-start"[Title/Abstract]	#7 (randomizedcontrolledtrial[pt] OR controlledclinicaltrial[pt] OR randomizedcontrolledtrials[mh] OR randomallocation[mh] OR double-blindmethod[mh] OR single-blindmethod[mh] OR clinicaltrial[pt] OR clinicaltrials[mh] OR ("clinicaltrial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparativestudy[pt] OR evaluationstudies as topic[mh] OR follow-up studies[mh] OR prospectivestudies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])
#1 AND #2 AND 3		
Cochrane		
#1 MeSHdescriptor: [ToothDiscoloration] explode alltrees #2 MeSHdescriptor: [Dentition, Permanent] explode alltrees #3 MeSHdescriptor: [Color] explode alltrees #4 t*thnextdiscoloration:ti,ab,kwor t*thnextstaining:ti,ab,kworstainednext t*th:ti,ab,kwordiscolorednext t*th:ti,ab,kw (Word variationshavebeensearched) #5 “permanentdention”:ti,ab,kwor dental nextstaining:ti,ab,kworcolor:ti,ab,kwor dental nextdiscoloration:ti,ab,kw (Word variationshavebeensearched) #6 #1 or #2 or #3 or #4 or #5		#7 MeSHdescriptor: [ToothBleaching] explode alltres #8 MeSHdescriptor: [ToothBleachingAgents] explode alltrees #9 MeSHdescriptor: [Peroxides] explode alltrees #10 MeSHdescriptor: [Hydrogen Peroxide] explode alltrees #11 MeSHdescriptor: [Dental Offices] explode alltree #12 “carbamide peroxide":ti,ab,kworbleaching:ti,ab,kworwhitening:ti,ab,kworperoxides:ti,ab,kwor "hydrogen peroxide":ti,ab,kw (Word variationshavebeensearched) #13 "dental office":ti,ab,kwor "in office":ti,ab,kwor "at home":ti,ab,kwor "home use":ti,ab,kwor "home care":ti,ab,kw (Word variationshavebeensearched) #14 "jump start":ti,ab,kwor "dental offices":ti,ab,kw (Word variationshavebeensearched) #15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#6 AND #15		
Lilacs/BBO		
(MH:"toothdiscoloration" OR MH:"permanentdentition" OR MH:color OR "toothdiscoloration" OR "permanentdentition" OR "color" OR "toothdiscolouration" OR "teethdiscoloration" OR "teethdiscolouration" OR color OR colour OR "discoloredtooth" OR "discolouredtooth" OR "discoloredteeth" OR "discolouredteeth" OR "dental discoloration" OR	(MH:"toothbleaching"OR MH:"toothbleachingagents" ORMH:peroxides OR MH:"hydrogenperoxide"OR "carbamide peroxide" OR MH:"dental offices" OR bleachingORwhiteningORperoxidesOR "hydrogenperoxide"OR "carbamideperoxide"OR "dental offices"OR "dental office"OR "in-office" OR "at-home"OR "home-use"OR "home-care" OR	

"dental discolouration" OR "toothstaining" OR "teethstaining" OR "stainedtooth" OR "stainedteeth" OR "dental staining" OR "descoloração de dente" OR "descoloração dos dentes" OR "decoloración de losdientes" OR "dentiçãopermanente" OR "denticiónpermanente" OR "de color" OR "dente descolorido" OR "dienteescurecido" OR "dentesdescoloridos" OR "dientesescurecidos" OR "descoloração dental" OR "descoloración dental" OR "manchamento dental" OR "manchado dental" OR "mancha no dente" OR "manchanosdentes" OR "manchaenlosdientes" OR "dente manchado" OR "dientemanchado" OR "dentesmanchados" OR "dientesmanchados")	"jump-start" OR "clareamento dental" OR "blanqueamiento dental" OR peróxidos OR peroxidos OR "peróxido de hidrogênio" OR "peroxido de hidrogeno" OR "peróxido de carbamida" OR "consultório dental" OR "consultorio dental" OR "consultóriosdentais" OR "consultoriosdentales" OR branqueamento OR blanqueo OR blanqueamiento OR "emconsultório" OR "enelconsultorio" OR caseiro OR casero OR "usodoméstico" OR "cuidadosdomiciliários" OR associado OR asociado)
#1 AND #2	
Scopus	
#1 (TITLE-ABS-KEY ("T??thdiscoloration") OR TITLE-ABS-KEY ("t??thstaining") OR TITLE-ABS-KEY ("stained t??th") OR TITLE-ABS-KEY ("t??thdiscolouration") OR TITLE-ABS-KEY ("discolored t??th") OR TITLE-ABS-KEY ("discoloured t??th") OR TITLE-ABS-KEY (colo*r) OR TITLE-ABS-KEY ("dental discolo*ration") OR TITLE-ABS-KEY ("dental staining") OR TITLE-ABS-KEY ("permanentdentition"))	#2 (TITLE-ABS-KEY (peroxides) OR TITLE-ABS-KEY ("hydrogenperoxide") OR TITLE-ABS-KEY ("carbamideperoxide") OR TITLE-ABS-KEY ("dental office*") OR TITLE-ABS-KEY (bleaching) OR TITLE-ABS-KEY (whitening) OR TITLE-ABS-KEY ("in-office") OR TITLE-ABS-KEY ("home-use") OR TITLE-ABS-KEY ("at-home") OR TITLE-ABS-KEY ("home-care") OR TITLE-ABS-KEY ("jump-start"))) AND ((TITLE-ABS-KEY ("T??th discoloration") OR TITLE-ABS-KEY ("t??thstaining") OR TITLE-ABS-KEY ("stained t??th") OR TITLE-ABS-KEY ("t??thdiscolouration") OR TITLE-ABS-KEY ("discolored t??th") OR TITLE-ABS-KEY ("discoloured t??th") OR TITLE-ABS-KEY (colo*r) OR TITLE-ABS-KEY ("dental discoloration") OR TITLE-ABS-KEY ("dental discolouration") OR TITLE-ABS-KEY ("dental staining") OR TITLE-ABS-KEY ("permanentdentition")))
#1 AND #2	
Web of Science	
#1 TS=("T*thdiscolo*ration") OR TS=(colo?r) OR TS=("permanent dention") OR TS=("discolo*red t*th") OR TS=("dental discolo*ration") OR TS=("t*th staining") OR TS=("stained t*th") OR TS=("dental staining")	#2 TS=(“t*th bleaching agents”) OR TS=(bleaching) OR TS=(peroxides) OR TS=(“hydrogen peroxide”) OR TS=(“carbamide peroxide”) OR TS=(“dental office*”) OR TS=(whitening) OR TS=(“in-office”) OR TS=(“at-home”) OR TS=(“home-use”) OR TS=(“home-care”) OR TS=(“jump-start”)
#1 AND #2	

Table 4.5-2. Summary of the primary studies included in the systematic review.

							Bleaching protocol	Collection of the results	
Study ID	**Study design**	**Number of patients [drop-outs]**	**Subjects age's mean ± SD [range] (years)**	**No. of males [%]**	**Baseline color/ evaluated tooth**	**Groups/Materials**	**Gel protocol applications x min [sessions] (interval)**	**Color assessment [outcome]**	**Tooth sensitivity: scale [Outcome]**
Bernardon, 2010[21]	Split-mouth	90 [n.r.]	n.r ± n.r. [n.r.-n.r]	n.r. [n.r.]	A2/Anterior teeth	Sole$^{AH\ vs.\ IO}$: 10% CP^{a}vs. 35% HP^{b} w/light Sole$^{IO\ vs.\ IO}$: 35% HP^{b} w/light vs. 35% HP^{b} Sole andCombined$^{AH\ vs.\ IO\ +\ AH}$: 10% CP^{a} vs. 35% HP^{b} w/ light [1 session] + 10% CP^{a}	Sole^{AH}: 8h/daily (14 days) Sole^{IO}: 3 x 15 min [2] (15 days) Combined$^{IO+\ AH}$: 3 x 15 min [1] + 8h/daily (14 days)	Vita Classical^{p}; Spectrophotometer^{q}; Photography [ΔSGU; ΔE*]	VAS 0-10 [Intensityof TS]
Coban, 2011[34]	Parallel	45 [n.r]	24.9±4.5 (n.r.-n.r.)	n.r. [n.r.]	A3/Anterior teeth	Sole^{IO}: 35% HP^{c} Sole^{AH}: 15% CP^{d} Combined$^{IO\ +\ AH}$: 35% HP^{c} + 6% HP^{e}	Sole^{IO}: 1 x 30 min [3] (7 days) Sole^{AH}: 8h/daily (14 days) Combined$^{IO\ +\ AH}$: 1 x 30 min [1] + 4h/daily (14 days)	Spectrophotometer^{q} [ΔE*]	n.r.
Dawson, 2011[16]	Parallel	36 [0]	29.8 ± n.r. [19-58]	n.r. [n.r.]	A3/Anterior teeth	Sole^{AH}: AH 16% CP^{f} Combined$^{AH\ +\ IO}$: 16% CP^{f}+ 9% HP^{g} Combined$^{AH\ +\ IO}$: 16% CP^{f} + 27% HP^{g}	Sole^{AH}: 7h/night (14 days) Combined$^{AH\ +\ IO}$:7h/night (14 days) + 2 x 20 min [1]	Vita Classical^{p}; [ΔSGU]	VAS 0-10 [Intensityof TS]
Dias, 2011[33]	Parallel	20 [n.r.]	n.r ± n.r. [n.r.-n.r]	n.r. [n.r.]	n.r./n.r	Sole^{AH}: 16% CP^{h} Sole^{IO}: 35% HP^{i} Combined$^{IO\ +\ AH}$: 35% HP^{i} + 16% CP^{h}	Sole^{AH}: 8h/daily (7 days) Sole^{IO}: 2 x 15 min [4] (7 days) Combined$^{IO\ +\ AH}$: 2 x 15 min [4] + 8h/daily (7 days)	Vita Bleachdguide^{r}; Photography [ΔSGU]	n.r.
Franz-Montan, 2009[30]	Parallel	32 [n.r.]	n.r ± n.r. [18-31]	n.r. [n.r.]	n.r./n.r	Sole^{IO}: 37% HP^{b} Sole^{AH}: 10% HP^{a} Combined$^{IO\ +\ AH}$: 37% HP^{b} + 10% CP^{a}	Sole^{IO}: 1 x 60 min [3] (7 days) Sole^{AH}: 6h/daily (21 days) Combined$^{IO\ +\ AH}$: 1 x 60 min [3] + 6h/daily (21 days)	n.r.	n.r.
Kugel, 1997[31]	Parallel	20 [0]	n.r ± n.r. [n.r.-n.r]	n.r. [n.r.]	n.r./n.r	Sole^{IO}: 35% HP^{j} Combined$^{IO\ +\ AH}$: 35% HP^{j} + 15%^{k} CP	Sole^{IO}: 1 x 15 min [2] (6 days) Combined$^{IO\ +\ AH}$: 1 x 15 min [2] + 2h/daily (5 days)	Vita Classical^{p}; Photography [ΔSGU]	n.r.
Machado, 2016[32]	Split-mouth	21 [0]	23 ± n.r. [18-25]	6 [28.6]	A2/Anterior teeth	Combined^{IO+AH}: 38% HP^{l} + 10% CP^{d} Sole^{AH}: 10% CP^{d}	Combined$^{IO\ +\ AH}$: 2 x 15 min [2] (8 days) + 4h/daily (14 days) Sole^{AH}: 4h daily/14 days	Vita Classical^{p}; Spectrophotometer^{q} [ΔSGU; ΔE*]	VAS 0-10 [Intensityof TS]

Matis, 2009[18]	Split-mouth	37 [3]	53.7 ± n.r. [35-78]	14 [37.8]	A3/Anterior teeth	Combined^{IO+AH}: 36% HP^{i} + 15% CP^{h} Sole^{IO}: 36% HP^{i} Combined^{IO+AH}: 36% HP^{i} + 15% CP^{h} Sole^{IO}: 36% HP^{i}	Combined^{IO+AH}: 3 x 15 min [1] + Overnight (7 days) Sole^{IO}: 3 x 15 min [1] Combined^{IO+AH}: 1 x 40 min [1] + Overnight (7 days) Sole^{IO}: 1 x 40 min [1]	Vita Classical^{p}; ChromoMeter^{s}; Photography [ΔSGU; ΔE*]	VAS 0-10 [Intensityof TS]
Rezende, 2014[11]	Parallel	30 [0]	n.r ± n.r. [n.r.-n.r]	n.r. [n.r.]	A2/Anterior teeth	Combined^{IO+AH}: 35% HP^{m} + 6% HP^{n} Sole^{IO}: 35% HP^{m}	Combined^{IO+AH}: 3 x 15 min [2] + 1h/daily (28 days) Sole^{IO}: 3 x 15 min [2] (7 days)	Vita Classical^{p} [ΔSGU]	NRS 0-4 [Risk of TS]
Vochikovski, 2018[35]	Parallel	80 [0]	23.1 ± 4.8 [18-41]	31 [38.7]	A2/Upperincisors	Combined^{IO+AH}: 35% HP^{b} + 4% HP^{o} Sole^{AH}: 4% HP^{o}	Combined^{IO+AH}: 3 x 15 min [1] + 1h/daily (21 days) Sole^{AH}: 1h/daily (21 days)	Vita Classical^{p}; Vita Bleachedguide^{r}; Spectrophotometer^{q} [ΔSGU; ΔE*]	NRS 0-4 VAS 0-10 [Risk and intensity of TS]
Wetter, 2009[10]	Parallel	90 [2]	n.r. ± n.r. [18-45]	32 [35.5]	n.r./Upper central incisors and canines	Combined^{IO+AH}: 35% HP^{b} w/light + 10% CP^{a} Combined^{IO+AH}: 35% HP^{b} w/light + 10% CP^{a} Sole^{AH}: 10% CP^{a}	Combined^{IO+AH}: 1 x 20 min [1] + 1h/daily (7 days) Sole^{AH}: 1h/daily (14 days)	Vita Classical^{p}; Portablespectrometer^{t} [ΔSGU; ΔE*]	NRS 0-4 [Risk of TS]

Abbreviations: ID–identification; SD–standard deviation; n.r.–not reported in the study; AH–At-Home bleaching; IO–In-Office bleaching; CP–Carbamide Peroxide; HP–Hydrogen Peroxide; ΔSGU–shade guide units; ΔE*–color difference measured with a spectrophotometer; VAS–Visual Analog Scale; TS–Tooth Sensitivity; NRS–Numeric Rating Scale.

a WhitenessPerfect (FGM, Joinville, Brazil)
b Whiteness HP Maxx (FGM, Joinville, Brazil)
c Beyond Max (Beyound Technology Corp. NanchangNanchang, Jiangxi, China)
d Opalescence PF (Ultradent, South Jordan UT, USA)
e Beyond Stay White (Beyond Technology Corp. NanchangNanchang, Jiangxi, China)
f Enlighten Home (London, UK)
g Enlighten In-Office (London, UK)
h Nupro White Gold at-home gel (Dentsply, 38West Clarke Ave., Milford, USA)
iNupro White Gold Office (Dentsply, 38West Clarke Ave., Milford, USA)
j Quik Start (DenMat Corp., USA)
k Rembrandt Gel Plus (Den-MatCorp, Santa Maria, California)
l OpalescenceXtraBoost (Ultradent Inc., South Jordan, UT, USA)
m Mix OneSupreme (Villevie, Joinville, SC, Brazil)
n Mix Day (Villevie, Joinville, SC, Brazil)
o White Class (FGM, Joinville, Brazil)
p Vita ClassicalShade (Vita Zahnfabrik, BadSäckingen, Germany)
q Spectrophotometer (Vita Easyshade, Vident, Brea, CA, USA)
r Vita Bleachedguide 3D-Master (Vita Zahnfabrik, BadSäckingen, Germany)
s CR-321 Chromameter (Minolta, Ramsey, N.J.)
t Portablespectrometer (PS4, Imbotec, New York, NY)

Table 4.5-3. Summary-of-findings table and quality of the evidence. Only comparisons with meta-analysis were included in the table.

Patient or population: [dental discoloration in adults]
Intervention: [Combined bleaching]
Comparison: [Sole at home or sole in-office bleaching]

Outcome	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			№ of participants (studies)	Certainty
		Risk with [Sole at-home or in-office bleaching]	**Risk with [Combined bleaching]**	**Difference**		
Color change in Delta E (combined vs. IO bleaching) assessed with: spectrophotometer/colorimeter	-	-	-	SMD **1.76 higher** (0.48 lower to 4 higher)	192 (3 RCTs)	⊕◯◯◯ VERY LOW[a,b,c]
Color change in Delta E (combined vs. AH bleaching) assessed with: spectrophotometer/colorimeter	-	-	-	SMD **0.09 higher** (0.18 lower to 0.37 higher)	242 (4 RCTs)	⊕⊕⊕◯ MODERATE[a]
Color change in Delta SGU (combined vs. IO bleaching) assessed with: shade guide	-		-	MD **1.27 higher** (1.05 lower to 3.59 higher)	212 (4 RCTs)	⊕◯◯◯ VERY LOW[a,b,c]
Color change in Delta SGU (combined vs. AH bleaching) assessed with: shade guide	-	-	-	MD **0.18 lower** (0.54 lower to 0.18 higher)	261 (5RCTs)	⊕⊕◯◯ LOW[a,b]
Risk of TS (combined vs. AH bleaching)	**RR 1.36** (0.84 to 2.19)	24.6%	**33.5%** (20.7 to 54.0)	**8.9% more** (3.9 fewer to 29.3 more)	168 (2 RCTs)	⊕⊕◯◯ LOW[a,c]
Intensity of TS (combined vs. AH bleaching) assessed with: VAS pain scale	-	-	-	SMD **0.86 higher** (0.31 higher to 1.41 higher)	248 (4 RCTs)	⊕◯◯◯ VERY LOW[a,b]

Follow up to color change: periods ranging from 1 to 2-week post bleaching
Follow up to TS: the worst mean value reported for the group
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; SMD: Standardized mean difference; **MD:** Mean difference; **RR:** Risk ratio
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Most RCTs are at unclear risk of bias
b. Inconsistency in the data due to high and non-explained heterogeneity
c. High confidence interval that does not exclude great benefit or great harm

Figure 4.5-1. Flow diagram of study identification.

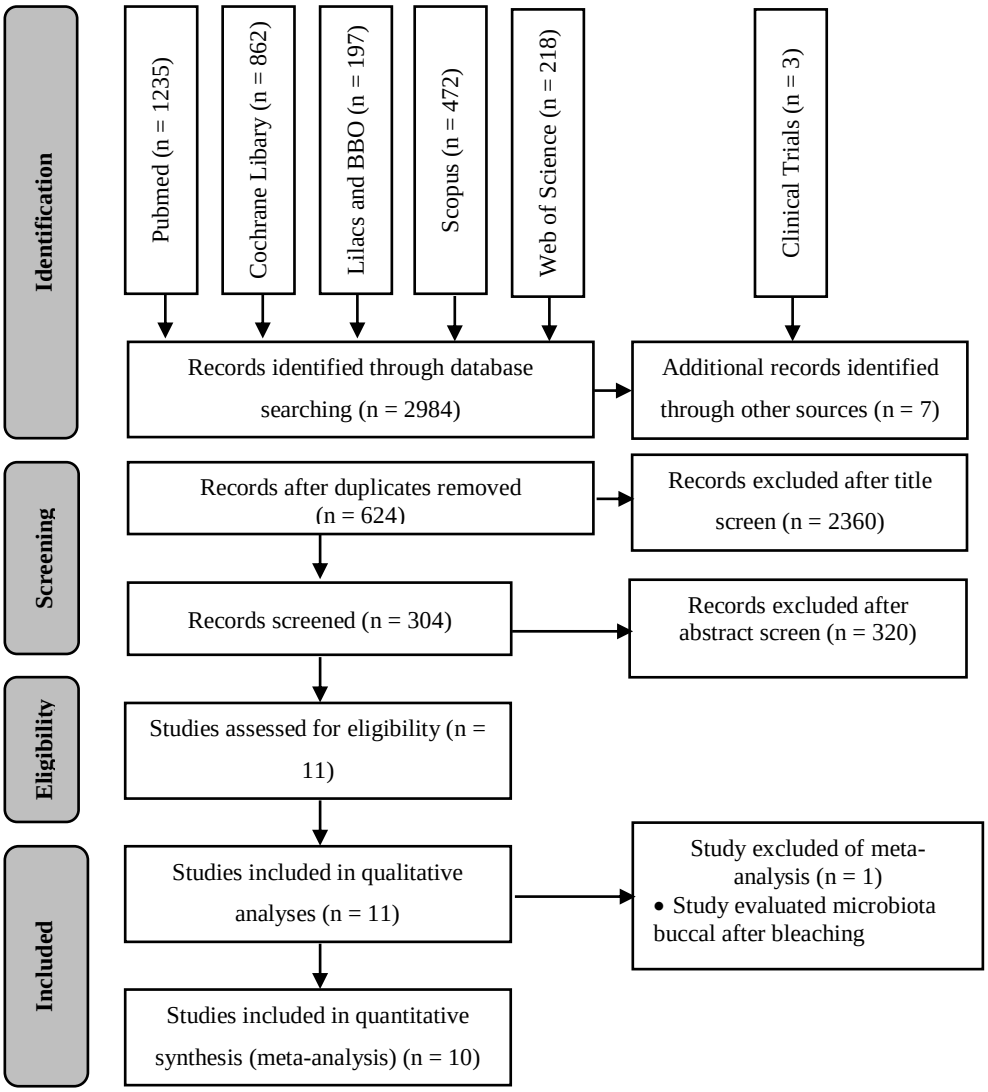


Figure 4.5-2. Summary of the risk of bias assessment according to the Cochrane Collaboration tool.

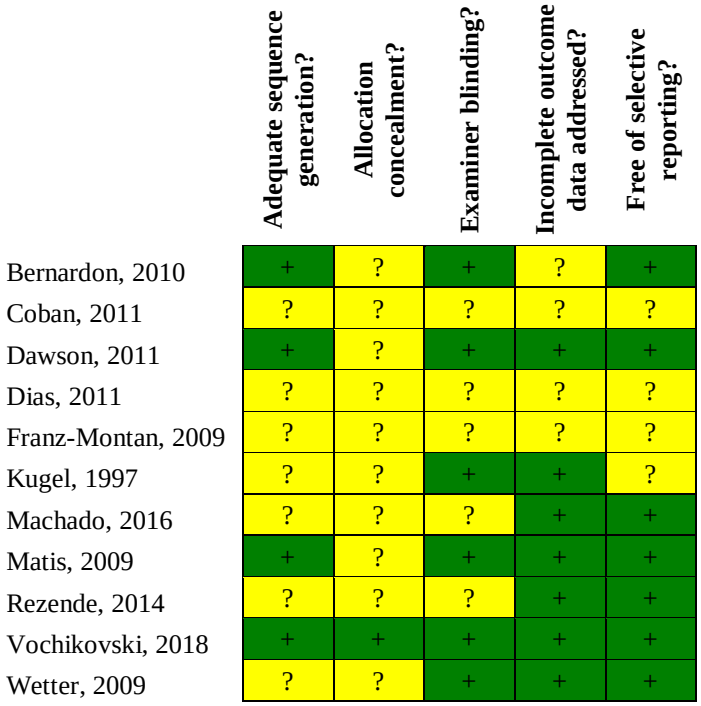


Figure 4.5-3. Forest plot of the color change in ΔE* (A) for combined bleaching vs. in-office bleaching (B) for combined vs. at-home bleaching.

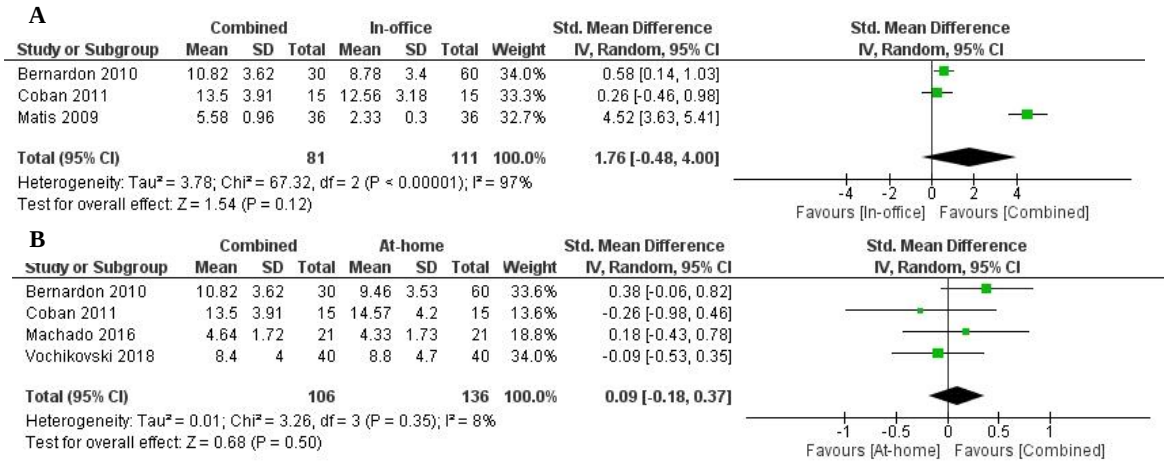


Figure 4.5-4. Forest plot of the color change in ΔSGU (A) for combined bleaching vs. in-office bleaching (B) for combined vs. at-home bleaching.

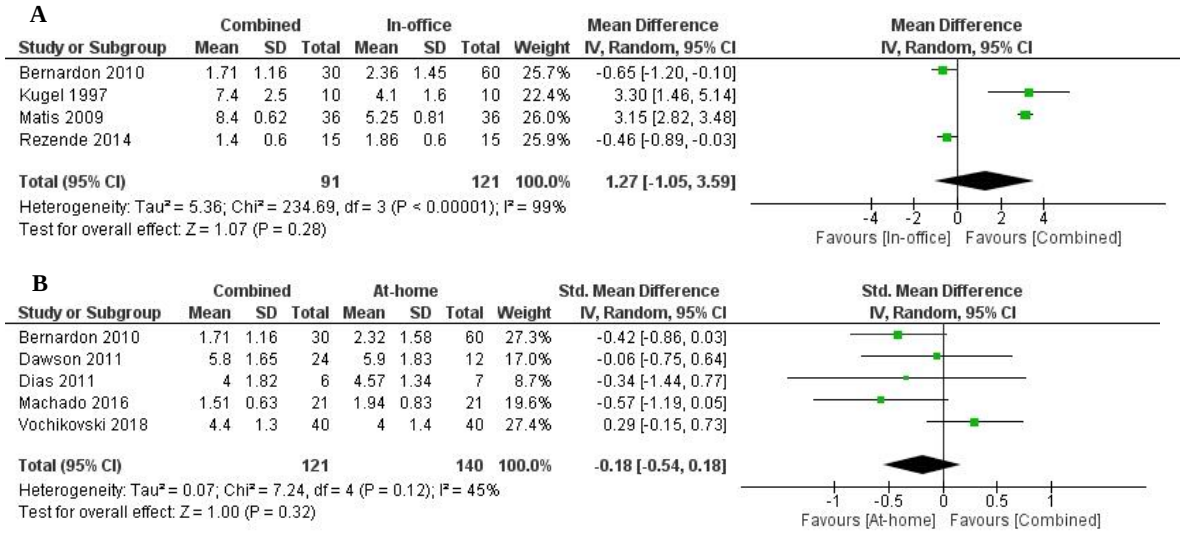


Figure 4.5-5. Forest plot of the risk of TS for combined bleaching vs. at-home bleaching.

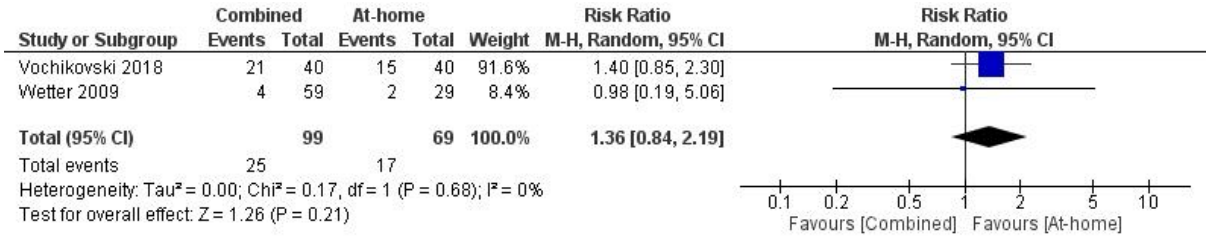
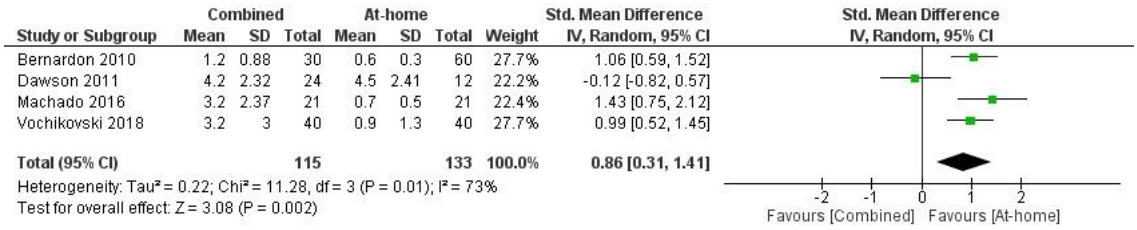


Figure 4.5-6. Forest plot of the intensity of TS for combined bleaching vs. at-home bleaching



REFERENCES

[1] D.C. Sarrett, Tooth whitening today, J Am Dent Assoc, 133 (2002) 1535-1538; quiz 1541.
[2] A. Joiner, The bleaching of teeth: A review of the literature, J Dent, 34 (2006) 412-419.
[3] T.M. Auschill, E. Hellwig, S. Schmidale, A. Sculean, N.B. Arweiler, Efficacy, side-effects and patients' acceptance of different bleaching techniques (otc, in-office, at-home), Oper Dent, 30 (2005) 156-163.
[4] S.S. Meireles, M.L. Goettems, R.V. Dantas, D. Bona Á, I.S. Santos, F.F. Demarco. Changes in oral health related quality of life after dental bleaching in a double-blind randomized clinical trial. Journal of Dentistry; 2014. p. 114-121.
[5] G.R. Samorodnitzky-Naveh, Y. Grossmann, Y.G. Bachner, L. Levin, Patients' self-perception of tooth shade in relation to professionally objective evaluation, Quintessence International, 41 (2010) E80-E83.
[6] V.B. Haywood, R.H. Leonard, C.F. Nelson, W.D. Brunson, Effectiveness, side effects and long-term status of nightguard vital bleaching, J Am Dent Assoc, 125 (1994) 1219-1226.
[7] J.E. Dahl, U. Pallesen, Tooth bleaching - a critical review of the biological aspects, Critical Reviews in Oral Biology & Medicine, 14 (2003) 292-304.
[8] A. Gallagher, B. Maggio, J. Bowman, L. Borden, S. Mason, H. Felix, Clinical study to compare two in-office (chairside) whitening systems, J Clin Dent, 13 (2002) 219-224.
[9] S. Gurgan, F.Y. Cakir, E. Yazici, Different light-activated in-office bleaching systems: A clinical evaluation, Lasers Med Sci, 25 (2010) 817-822.
[10] N.U. Wetter, E.P. Branco, A.M. Deana, J.E. Pelino, Color differences of canines and incisors in a comparative long-term clinical trial of three bleaching systems, Lasers Med Sci, 24 (2009) 941-947.
[11] M. Rezende, S.H. Siqueira, S. Kossatz, Clareamento dental - efeito da técnica sobre a sensibilidade dental e efetividade, Rev Assoc Paul Cir Dent, 68 (2014) 208-212.
[12] A.P. Mena-Serrano, S.O. Parreiras, E.M. Do Nascimento, C.P. Borges, S.B. Berger, A.D. Loguercio, et al., Effects of the concentration and composition of in-office bleaching gels on hydrogen peroxide penetration into the pulp chamber, Oper Dent, 40 (2015) E76-82.
[13] D.G. Soares, F.G. Basso, J. Hebling, C.A. De Souza Costa, Immediate and late analysis of dental pulp stem cells viability after indirect exposition to alternative in-office bleaching strategies, Clin Oral Investig, 19 (2015) 1013-1020.
[14] L.C. De Almeida, D.G. Soares, M.O. Gallinari, C.A. De Souza Costa, P.H. Dos Santos, A.L. Briso, Color alteration, hydrogen peroxide diffusion, and cytotoxicity caused by in-office bleaching protocols, Clin Oral Investig, 19 (2015) 673-680.
[15] M. Rezende, K. Chemin, S.C. Vaez, A.C. Peixoto, J. De Freitas Rabelo, S.S.L. Braga, 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)
[16] P.F. Dawson, M.O. Sharif, A.B. Smith, P.A. Brunton. A clinical study comparing the efficacy and sensitivity of home vs combined whitening. Operative Dentistry; 2011. p. 460-466.
[17] S. Deliperi, D.N. Bardwell, A. Papathanasiou, Clinical evaluation of a combined in-office and take-home bleaching system, J Am Dent Assoc, 135 (2004) 628-634.
[18] B.A. Matis, M.A. Cochran, G. Wang, G.J. Eckert, A clinical evaluation of two in-office bleaching regimens with and without tray bleaching, Operative Dentistry, 34 (2009) 142-149.
[19] W. Buchalla, T. Attin, External bleaching therapy with activation by heat, light or laser--a systematic review, Dent Mater, 23 (2007) 586-596.
[20] M. Rezende, L. Ferri, S. Kossatz, A.D. Loguercio, A. Reis, Combined bleaching technique using low and high hydrogen peroxide in-office bleaching gel, Oper Dent, 41 (2016) 388-396.
[21] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[22] G. Kugel, R.D. Perry, E. Hoang, W. Scherer, Effective tooth bleaching in 5 days: Using a combined in-office and at-home bleaching system, Compend Contin Educ Dent, 18 (1997) 378, 380-373.
[23] K. Zhao, L. Zong, Q. Zhang, W. Att. Clinical comparison between two bleaching techniques: A 180-day follow-up study. Quintessence international (Berlin, Germany : 1985); 2013. p. 601-607.

[24] G. Radz, Effectiveness of a combined in-office and take-home whitening system for teeth shades a3. 5 to a4, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 35 (2014) 696-700.
[25] E. Paula, S. Kossatz, D. Fernandes, A. Loguercio, A. Reis, The effect of perioperative ibuprofen use on tooth sensitivity caused by in-office bleaching, Oper Dent, 38 (2013) 601-608.
[26] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: The prisma statement, Int J Surg, 8 (2010) 336-341.
[27] C.I. De L'eclairage, Recommendations on uniform color spaces-color difference equations, psychomettic color terms, Paris: CIE, (1978)
[28] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ, 343 (2011) d5928.
[29] G. Guyatt, A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, et al., Grade guidelines: 1. Introduction—grade evidence profiles and summary of findings tables, J Clin Epidemiol, 64 (2011) 383-394.
[30] M. Franz-Montan, J.C. Ramacciato, J.A. Rodrigues, G.M. Marchi, P.L. Rosalen, F.C. Groppo, The effect of combined bleaching techniques on oral microbiota, Indian Journal of Dental Research, 20 (2009) 304.
[31] G. Kugel, R. Perry, E. Hoang, W. Scherer, Effective tooth bleaching in 5 days: Using a combined in-office and at-home bleaching system, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 18 (1997) 378, 380-373.
[32] L.S. Machado, R.B. Anchieta, P.H. Dos Santos, A.L. Briso, N. Tovar, M.N. Janal, et al., Clinical comparison of at-home and in-office dental bleaching procedures: A randomized trial of a split-mouth design, Int J Periodontics Restorative Dent, 36 (2016) 251-260.
[33] K.R.H.C. Dias, J.P. Lima, S.T.M. P., R.V. Monte Alto, O.B. Oliveira Junior. Evaluation of efficacy of three tooth bleaching technique. IADR/AADR/CADR 89th General Session. San Diego, California: J Dent Res; 2011.
[34] A. Coban, E. Can, M. Soyman. Clinical evaluation of in office at home and combined bleaching. IADR/AADR/CADR 89th General Session. San Diego, California: J Dent Res; 2011.
[35] L. Vochikovski. Sensibilidade dental e efetividade de um novo protocolo de aplicação da técnica de clareamento associado com aplicação de dessensibilizante [Dissertation]. Ponta Grossa: State University of Ponta Grossa; 2018.
[36] B.A. Matis, M.A. Cochran, G. Wang, G.J. Eckert, A clinical evaluation of two in-office bleaching regimens with and without tray bleaching, Oper Dent, 34 (2009) 142-149.
[37] J. Ma, W. Liu, A. Hunter, W. Zhang, Performing meta-analysis with incomplete statistical information in clinical trials, BMC medical research methodology, 8 (2008) 56.
[38] P.F. Dawson, M.O. Sharif, A.B. Smith, P.A. Brunton, A clinical study comparing the efficacy and sensitivity of home vs combined whitening, Oper Dent, 36 (2011) 460-466.
[39] J. Higgins, S. Green. Cochrane handbook for systematic reviews of interventions. In: Wiley-Blackwell N, USA, editor. The Cochrane Collaboration. (http://handbook.cochrane.org); 2010.
[40] J.D. Harris, C.E. Quatman, M.M. Manring, R.A. Siston, D.C. Flanigan, How to write a systematic review, Am J Sports Med, 42 (2014) 2761-2768.
[41] A.D. Loguercio, B.M. Maran, T.A. Hanzen, A.M.D. Paula, J. Perdigão, A. Reis, Randomized clinical trials of dental bleaching – compliance with the consort statement: A systematic review, Brazilian Oral Research, 31 (2017)
[42] K.F. Schulz, I. Chalmers, R.J. Hayes, D.G. Altman, Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials, JAMA, 273 (1995) 408-412.
[43] J.B. Da Costa, R. Mcpharlin, R.D. Paravina, J.L. Ferracane, Comparison of at-home and in-office tooth whitening using a novel shade guide, Oper Dent, 35 (2010) 381-388.
[44] L. Giachetti, F. Bertini, C. Bambi, M. Nieri, D. Scaminaci Russo, A randomized clinical trial comparing at-home and in-office tooth whitening techniques: A nine-month follow-up, J Am Dent Assoc, 141 (2010) 1357-1364.

[45] F.V. Moghadam, S. Majidinia, J. Chasteen, M. Ghavamnasiri, The degree of color change, rebound effect and sensitivity of bleached teeth associated with at-home and power bleaching techniques: A randomized clinical trial, Eur J Dent, 7 (2013) 405-411.
[46] K. Pintado-Palomino, O. Peitl Filho, E.D. Zanotto, C. Tirapelli, A clinical, randomized, controlled study on the use of desensitizing agents during tooth bleaching, J Dent, 43 (2015) 1099-1105.
[47] C. Kose, A.L. Calixto, J.R. Bauer, A. Reis, A.D. Loguercio, Comparison of the effects of in-office bleaching times on whitening and tooth sensitivity: A single blind, randomized clinical trial, Oper Dent, 41 (2016) 138-145.
[48] P.W. Kihn, D.M. Barnes, E. Romberg, K. Peterson, A clinical evaluation of 10 percent vs. 15 percent carbamide peroxide tooth-whitening agents, J Am Dent Assoc, 131 (2000) 1478-1484.
[49] K. Chemin, M. Rezende, A.D. Loguercio, A. Reis, S. Kossatz, Effectiveness of and dental sensitivity to at-home bleaching with 4% and 10% hydrogen peroxide: A randomized, triple-blind clinical trial, Oper Dent, 43 (2018) 232-240.
[50] R.H. Leonard, Jr., G.E. Garland, J.C. Eagle, D.J. Caplan, Safety issues when using a 16% carbamide peroxide whitening solution, J Esthet Restor Dent, 14 (2002) 358-367.
[51] B.A. Matis, H.N. Mousa, M.A. Cochran, G.J. Eckert, Clinical evaluation of bleaching agents of different concentrations, Quintessence Int, 31 (2000) 303-310.
[52] I. Luque-Martinez, A. Reis, M. Schroeder, M.A. Munoz, A.D. Loguercio, D. Masterson, 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, 20 (2016) 1419-1433.
[53] B. Matis, Degradation of gel in tray whitening, Compendium of continuing education in dentistry(Jamesburg, NJ: 1995) Supplement, (2000) S28, S31-25; quiz S49.
[54] T. Al-Qunaian, B. Matis, M. Cochran, In vivo kinetics of bleaching gel with three-percent hydrogen peroxide within the first hour, OPERATIVE DENTISTRY-UNIVERSITY OF WASHINGTON-, 28 (2003) 236-241.
[55] B. Matis, M. Yousef, M. Cochran, G. Eckert, Degradation of bleaching gels in vivo as a function of tray design and carbamide peroxide concentration, Operative Dentistry, 27 (2002) 12-18.
[56] T.M. Auschill, E. Hellwig, S. Schmidale, A. Sculean, N.B. Arweiler. Efficacy, side-effects and patients' acceptance of different bleaching techniques (otc, in-office, at-home). Operative dentistry; 2005. p. 156-163.
[57] Y. Wang, J. Gao, T. Jiang, S. Liang, Y. Zhou, B.A. Matis, Evaluation of the efficacy of potassium nitrate and sodium fluoride as desensitizing agents during tooth bleaching treatment - a systematic review and meta-analysis, J Dent, 43 (2015) 913-923.
[58] S. Cook, E. Mccleskey, Cell damage excites nociceptors through release of cytosolic atp, Pain, 95 (2002) 41-47.
[59] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[60] F. Krause, S. Jepsen, A. Braun, Subjective intensities of pain and contentment with treatment outcomes during tray bleaching of vital teeth employing different carbamide peroxide concentrations, Quintessence International, 39 (2008) 203-209.
[61] C. Kose, A. Reis, L.N. Baratieri, A.D. Loguercio. Clinical effects of at-home bleaching along with desensitizing agent application. Am J Dent; 2011. p. 379-382.
[62] S.S. Meireles, S.S. Heckmann, I.S. Santos, A. Della Bona, F.F. Demarco, A double blind randomized clinical trial of at-home tooth bleaching using two carbamide peroxide concentrations: 6-month follow-up, Journal of Dentistry, 36 (2008) 878-884.
[63] P. Charakorn, L. Cabanilla, W. Wagner, W. Foong, J. Shaheen, R. Pregitzer, et al., The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching, Oper Dent, 34 (2009) 131-135.
[64] F.C. Marson, L.G. Sensi, L.C.C. Vieira, E. Araujo, Clinical evaluation of in-off ice dental bleaching treatments with and without the use of light-activation sources, Oper Dent, 33 (2008) 15-22.

TÍTULO: RANDOMIZED CLINICAL TRIALS OF DENTAL BLEACHING – COMPLIANCE WITH THE CONSORT STATEMENT: A SYSTEMATIC REVIEW

STATUS: PUBLICADO

REVISTA: BRAZILIAN ORAL RESEARCH

4.6 ARTIGO 6 – RANDOMIZED CLINICAL TRIALS OF DENTAL BLEACHING – COMPLIANCE WITH THE CONSORT STATEMENT: A SYSTEMATIC REVIEW

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ABSTRACT

We reviewed the literature to evaluate: a) The compliance of randomized clinical trials (RCTs) on bleaching with the CONSORT; and b) the risk of bias of these studies using the Cochrane Collaboration risk of bias tool (CCRT). We searched the Cochrane Library, PubMed and other electronic databases, to find RCTs focused on bleaching (or whitening). The articles were evaluated in compliance with CONSORT in a scale: 0 = no description, 1 = poor description and 2 = adequate description. Descriptive analysis of the number of studies by journal, follow-up period, country and quality assessments were performed with CCRT for assessing risk of bias in RCTs. 185 RCTs were included for assessment. More than 30% of the studies received score 0 or 1. Protocol, flow chart, allocation concealment and sample size were more critical items, as 80% of the studies scored 0. The overall CONSORT score for the included studies was 16.7 ± 5.4 points, which represents 52.2% of the maximum CONSORT score. A significant difference among journal, country and period of time was observed ($p < 0.02$). Only 7.6% of the studies were judged at "low" risk; 62.1% were classified as "unclear"; and 30.3% as "high" risk of bias. The adherence of RCTs evaluating bleaching materials and techniques to the CONSORT is still low with unclear/high risk of bias.

Clinical significance: Systematic reviews are on the top level of evidence; therefore their results may help clinical decisions to provide the best treatment for our patients.

Keywords: Tooth Bleaching. Dental Sensitivity.

INTRODUCTION

Dental bleaching (or whitening) has become the most sought treatment by patients in search for esthetics. According to study of Al-Zaera, 2013 [1], which investigated the research subjects' satisfaction with dental appearance, nearly 66% of the individuals were dissatisfied with the color of their teeth. Another survey conducted in Ankara, Turkey [2], focused on the treatment of patients who were unhappy with their smile, questioning which treatment these patients would like to receive. About half of the patients suggested dental bleaching (49.9%), followed by esthetic restorations (25.4%), orthodontic treatment (24.5%), and prosthetic restorations (16.9%).

Linked to growing demand, the effectiveness of various protocols and materials used by dental professionals has been extensively studied in the last decades, including longevity of the bleaching outcome [3-6]. Researchers have used clinical or in vitro studies to obtain data that can predict clinical performance, as some subjective factors related to the bleaching protocol, such as postoperative sensitivity and other adverse reactions, cannot be evaluated directly [7-9].

While laboratory testing is a very useful method to study the diffusion of the components of bleaching gels, such H_2O_2, into dental pulp [10,11] clinical trials can provide reliable and direct evidence to guide clinicians in their choice of materials for in-office and at-home bleaching [12-15].

Hence, randomized controlled trials (RCTs) are considered the standard research design for the evaluation of health interventions. In fact, RCTs and systematic reviews are at the top level of the evidence hierarchy [16]. RCTs, however, may incur risk of spurious results if their design is flawed or if the respective methodology lacks accuracy [17]. Several problems with the design and execution of RCTs raise questions regarding the validity and reliability of the respective findings. This situation may lead to an underestimation or overestimation of the true intervention effect [18].

Therefore readers should appraise any RCT before a clinical decision is made. This evaluation depends on a good report/writing of the methods and results sections of RCTs. A group of experts joined efforts in 1996 and proposed several items that should be described in a RCT (CONsolidate Standard of Randomized Trials [CONSORT] Statement), with the objective of standardizing the reporting of RCTs. The CONSORT Statement was reviewed in 2001 [19] and the most recent version was published in 2010 [20,21].

Given the importance of RCTs in dental bleaching to make decisions regarding protocols, application time, and commercial brand, the aim of this study was to systematically review the literature in peer-reviewed journals to evaluate a) the compliance of RCTs with the CONSORT Statement and b) the risk of bias in these RCT studies through the Cochrane Collaboration risk of bias tool (CCRT).

MATERIAL AND METHODS

This study was not registered, as there are no currently known systematic review registries of methodologies.

Search Methods

We following databases: MEDLINE via PubMed, Cochrane Library, Brazilian Library in Dentistry (BBO) and Latin American and Caribbean Literature in Health Sciences database (LILACS) and citation bases: Scopus and Web of Science were consulted (Table 4.6-1). The reference lists of all primary studies, as well as the related articles link from the PubMed database from each primary study, were manually searched. Articles in Korean, Japanese, Chinese, Arabic and related languages were not included due to difficult translation.

According to the MEDLINE database, a search strategy was defined according to a terminology for indexing biomedical information (MeSH, Medical Subject Headings, U.S. National Library of Medicine, Bethesda, MD, USA) along with free keywords. For each database, the search strategy was adapted for consultation. In order to standardize the articles evaluated, only studies published since the CONSORT Statement declaration in 1996 were included.

Eligibility criteria

We included parallel and split-mouth RCTs that evaluated the effectiveness of different types of bleaching systems and techniques on color change, toxicity, postoperative sensitivity and application technique. We did not restrict studies with patients of different age groups or populations (Table 4.6-2).

Laboratory studies were excluded, as well as those presented as conference abstracts, theses and reports published in any media other than peer-reviewed journals. Additionally, all studies that were published before 1996 were excluded (Table 4.6-2).

Three reviewers (A.P., B.M.M. and T.H.) catalogued articles that met the inclusion criteria. Article selection was carried out by first reading the titles and abstracts; then the full text of the paper was read in case of doubts.

Adherence to CONSORT Statement

An evaluation tool based on the items related to the methods and results from the 2010 CONSORT Statement [20] was developed to evaluate the reporting completeness of RCTs (Table 4.6-3) [22]. The items related to the title and abstract, introduction and discussion were not evaluated since the evaluation would have been very subjective and the adherence to these items would not weaken the quality of the study report or the risk of bias of the studies.

A total of 12 items of the CONSORT Statement were included in this CONSORT evaluation tool. As some of these items were subdivided, a total of 16 items were evaluated. The given score per item ranged from 0 to 2. In general words, 0 = no description, 1 = poor description and 2 = adequate description. More details regarding the scoring process for each score of each item are displayed in Table 4.6-3. Each item was given an equal weighting.
Prior to evaluation, the instrument was discussed between two experienced authors in clinical trials (A.D.L. and A.R.), pilot-tested in 15 articles and checked for accuracy and reproducibility by three evaluators. This process yielded modification of the instrument tool, as new possibilities for each score were observed and discussed during pilot testing.

Three reviewers (A.P., B.M.M. and T.H.) performed the round of scoring using the CONSORT evaluation tool as guide (Table 4.6-3). In case of disagreement a discussion followed and the consensus was used to determine the final score. Evaluators were not blinded to the study authors. This was not feasible, as reviewers were familiar with the studies and could easily guess the researchers' affiliation by reading the paper.

Scoring system and statistical analysis

The number of studies by journal, follow-up period and country were analyzed descriptively. Compliance with individual items of the statement was analyzed to indicate where researchers could improve their description. A chart with the percentage of studies per score in each item was provided.

To achieve an overall compliance score, the scores for the 16 items were added in each article. A trial with adequate descriptions (score 2) for all CONSORT items would receive a maximum score of 32. A mean average score was calculated by period of time, journal and country. Comparison within each factor was performed with the Kruskall-Wallis and Mann-Whitney test at a level of confidence of 95%. Linear correlation analysis between 2015 ISI journal impact factor and the average CONSORT score was also performed.

These additional analyses aimed at offering information about whether improvements in the average CONSORT score occurred over the time and if these improvements were related to the journal and respective impact factor, as well as the living country of the first author.

Risk of bias in individual studies

Quality assessments were performed by three independent reviewers, using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (CCRT) [23]. The assessment criteria contain six domains: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Each domain of the Cochrane risk of bias tool was evaluated at low, high or unclear risk of bias. After assessment of the domains, each study was then evaluated into low risk of bias if all domains were at low risk. The study was judged as at high risk of bias if at least one of the key domains was evaluated as high risk of bias. And finally, the study would be considered at unclear risk, if at least one domain were judged at unclear risk of bias.

RESULTS

Characteristics of the included studies

From the 1925 articles that were originally screened, after removal of duplicates, 1691 were excluded for not complying with the inclusion criteria. The full-text of 234 papers were assessed and 49 papers were excluded for the following reasons: 1) 15 studies were not randomized clinical trials; 2) 7 studies were case reports; 3) 3 studies were duplicates; 4) 2 studies were abstracts; 5) 1 study was published in Korean language; 6) 4 studies were in vitro; 7) 2 studies were case series; 8) 1 study was a literature review; 9) 1 study was an ex-vivo study; 10) 1 study is currently in the recruitment phase and evaluation of tooth color (results not yet available); 11) 1 study evaluated the color change of the composite resin after bleaching; 12) 11 studies were not accessible. After these exclusions, 185 RCTs remained for assessment (Figure 4.6-1).

The included RCTs investigated several topics, such as the comparison of 1) at-home dental bleaching techniques; 2) in-office dental bleaching techniques; 3) patient related factors; 4) in-office vs. at-home and 5) combined bleaching techniques.

Table 4.6-4 displays the 185 RCTs tabulated by their collected characteristics. The journals contributing with the most RCTs were Oper Dent (17.8%), followed by Comp Cont Educ Dent (11.4%), Am J Dent (7.6%) and Quintessence Int (7.0%). Approximately 29.2% of the publications were published in 37 different journals. The countries with most publications were USA (40.5%) and Brazil (28.1%), representing together about 70% of all publications in the field. The most frequent follow-up period (days) reported in the articles occurred between 14 (22.7%) and 28 (10.3%) days.

Study compliance with each of the CONSORT instrument tool items

Figure 4.6-2 displays the percentage of studies per score for each item of the CONSORT Statement in percentage of studies. In regard to the items' intervention and outcomes, more than 80% of the studies were scored as 2, with an adequate reporting. For the items eligibility, hypothesis testing, losses/exclusion and numbers analyzed, more than 50% of the studies were scored as 2.

More than 50% of the studies received score 1 (poor reporting) or score 0 (no reporting) for all other items. This was more critical with the items protocol, flow chart, allocation concealment and sample size where more than 80% of the studies were scored as 0 (no reporting).

In order to help future randomized clinical trials of bleaching, some examples of adequate description of each item of the results, material and methods of CONSORT were added in Table 4.6-5 to 9.

Average CONSORT score per study characteristics

The overall CONSORT score for the included studies in this review was 16.7 ± 5.4 points, which represents 52.2% of the maximum CONSORT score of 32 points. We observed a significant influence of journal, country, and period of time on the average CONSORT score (Table 4.6-10). Significant differences among journals were observed ($p < 0.0001$; Table 4.6-10), with the average CONSORT scores of J Dent (higher score), Oper Dent, Clin Oral Investig and JADA being higher than the remaining journals. 'Other journals' are composed of 37 different journals, which published 54 different papers (29.1% of total). A significant but weak correlation between average CONSORT score and impact journal factor was observed ($r = 0.16$; $p < 0.0001$, Figure 4.6-3).

Regarding country, a significant difference was also observed ($p = 0.02$; Table 4.6-10). Brazil showed the highest average CONSORT score, being statistically higher than those of UK, Italy and USA. On the same line, the period of time in years had a significant influence on the average CONSORT score ($p = 0.004$; Table 4.6-10). We observed an increase in the average CONSORT score in the 2011-2016 interval (19.03 ± 6.87) in comparison with the 1996-2000 period (13.47 ± 4.03). The individual CONSORT score for each one of the included studies can be seen in Table 4.6-11.

Risk of bias of the included studies

Except for the selective outcome reporting and incomplete outcome data, most of the studies were judged to be at "unclear" or "high" risk of bias in the Cochrane Collaboration tool domains (Figure 4.6-4). Table 4.6-11 reports the individual risk of bias in each domain for all

included studies. This table facilitates the analysis of the risk of bias within each study. Only 14 included studies (7.6%) were judged to be at "low" risk of bias in all domains; 115 studies were classified as at "unclear" risk of bias in at least one domain, resulting in 62.2% of the studies being classified at "unclear" risk of bias at the study level. The remaining 56 studies were classified as at "high" risk of bias in at least one domain, representing 30.3% of studies judged as at "high" risk of bias.

DISCUSSION

Study compliance with the CONSORT

Although the CONSORT statement has been misleadingly used as an instrument to evaluate the quality of the RCTs available in the literature [24], the aim of the CONSORT Statement is to guide authors to describe details on their studies to enable the evaluation of the risk of bias of RCTs [25]. This is why adherence to CONSORT statement is of ultimate importance so that readers can appraise the available literature and translate this literature into clinical knowledge pertinent to evidence-based practice. In the present study, we assessed the adherence of RCTs of bleaching materials and techniques to the CONSORT Statement [26,27]. In other to provide a better analysis of the compliance of the studies with each item of the CONSORT score, a 0-2 scale was developed in a way that zero means no reporting, 1 poor reporting, and 2 adequate reporting [22]. This is different from what had been done in other papers, which have reported the adherence of RCTs in other dental areas, such as orthodontics, prosthodontics, oral implants, periodontics and pediatric dentistry [28-33]. These earlier studies were more focused on the journal's compliance rather than the article's compliance with a specific subjected. Subsequently, few of these earlier studies performed a comprehensive search review of the articles published in a specific research area, as we have tried to do in the present study. To the extent of the authors' knowledge this is the first study that has attempted to evaluate the adherence of RCTs of bleaching materials and techniques to the CONSORT Statement, which was one of the aims of the present study.

To evaluate the risk of bias of the RCTs it is imperative that we concentrate on the design and the results of any study report. CONSORT adherence to introduction or discussion section increases the quality of the article reporting but does not affect the risk of bias of the studies. This is the reason behind our decision to only evaluate each study's compliance with the items related to methodology and results. Earlier studies with the same aim, conducted on different specialties of dentistry, evaluated additional items, including the subjective items of introduction and discussion sections [28-33].

In the present study we observed that the overall CONSORT score for the included studies was 16.7 ± 5.4 points, which represents only 52.2% of the maximum CONSORT score a study could have reached. This reduced compliance with CONSORT Statement was also observed in an earlier study from our research group evaluating the compliance of RCTs in non-carious cervical lesions with the CONSORT [22]. Similarly, other dental specialties such as periodontics and pediatric dentistry yielded similar results. For instance, a CONSORT compliance of approximately 60% was observed for RCTs in prosthodontics and implant dentistry. In orthodontics, this compliance ranged from 40 to 70% [28-30,34,35]. Although these variations are small, they may reflect the inclusion criteria of the RCTs, the method of compliance evaluation, the number of CONSORT items evaluated, and also the period of publication. Our previous study of RCTs in non-carious cervical lesions demonstrated that the adherence of the study increases when the study is more recent [22].

The results of the present study confirmed that the journal endorsement of the CONSORT Statement might beneficially influence the completeness of reporting of RCTs, mainly because three out of four journals with high average CONSORT score (J Dent, Clin Oral Investig, and JADA) have adopted this policy within the last decade. The same tendency has been observed for medical journals [36] and for orthodontics journals [28,37], but not for RCTs conducted in non-carious cervical lesions [22]. Braz Oral Res is another journal that clearly endorse the CONSORT Statement. Although there is an increasing number of journals endorsing the CONSORT statement in medical journals as well as dental journals, the CONSORT compliance is still considered suboptimal even in these journals [38].

Theoretically, one should expect that journals with high impact factor would publish studies with better reporting standards. Indeed, a significant correlation between journal impact factor and journal average CONSORT score was observed in the present and in earlier investigations [39,40], but this correlation is usually weak. In the present study the correlation coefficient ($R^2 = 0.1602$) was also very weak, which means that the great variation observed in the average CONSORT score is not explained by the journal impact factor.

We hypothesize that not all members of the editorial board of these journals check the submitted articles for compliance with the CONSORT Statement, which prevents them from reaching an improved reporting score of RCTs. More attention to these items during the peer-review process may be required. Apart from that, the ambiguous language of what was meant by CONSORT endorsement [25,41,42] in journals may prevent better CONSORT adherence. In fact, instructions on how CONSORT should be used by authors are inconsistent across

journals and publishers. For instance, J Dent recommends the use of CONSORT and submission of the checklist and flow diagram in the instructions for authors, while Clin Oral Investig does not recommend the use of reporting guidelines in the instructions [38]. Publishers and journals should encourage authors to use CONSORT and set clear instructions for authors regarding full compliance with CONSORT. Braz Oral Res, for example, clearly indicates that authors must fully comply with the CONSORT Statement.

In regard to the period of time, better compliance was observed in more recent studies (2011-2016; mean CONSORT score of 19.03 ± 6.87) than in earlier periods (1996-2000; mean CONSORT score of 13.47 ± 4.03). This finding had been reported by other authors [28,35] and in an earlier RCT study of adhesive materials applied onto non-carious cervical lesions [22]. However, this increase is still small and substandard, as it reached slightly more than 50% of the maximum CONSORT score (32 points). Had all trials described the evaluated items correctly, the score might have reached a score closer to 32.

Regarding the country, there is not a clear explanation why papers published by Brazilian researchers reached higher average CONSORT score than authors from more developed countries, such as USA, UK and Italy. We believe that the policies and efforts of Brazil government agencies in supporting training of specialized researchers in Science and Technology, implemented by Periódicos Capes Theses databases (www.capes.gov.br [Coordination of Personal Formation for Higher Education]) in the last 40 years, has led to an increasing number and quality of Brazilian articles in all science fields. Based on data from the SCImago database (www.scimagojr.com), the number of published papers in Dentistry is higher than those in other areas [43].

As reported in the results section, the item sample size was reported poorly. This is also problematic in the medical field. For instance, Chan and Altman [44] reported that 73% of the 519 medical trials indexed in PubMed in December 2000 did not report sample size calculation. Although sample size does not affect the validity of the study and its risk of bias, if not done properly and based on a clinically important effect, it may result in underpowered studies, which is usually misunderstood as groups being statistically similar. However, the lack of evidence to reject the null hypothesis does not mean that the groups are similar to one another. It may also mean that the study did not have a sample size big enough to detect a smaller difference if it really existed.

Based on the same premise, by using an infinite sample size we can prove any small and non-clinical relevant difference as being statistically different which may induce readers to

change equivocally the standard protocol or technique for others that may be more costly or with higher side effects [45]. This is why authors from RCTs should describe in their study the effect size rather than only the results of the hypothesis testing. Effect sizes and confidence intervals make the interpretation of the results easier. If a protocol has a fictitious relative risk for tooth sensitivity of 0.75 (95% CI 0.5 to 0.8), this means that the experimental group has a chance of 25% lower (from 50% to 20% lower) to develop tooth sensitivity. This response carries much more information than only stating that two groups were statistically different based on a probability value of 0.1%, for instance. Unfortunately, in the present study 88.1% of the studies did not report well, or did not report at all, the effect sizes, which is also a problem in medical journals [46].

Based on these ideas, researchers are advised to move away from significance tests and to display, instead, an estimate of effect size delimited by confidence intervals. This method incorporates all the information normally included in a hypothesis, but in a way that emphasizes what is really important (clinical significance rather than statistical significance) [46-48].

Another concern in the included bleaching studies is related to randomization. Ideally, such description should include details about both the methods used to generate the random sequence, as well as the method used to conceal this the random sequence. Inadequately and unclearly concealed trials have been shown to result in exaggerated effect sizes in favor of the experimental group [49]. This problem also occurs in other areas: poor reporting of allocation concealment was observed in 78% of the RCTs among dental journals [50] and 93% in the specialty of periodontology [31] In the present study problems in random sequence generation and allocation concealment (scores 0 and 1) were seen in 53.5% and 84.8% of the trials, respectively.

These two items (random sequence and allocation concealment) allow readers to evaluate if the study is free of selection bias. A well-done random sequence generation is worthless if not well concealed. The objective of the randomization process is to balance the participants in terms of known and unknown factors so that no other variable apart from the one under investigation can account for the differences observed among participants from distinct groups.

Usually, authors refer to terms such as “random allocation” or “the groups were randomized”, without further elaboration. Authors should specify the method of sequence generation (such as a random-number table or a computerized random number generator, coin

toss, dice throwing, etc.) as well as restrictions to the process such as stratification, block randomization, etc [45].

Blinding is also a key element in RCT reporting and should not be confused with allocation concealment, as blinding prevents performance and detection bias [45] instead of selection bias. In some research questions of bleaching studies, operator and patient blinding may be not possible, when for instance light activated systems are being tested. However, evaluator blinding may be always possible and it could be implemented in the study design, mainly if the primary outcome color change is being checked against a shade guide unit. In such case, lack of evaluator blindness would put the study at a higher risk of bias. For objective outcomes, however, such as color measurements with a spectrophotometer, the lack of examiner blindness is not that important. When the primary outcome is tooth sensitivity, which is a patient-centered subjective outcome, it is the lack of participants' blinding and not evaluators' that downgrade the level of confidence in the research findings.

Failures to describe who is blinded in the study are the most common problems observed in the eligible studies. Reports like "this study was single-blind", "this was a double-blind study", are useless, as it does not inform readers of who was in fact blind. In agreement with these ideas, Pandis et al. [50] reported that inadequate description of blinding in RCTs published in leading dental journals ranged from 74 to 100%. In implant dentistry, the lack of adequate blinding reporting was informed to be 58% [51].

The design and conduct of some RCTs may be not straightforward, particularly when there are losses to follow-up, or exclusions. This precludes the description of the numbers of participants through each phase of the study in a few sentences [52]. This can be simply described by introducing a flow chart with the number of participants in each phase of the trial. Although the CONSORT Statement recommends the inclusion of a flow chart, we observed that only 48.1% of the clinical trials followed this recommendation.

Another type of bias commonly found in RCTs is selective outcome reporting. In general, there is most enthusiasm about the publication of RCTs that show either a large effect of a new treatment (positive trials) or equivalence of two approaches. Consequently, articles with negative findings are less submitted or accepted for publication by journals. This may even be more relevant in sponsored RCTs if the results of the trial place financial interests at risk [53].

To manage such problems, the International Committee of Medical Journal Editors (ICMJE) has proposed comprehensive trials registration. Trials must register at or before the

onset of patient enrollment [53]. For the ICMJE, this policy applies to any clinical trial that started enrollment after July 1, 2005. However, only 12 out of 120 included studies of this review published in 2005 or later performed trial registration. Such earlier registration prevents selective reporting and reduces publication bias, two important issues that may downgrade the level of evidence of a randomized clinical trial [54]. Some dental journals as J Dent, Oper Dent, and Braz Oral Res have added this indication as mandatory in their instructions for authors.

In regard to numbers analyzed, the number of participants per group in all analyzes should be clear. Reporting summary statistics without their spread over the mean or only percentages, relative risks, odds ratios is not enough as does not allow assessment of whether or not some of the randomly assigned participants were excluded from the analysis. The same should be applied to losses and exclusions. Along with the description of these figures per group, reasons for the losses and exclusions should be given as they may be related to the intervention. For instance, when a patient gives up the treatment because another disease is requiring his/her attention, this is unlikely to be related to the intervention; but if a patient does not attend the recalls because he/she wants to be withdrawn from the trial, the reason may be related to side effects or lack of efficacy of the treatments under evaluation.

Baseline information was adequately reported in only 34% of the papers and it is important to check comparability at baseline. Any differences in baseline characteristics are, however, the result of chance rather than bias; the reason of why there is no need to perform hypothesis testing for these characteristics [55].

For any item, when reporting data, authors should be careful. They should not display percentages instead of raw figures, as it is risky. Rounded percentages may be compatible with more than one numerator and if the authors fail to provide the total number of participants, the number of participants with the event under evaluation will be unclear. For instance, 90% may represent 1 out of 10 but also 100 out of 1000 – this makes a profound influence on the precision of the data. Merging data of groups can done as long as their individual data are also reported. Finally, summary statistics for continuous variables should be presented with their measure of spread; for dichotomous variables authors should describe the number of counts vs. total number of observations [22].

The trial design involves the description of type of the trial (parallel, cross-over, factorial, split-mouth and or multiple restorations); the conceptual framework (superiority, non-inferiority or equivalence trial) and also the allocation ratio (example 1:1 or 1:2) [20]. The settings (where and when the study was performed) are also essential to place the study in

historical context and to evaluate its external validity (generalization of the findings to other populations).

Risk of bias

Although incomplete outcome data and selective reporting were poorly described, this occurred in a few percentages of the studies. In all other domains of the Cochrane Collaboration risk of bias tool, most the RCTs were judged to be at "unclear" or at "high" risk of bias. The implications of inadequate sequence generation, allocation concealment and examiner blinding were already discussed in details.

At the study level, only 7.6% of the studies were considered to be at low risk of bias, which means being low risk of bias in all domains. The remaining studies were at unclear or high risk of bias. This is very worry since our treatment decisions are being based on studies that do not have a rigorous methodology and therefore they may lead to biased results.

Final remarks

Although CONSORT guidelines have been included in the instructions for authors of some journals, active compliance is far from being achieved. Perhaps, the inclusion of additional subheadings, as suggested by Kloukos et al. [29] might result in better compliance with the CONSORT Statement. The results of the present study indicate that adherence of RCTs of bleaching systems to the CONSORT Statement requires improvements. Adherence to the CONSORT Statement will also make readers to rethink their methodology and ultimately reduce the high risk of bias of studies in the field.

There are some limitations in the present study. Although a very comprehensive search in terms of different databases with specific vocabulary and keywords were performed, we may have missed some articles in the search.

However, looking at Table 4.6-4, the higher numbers of the papers were produced in USA and Brazil and the majority of them were published in English language journals. Only a few papers were published in Portuguese or Spanish (10 in total). Also, as mentioned in the results section, only one paper was excluded by language. These details make us to be confident in the results herein presented. Although other studies on the field may not be cited here they are unlikely to change the results herein presented.

Acknowledgments

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Table 4.6-1. Search strategy (07th February 2017.

PubMed

#1 ((((((((((((((((((((tooth discoloration[MeSH Terms]) OR dentition, permanent[MeSH Terms]) OR color[MeSH Terms]) OR color[Title/Abstract]) OR colour[Title/Abstract]) OR "tooth discoloration"[Title/Abstract]) OR "tooth discolouration"[Title/Abstract]) OR "teeth discoloration"[Title/Abstract]) OR "teeth discolouration"[Title/Abstract]) OR "discolored tooth"[Title/Abstract]) OR "discoloured tooth"[Title/Abstract]) OR "discolored teeth"[Title/Abstract]) OR "discoloured teeth"[Title/Abstract]) OR "dental discoloration"[Title/Abstract]) OR "dental discolouration"[Title/Abstract]) OR "tooth staining"[Title/Abstract]) OR "teeth staining"[Title/Abstract]) OR "stained tooth"[Title/Abstract]) OR "stained teeth"[Title/Abstract]) OR "dental staining"[Title/Abstract]

#2 ((((((((((((((((((tooth bleaching[MeSH Terms]) OR tooth bleaching agents[MeSH Terms]) OR peroxides[MeSH Terms]) OR hydrogen peroxide[MeSH Terms]) OR carbamide peroxide[Supplementary Concept]) OR peroxides[Title/Abstract]) OR "hydrogen peroxide"[Title/Abstract]) OR "carbamide peroxide"[Title/Abstract]) OR bleaching[Title/Abstract]) OR whitening[Title/Abstract]) OR "in office"[Title/Abstract]) OR "at home"[Title/Abstract]) OR "light activation"[Title/Abstract]) OR "light activated"[Title/Abstract]) OR "laser assisted"[Title/Abstract]) OR "dentist-supervised"[Title/Abstract]) OR nightguard[Title/Abstract]) OR "tray-delivered"[Title/Abstract]) OR "jump-start"[Title/Abstract]

#3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))

#1 AND #2 AND #3

Cochrane Library

#1 MeSH descriptor: [Tooth Discoloration] explode all trees
#2 MeSH descriptor: [Dentition, Permanent] explode all trees
#3 MeSH descriptor: [Color] explode all trees
#4 color:ti,ab,kw or t*th next discoloration:ti,ab,kw or discolored next t*th:ti,ab,kw or dental next discoloration:ti,ab,kw or t*th next staining:ti,ab,kw (Word variations have been searched)
#5 stained next t*th:ti,ab,kw or dental next staining:ti,ab,kw (Word variations have been searched)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Tooth Bleaching] explode all trees
#8 MeSH descriptor: [Tooth Bleaching Agents] explode all trees
#9 MeSH descriptor: [Peroxides] explode all trees
#10 MeSH descriptor: [Hydrogen Peroxide] explode all trees
#11"carbamide peroxide":ti,ab,kw or peroxides:ti,ab,kw or "hydrogen peroxide":ti,ab,kw or bleaching:ti,ab,kw or whitening:ti,ab,kw (Word variations have been searched)
#12 "in office":ti,ab,kw or "at home":ti,ab,kw or light next activat*:ti,ab,kw or laser next assisted:ti,ab,kw or dentist supervised:ti,ab,kw (Word variations have been searched)
#13 nightguard:ti,ab,kw or tray delivered:ti,ab,kw or jump start:ti,ab,kw (Word variations have been searched)
#14 #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 #6 AND #14

Lilacs and BBO

#1 (MH: "tooth discoloration" OR MH: "permanent dentition" OR MH:color OR color OR cor OR colour OR "tooth discoloration" OR "descoloração do dente" OR "decoloración del diente" OR "descoloración del diente" OR "tooth discolouration" OR "teeth discoloration" OR "descoloração dos dentes" OR "decoloración de los dientes" OR "descoloración de los dientes" OR "teeth discolouration" OR "discolored tooth" OR "dente descolorido" OR "discoloured tooth" OR "discolored teeth" OR "dentes

#2 (MH:"tooth bleaching" OR MH:"tooth bleaching agents" OR MH:peroxides OR MH:"hydrogen peroxide" OR peroxides OR peróxidos OR "hydrogen peroxide" OR "peróxido de hidrogênio" OR "carbamide peroxide" OR "peróxido de carbamida" OR bleaching OR branqueamento OR blanqueo OR whitening OR clareamento OR blanqueamiento OR clareamiento OR "in-office" OR "em consultório" OR "en ambulatorio" OR "at home" OR caseiro OR "casero" OR "light activation" OR

descoloridos" OR "diente pigmentado" OR "dientes pigmentados" OR "dentes pigmentados" OR "dente pigmentado" OR "discoloured teeth" OR "dental discoloration" OR "descoloração dental" OR "decoloración dental" OR "decoloración dentaria" OR "descoloración dental" OR "descoloración dentaria" OR "dental discolouration" OR "tooth staining" OR "manchamento dental" OR "tinción dental" OR "tinción dentaria" OR "pigmentación dental" OR "pigmentación dentaria" OR "teeth staining" OR "dentes manchados" OR "stained tooth" OR "dente manchado" OR "stained teeth" OR "mancha nos dentes" OR "mancha en los dientes" OR "dental staining" OR "mancha en lo diente" OR "mancha no dente")	fotoativação OR "activación por luz" OR "light activated" OR "ativado por luz" OR "activado por luz" OR "laser assisted" OR "a laser" OR "con láser" OR "dentist-supervised" OR "superviosionado por dentista" OR "supervisado por el dentista" OR nightguard OR "tray-delivered" OR moldeira OR cubeta OR "jump-start" OR associado OR combinado)
#1 AND #2	
Web of science	
#1 Tópico: ("t*th discolo*ration") OR Tópico: ("permanent dentition") OR Tópico: (colo$r) OR Tópico: ("discolo*red t*th") OR Tópico: ("dental discolo*ration") OR Tópico: ("t*th staining") OR Tópico: ("stained t*th") OR Tópico:("dental staining")	**#2** Tópico:("t*th bleaching") OR Tópico:(peroxides) OR Tópico: ("hydrogen peroxide") OR Tópico: ("carbamide peroxide") OR Tópico: (bleaching) ORTópico: (whitening) OR Tópico: ("in-office") OR Tópico: ("at home") ORTópico: ("light activat*") OR Tópico:("laser assisted") OR Tópico:("dentist-supervised") OR Tópico:(nightguard) OR Tópico: ("tray-delivered") OR Tópico: ("jump-start")
#1 AND #2	
Scopus	
#1 (TITLE-ABS-KEY ("t??th discoloration") OR TITLE-ABS-KEY ("permanent dentition") OR TITLE-ABS-KEY (colo*r) OR TITLE-ABS-KEY ("t??th discolouration") OR TITLE-ABS-KEY ("discolored t??th") OR TITLE-ABS-KEY ("discoloured t??th") OR TITLE-ABS-KEY ("dental discolo*ration") OR TITLE-ABS-KEY ("t??th staining") OR TITLE-ABS-KEY ("stained t??th") OR TITLE-ABS-KEY ("dental staining"))	**#2** (TITLE-ABS-KEY ("t??th bleaching") OR TITLE-ABS-KEY (peroxides) OR TITLE-ABS-KEY ("hydrogen peroxide") OR TITLE-ABS-KEY ("carbamide peroxide") OR TITLE-ABS-KEY (bleaching) OR TITLE-ABS-KEY (whitening) OR TITLE-ABS-KEY ("in office") OR TITLE-ABS-KEY ("at home") OR TITLE-ABS-KEY ("light activat*") OR TITLE-ABS-KEY ("laser assisted") OR TITLE-ABS-KEY ("dentist-supervised") OR TITLE-ABS-KEY (nightguard) OR TITLE-ABS-KEY ("tray-delivered") OR TITLE-ABS-KEY ("jump-start"))
#1 AND #2	

Table 4.6-2. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Parallel and Split-mouth RCTs published in 1996 or later • Different types of bleaching systems (in-office, at home and jump-start) (bleaching strips, gels, dentifrices, use of light) regarding. • Studies that evaluate color change, toxicity, postoperative sensitivity and application technique • The studies included patients of any age group	• Laboratory studies • Conference abstracts • Thesis • Reports published in any media other than peer-reviewed journals • Reported cases

Table 4.6-3. Instrument tool developed from the 2010 CONSORT Statement to evaluate the compliance of the studies to the CONSORT Statement.

			ADHERENCE TO THE METHODS AND RESULTS ITEMS OF THE CONSORT STATEMENT
CONSORT item	**SUB-ITEM**	**SCORE**	**DESCRIPTION**
Trial design		Positive [2]	The trial design is clearly written in the text (split mouth, cross-over, factorial, cluster).
		Negative [0]	This information is not reported.
		Poor [1]	1. Information can be obtained during reading the manuscript, although this is not explicity reported by the authors. 2. There is lack of consistence between sections of the article (examples - abstract does not match the material and methods section; the presentation of the results does not match the description of the trial design; flow diagram presents different information, etc.).
Participants	**Eligibility criteria**	Positive [2]	The inclusion and exclusion criteria is clear, so that readers can know exactly which population the data can be extrapolated to.
		Negative [0]	The information is not reported.
		Poor [1]	1. Incomplete information of eligibility criteria compared to most of the studies on the field. 2. Presence of inconsistencies in the inclusion/exclusion criteria that prevents the readers from knowing the population at which the intervention/control groups were performed.
	Settings and location	Positive [2]	Clear description of the setting (academic, practice-based research, university, private clinics, etc.) as well as the date at which the intervention was implemented.
		Negative [0]	The setting and/or the location is not reported in the text.
		Poor [1]	1. Authors describe either the setting or the date but never both. 2. This information can be obtained indirectly in the text
Interventions		Positive [2]	The interventions for each group are described with sufficient details to allow replication, including how they were actually administered.
		Negative [0]	There is no description.
		Poor [1]	There are missing information that prevents the replication of the interventions/comparators.
Outcomes		Positive [2]	At least the primary outcomes were defined in details, including how and when they were assessed. Consider it as clear when the details are clear, but the authors did not use the term "primary outcome" or related synonyms.
		Negative [0]	There is no definition of the primary outcome and/or secondary outcomes.
		Poor [1]	1. The authors only report they have used a specific criteria without detailing the most important outcomes of such criteria. 2. The

			description of the primary outcome and/or secondary outcomes is very superficial and does not allow replication of the method.
Sample size		Positive [2]	Method of sample size calculation is described in a way to allow replication. It should be identified the primary outcome for each the sample size was calculated for. Elements of the sample size calculation are (1) the estimated outcomes in each group (which implies the clinically important target difference between the intervention groups); (2) the α (type I) error level; (3) the statistical power (or the β (type II) error level); and (4), for continuous outcomes, the standard deviation of the measurements should be reported. For equivalence trials, the equivalence limit, instead of the effect size should be reported.
		Negative [0]	There is no description in the article.
		Poor [1]	The sample size is described but some parameters are missing so that it prevents replication.
Randomization	**Sequence generation**	Positive [2]	1. Clear description of the random sequence generation. 2. or clear description of a non-random sequence method.
		Negative [0]	There is no information in the text.
		Poor [1]	The authors only provide a very superficial description (such as the "groups were randomly allocated") or do not provide sufficient information to allow replication of the randomization process.
	Allocation concealment	Positive [2]	Clear description of the allocation concealment. See next columns for evaluation of the Risk of Bias.
		Negative [0]	There is no information in the text.
		Poor [1]	not applicable
Blinding		Positive [2]	1) The authors describe who is blinded in the study. 2. In single-blind studies (when this is clearly reported by the authors), just the description of participant or evaluator (the one blinded) is enough; however when the study is double blind or triple blind all blinded people should be described. 2) The study describes just the participant or examiner blinded but one of these people cannot be blinded by intrinsic features of the study design.
		Negative [0]	There is no description of the blinding.
		Poor [1]	Insufficient/partial information. For instance, (1) the authors describe examiners' blinding or participants' blinding, but never both. (2) The authors describe the study was blind or double-blind but does not specify who was blinded.
Statistical methods	**Hypothesis testing**	Positive [2]	Statistical methods are described with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Additionally, statistical tests employed by the authors seem to be adequate for the type of trial design and nature of the data collected.

		Negative [0]	Statistical methods are not described.
		Poor [1]	1) There is not enough information to evaluate the statistical method used by the authors and/or the type of statistical tests employed by the authors are inadequate for the trial design and/or nature of the data (for instance, tests that do not take into account the paired nature of the data when this is the case). 2) The authors describe several statistical tests but does not specify for each outcome they were applied.
	Estimated effect size	Positive [2]	Authors report at least for the primary outcome the effect size and its precision (such as 95% confidence interval). Odds ratio, risk ratio, risk difference, mean difference, etc.
		Negative [0]	There is no description of the effect size and 95% confidence interval
		Poor [1]	There is incomplete information.
Participant flow	**Flow diagram**	Positive [2]	For each group, the numbers of participants who were randomly assigned, received intended treatment and were analyzed for the primary outcome is described in the flow chart CONSORT diagram.
		Negative [0]	The flow-chart is not presented in the article.
		Poor [1]	1. There are inconsistencies between the numbers described in the flow-chart and other parts of the manuscript. 2. Incomplete diagram with missing information
	Losses/Exclusions	Positive [2]	1. For each group, losses and exclusions after randomization are described with reasons. 2. During reading, reviewer observes that there is no loss to follow-up.
		Negative [0]	1. There is no description of losses and exclusions.
		Poor [1]	Incomplete information. For instance, 1. the authors describe the overall percentage of losses but this information is not specified per group. 2. The authors describe the losses and exclusions but does not specify the reasons
Baseline data		Positive [2]	A table/text description containing baseline demographic and clinical characteristics of each group are presented in the article.
		Negative [0]	There is no table/text description with baseline data or description in the body of the text.
		Poor [1]	1. A table/ text description with baseline data is presented but the data is not distributed between the study groups and/or given in percentages instead of raw numbers. 2. Insufficient information about participants is provided; 3. Inconsistencies in the data presented can be observed.
Numbers analysed		Positive [2]	For each group and for each outcome, the number or participants (denominator) included in the analysis are clear.
		Negative [0]	Authors do not report the numbers analyzed.

	Poor [1]	There is no clear description of the number of participants (denominator) included in the analysis of at least one of the outcomes. 2. Instead of reporting the raw number of participants, the authors report their data in percentages. 3. The authors fail to report the baseline number of patients included in each analysis. 4. Data can be obtained indirectly in the study.
Registration and protocol	Positive [2]	The study was registered in a trial registry and the protocol number is provided.
	Negative [0]	This information is not available in the manuscript. Registration in an Ethics Committee is valid as trial registry
	Poor [1]	The authors describe that the study was registered but does not provide the registration number and/or the number provided does not link to the study.

Table 4.6-4. Characteristics of the included studies by categories.

Characteristics	Categories	Number of studies	Percentage (%)
Journal	Clin Oral Investig	5	2.7
	J Clin Dent	10	5.4
	J Esthet Restor Dent	11	5.9
	J Dent	12	6.5
	JADA	12	6.5
	Quintessence Int	13	7.0
	Am J Dent	14	7.6
	Comp Cont Educ Dent	21	11.4
	Oper Dent	33	17.8
	Others*	54	29.2
Country	UK	6	3.2
	Italy	7	3.8
	Germany	14	7.6
	Brazil	52	28.1
	USA	75	40.5
	Others**	31	16.8
Period of time	1996 to 2000	17	9.2
	2001 to 2005	48	25.9
	2006 to 2010	52	28.1
	2011 to 2016	68	36.8
Follow-up period (days)	0	5	2.7
	7	12	6.5
	14	42	22.7
	21	10	5.4
	28	19	10.3
	30	6	3.2
	42	5	2.7
	168	12	6.5
	Others***	74	40.0

* Representing 37 different journals.

** Representing 18 different countries.

*** Representing 33 different follow-up period (days).

Table 4.6-5. Examples of adequate description of the evaluate parameters of the Instrument tool developed from the 2010 CONSORT Statement for bleaching studies.

Item		Examples
Trial design		Example 1: "This study was a randomized, single-blind, controlled trial with a parallel group and an allocation rate of 1:1."[56] Example 2: "This was a randomized, parallel, placebo-controlled, triple-masked clinical trial, in which the patient, operator, and evaluator were masked to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the randomization process, and delivery and guidance on the administration of the drugs."[57]
Participants	Eligibility criteria	The authors judged that it was not necessary to add some examples, because this item showed an adequate reporting as seen in Figure 4.6-2.
	Settings and locations	Example 1: "The study took place in the clinics of the dentistry schools at the State University of Ponta Grossa, Paraná, and the University of São Paulo, São Paulo, from June 2010 to June 2012."[58] Example 2: "This study was performed from February 2011 to March 2012 in the city of Guarapuava (Paraná, Brazil)."[12]
Interventions		The authors judged that it was not necessary to add some examples, because this item showed an adequate reporting as seen in Figure 4.6-2.
Outcomes		The authors judged that it was not necessary to add some examples, because this item showed an adequate reporting as seen in Figure 4.6-2.
Sample size	For Tooth sensitivity	For superiority trial: "The primary outcome of this study was the absolute risk of TS. The absolute risk of TS (that is, the number of patients [percent] who reported pain at some point during dental bleaching) was reported to be approximately 87% (4,8) for the bleaching product Whiteness HP Maxx (FGM Dental Products). Thus, a minimum sample size of 56 participants was required to have a 90% chance of detecting, as significant at the 2-sided 5% level, a decrease in the primary outcome measure from 86% in the control group to 50% in the experimental group."[57] For equivalent trial: We selected the absolute risk of TS as the primary study outcome. Considering the absolute risk of TS to be approximately 90% (19, 40) participants were required to be 90% (study power) sure that the limits of a two-sided 90% confidence interval will exclude a difference between the standard and experimental group of more than 30% (equivalence limit)."[59]
	For Color evaluation	For superiority trial: "The primary outcome of this study was color change of the participants' teeth. A previous study (34) reported that two bleaching sessions with the product Whiteness HP Maxx 35% (FGM Dental Products, Joinville, SC, Brazil) without light activation produced a whitening effect of about 7 ± 2 SGUs. To detect a difference of 2 SGUs between the means of any pair of the study groups, with a power of 80% and an alpha of 5%, a minimum sample size of 17 patients per group was required. This threshold of perceptibility was based on the fact that ''untrained'' people, such as the patients, do not detect easily changes of one shade guide unit at the lighter end of the vita classical guide."[58] For equivalent trial: We based the sample size calculation on the color change measured with the spectrophotometer (ΔE*), the primary outcome of the study. One hundred eighteen participants were required to exclude a difference of means of 2.0 units of ΔE* at 1 week and 1 month (equivalence limit) with a power of 90 % and α of 5 %. With these calculations, we took into consideration a standard deviation of 3.3 in the ΔE*. The equivalence limit we chose was lower than the ΔE threshold of 3.0, above which color differences become clinically perceptible (24-26)."[60]

Randomisation	Sequence generation, allocation concealment and implementation	Example 1: “The randomization process was performed by coin toss immediately before the bleaching procedure to provide adequate allocation concealment.”[61] Example 2: “Participants were randomly divided into four groups according to the combination of the main factors: HP (20% or 35%) and light activation (with or without). A third person who was not involved in the research protocol performed the randomization procedure by using computer-generated tables. We used blocked randomization (block sizes of 2 and 4) with an equal allocation ratio (*www.sealedenvelope.com*). Opaque and sealed envelopes containing the identification of the groups were prepared by a third party not involved in the study intervention.”[58]
Blinding		Example 1: “The participant and the operator could not be blinded to the procedure, as the application of bleaching gel for different times could not be masked. However, the examiners who evaluated the color changes were not aware of which group the participant was assigned to.”[62] Example 2: “Neither the participant nor the operator knew the group allocation, both being blinded to the protocol.” “The two examiners, blinded to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at baseline and 30 days after the procedure.”[63]
Statistical methods	Hypothesis testing	The authors judged that it was not necessary to add some examples, because this item showed an adequate reporting as seen in Figure 4.6-2.
	Estimated effect size	Two examples of how to report an effect size can be seen in Tables 6 and 7.
Participants	Flow diagram	Please see the following link to have access templates of the CONSORT flow diagram available in MS Word (http://www.consort-statement.org/consort-statement/flow-diagram)
	Losses and exclusions	The authors judged that it was not necessary to add some examples, because this item showed an adequate reporting as seen in Figure 4.6-2.
Baseline data		Two examples of how to report an effect size can be seen in Tables 8 and 9.
Numbers analysed		The authors judged that it was not necessary to add some examples, because this item showed an adequate reporting as seen in Figure 4.6-2.
Registration and protocol		Example 1: “The ClinicalTrials.gov identification number was NCT02017873.”[4] 'Example 2: “The clinical investigation was approved (protocol number 172.988) by the scientific review committee and by the committee for the protection of human participants of the local university. It was registered in the Brazilian clinical trials registry under the identification number RBR-6pt2n3.”[57]

Table 4.6-6. Means (standard deviations) of the change in shade guide units obtained with the VITA Classical and VITA Bleachedguide*

Color evaluation tools	Groups		P value	Mean difference (95% confidence interval)
	Placebo	Dexamethasone		
Vita Classical	3.1 ± 2.6	3.4 ± 2.3	0.642	- 0.3 (-9.9 to 10.5)
Dexamethasone	2.8 ± 2.2	2.7 ± 1.6	0.775	- 0.6 (-9.4 to 10.6)
p-value	6.0 ± 4.7	6.6 ± 4.0	0.582	- 0.6 (-11.4 to 12.6)

Adapted from Rezende et al., JADA [57].

Table 4.6-7. Absolute risk of tooth sensitivity, along with the risk ratio, for both groups at the different assessment points.

Periods	Group	Number of patients with TS		Absolute risk (95% CI)	Risk ratio (95% CI)	p-value*
		Yes	No			
During in-office session	HP35%	17	3	85.0 (64.0-95.0)	1.8 (1.1 – 3.2)	0.02
	HP20%	7	8	47.0 (25.0-69.0)		
Up to 48 h after in-office session	HP35%	13	7	65.0 (43.2-81.9)	2.0 (0.9 –4.3)	0.09
	HP20%	5	10	33.3 (15.2-58.3)		
During at-home bleaching	HP35%	5	15	25.0 (11.2-46.9)	1.3 (0.5 –3.8)	0.71
	HP20%	5	10	33.3 (15.2-58.3)		

* Fisher's exact test; TS – tooth sensitivity; CI – confidence interval.

Adapted from Rezende et al., Oper Dent 2016 [61]

Table 4.6-8. Baseline characteristics of the participants.

Characteristics	Smokers	Non-smokers
Age (years; mean ± SD)		
Brazil	26.3 ± 6.5	24.1 ± 6.8
Chile	29.3 ± 9.4	25.5 ± 6.6
Male (%)		
Brazil	46.7	53.3
Chile	63.3	36.7
Baseline color (L*; mean ± SD)		
Brazil	82.4 ± 4.9	82.3 ± 4.3
Chile	83.2 ± 4.0	84.9 ± 3.8
Baseline color (b*; mean ± SD)		
Brazil	22.6 ± 3.6	23.2 ± 3.6
Chile	22.2 ± 3.1	21.7 ± 2.5
Baseline color (a*; mean ± SD)		
Brazil	-1.0 ± 1.0	-0.5 ± 1.0
Chile	-0.0 ± 0.7	-0.2 ± 0.6
Baseline color (SGU; mean ± SD)		
Brazil	6.8 ± 2.3	7.4 ± 2.5
Chile	7.2 ± 1.7	8.4 ± 2.9
Smoking time (years; mean ± SD)		
Brazil	8 ± 5.9	--
Chile	11.8 ± 9.1	--
Number cigarettes/day (mean ± SD)		
Brazil	13.2 ± 4.0	--
Chile	12.8 ± 3.8	--

SD; L* = luminosity; b* = Color along the yellow-blue axis; a* = Color along the red-gree axis. Adapted from de Geus et al., JADA [64].

Table 4.6-9. Demographic features of the participants of each study group.

Feature	**20%**	**20% + light**	**35%**	**35% + light**
Age (mean ± SD)	22.9 ± 4.0	22.0 ± 4.4	23.0 ± 3.4	22.0 ± 3.6
Female (n, %)	13 (68)	12 (63)	13 (68)	12 (60)
Baseline SGU (median, 25 and 75 percentil)	12 (11 – 14)	12 (11 – 12)	12 (10,5 – 15)	11 (9 – 12)

Adapted from Mena-Serrano et al., Oper Dent [58].

Table 4.6-10. Means (standard deviations) of the change in shade guide units obtained with the VITA Classical and VITA Bleachedguide*

Color evaluation tools	Groups		P value	Mean difference (95% confidence interval)
	Placebo	Dexamethasone		
Vita Classical	3.1 ± 2.6	3.4 ± 2.3	0.642	- 0.3 (-9.9 to 10.5)
Dexamethasone	2.8 ± 2.2	2.7 ± 1.6	0.775	- 0.6 (-9.4 to 10.6)
p-value	6.0 ± 4.7	6.6 ± 4.0	0.582	- 0.6 (-11.4 to 12.6)

Adapted from Rezende et al., JADA [57].

Table 4.6-11. Absolute risk of tooth sensitivity, along with the risk ratio, for both groups at the different assessment points.

Periods	Group	Number of patients with TS		Absolute risk (95% CI)	Risk ratio (95% CI)	p-value*
		Yes	No			
During in-office session	HP35%	17	3	85.0 (64.0-95.0)	1.8 (1.1 – 3.2)	0.02
	HP20%	7	8	47.0 (25.0-69.0)		
Up to 48 h after in-office session	HP35%	13	7	65.0 (43.2-81.9)	2.0 (0.9 –4.3)	0.09
	HP20%	5	10	33.3 (15.2-58.3)		
During at-home bleaching	HP35%	5	15	25.0 (11.2-46.9)	1.3 (0.5 –3.8)	0.71
	HP20%	5	10	33.3 (15.2-58.3)		

* Fisher's exact test; TS – tooth sensitivity; CI – confidence interval.

Adapted from Rezende et al., Oper Dent 2016 [61].

Table 4.6-12. Average CONSORT score per journal, country and period of time.

Characteristics	Categories	Mean ± SD	Median (interquartile range)	p-value*
Journal	Clin Oral Investig	19.60 ± 6.58 A	18 (18 to 22)	< 0.0001
	J Clin Dent	16.30 ± 1.42 A,B	16 (15 to 17)	
	J Esthet Restor Dent	15.27 ± 3.04 A,B	14 (13 to 17.5)	
	J Dent	21.75 ± 6.50 A	20 (17.5 to 28.25)	
	JADA	19.33 ± 5.28 A	19.5 (13 to 22.5)	
	Quintessence Int	15.54 ± 4.33 A,B	14 (13 to 16)	
	Am J Dent	18.36 ± 4.22 A,B	18.5 (16.25 to 19.75)	
	Comp Cont Educ Dent	15.24 ± 3.06 A,B	15 (13 to 18)	
	Oper Dent	19.94 ± 6.32 A	18 (15 to 25)	
	Others	13.80 ± 4.99 B	13 (11 to 16)	
Country	UK	14.83 ± 2.99 B	15 (12.5 to 17.5)	0.02
	Italy	14.29 ± 6.80 B	13 (9.5 to 19)	
	Germany	16.71 ± 4.05 A,B	17 (14.25 to 18)	
	Brazil	19.48 ± 6.93 A	20.5 (13.75 to 25)	
	USA	15.25 ± 3.13 B	15 (13.5 to 18)	
	Others	16.10 ± 4.99 A,B	14.5 (12.25 to 18)	
Period of time	1996 to 2000	13.47 ± 4.03 B	14 (11 to 16)	0.004
	2001 to 2005	15.54 ± 2.81 A,B	16 (14 to 18)	
	2006 to 2010	15.75 ± 4.01 A,B	15 (13 to 19)	
	2011 to 2016	19.03 ± 6.87 A	18 (13.75 to 25)	

* Kruskall Wallis and Mann-Whitney tests.

Table 4.6-13. List of the scored papers along with their average CONSORT score and evaluation of the risk of bias in each domain.

Study identification	Year	Journal	Average CONSORT score	RISK OF BIAS TOOL				
				random sequence	allocation concealment	participant blinding	examiner blinding	incomplete outco data
Acosta Gómez et al.[34]	1999	Univ Odontol	11	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Al Shethri et al.[65]	2003	Oper Dent	18	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Almeida et al.[66]	2012	Int J Periodontics Restorative Dent	16	UNCLEAR	UNCLEAR	HIGH	HIGH	LOW
Alomari, El Daraa[67]	2010	J Contemp Dent Pract	13	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Alonso de la Peña, Balboa Cabrita[68]	2006	Quintessence Int	14	UNCLEAR	HIGH	HIGH	HIGH	HIGH
Alonso de la Peña, Lopez Ranton[69]	2014	Oper Dent	18	LOW	UNCLEAR	HIGH	HIGH	LOW
Auschill et al.[70]	2005	Oper Dent	18	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Auschill et al.[71]	2012	Quintessence Int	26	LOW	LOW	UNCLEAR	LOW	LOW
Barlow et al.[72]	2009	Int J Dent	21	LOW	UNCLEAR	UNCLEAR	LOW	LOW
Barnes et al.[73]	1998	Comp Cont Educ Dent	15	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Basting et al.[74]	2012	Oper Dent	21	LOW	LOW	UNCLEAR	LOW	LOW
Berga-Caballero et al.[75]	2006	Med Oral Patol Oral Cir Bucal	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Bernardon et al.[76]	2010	Oper Dent	16	LOW	UNCLEAR	UNCLEAR	LOW	LOW
Bernardon et al.[77]	2015	J Prosthet Dent	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Bernardon et al.[78]	2016	J Prosthet Dent	10	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Bizhang et al.[79]	2007	Am J Dent	20	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	LOW
Bizhang et al.[80]	2009	Oper Dent	18	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Bonafé et al.[81]	2014	Clin Oral Investig	22	LOW	UNCLEAR	LOW	LOW	LOW
Bortolatto et al.[82]	2016	Lasers Med Sci	26	LOW	LOW	LOW	LOW	LOW
Braun et al.[83]	2007	Dent Mater	15	HIGH	UNCLEAR	LOW	LOW	LOW

Browning et al.[84]	2012	J Esthet Restor Dent	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Browning et al.[85]	2004	Oper Dent	13	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Bruhn et al.[86]	2012	Int J Dent Hyg	16	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Callan et al.[87]	2008	Am J Dent	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Cardoso et al.[88]	2011	JADA	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Carvalho et al.[89]	2005	Rev Assoc Paul Cir Dent	6	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Cerqueira et al.[90]	2013	Rev Assoc Paul Cir Dent	19	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Cibirka et al.[91]	1999	J Esthet Dent	15	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Collins et al.[92]	2004	J Dent	19	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR
Corbella et al.[93]	2009	Dent Cadmos	8	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Cronin et al.[94]	2005	Comp Cont Educ Dent	16	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR
da Costa et al.[95]	2010	Oper Dent	19	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW
da Costa et al.[96]	2011	J Esthet Restor Dent	22	LOW	LOW	UNCLEAR	LOW	LOW
Dawson et al.[97]	2011	Oper Dent	19	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
de Almeida et al.[98]	2014	Photomed Laser Surg	20	UNCLEAR	UNCLER	LOW	LOW	LOW
de Freitas et al.[99]	2016	Quintessence Int	17	LOW	UNCLEAR	UNCLEAR	LOW	UNCLEAR
de Geus et al.[100]	2015	JADA	29	LOW	LOW	UNCLEAR	LOW	LOW
de Geus et al.[4]	2015	J Dent	28	LOW	LOW	UNCLEAR	UNCLEAR	LOW
de Geus et al.[64]	2015	Oper Dent	25	LOW	LOW	LOW	LOW	LOW
de Paula et al.[63]	2013	Clin Oral Invest	29	LOW	LOW	LOW	LOW	LOW
de Paula et al.[59]	2015	J Dent	29	LOW	LOW	UNCLEAR	LOW	LOW
de Paula et al.[12]	2014	Oper Dent	30	LOW	LOW	LOW	LOW	LOW
Delgado et al.[101]	2007	P R Health Sci J	16	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Deliperi et al.[102]	2004	JADA	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Donly et al.[103]	2002	Comp Cont Educ Dent	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Donly et al.[104]	2005	Pediatr Dent	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Donly et al.[105]	2006	Gen Dent	15	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR

Donly et al.[106]	2007	Gen Dent	21	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Donly et al.[107]	2010	Am J Dent	19	HIGH	UNCLEAR	UNCLEAR	LOW	LOW
Farrel et al.[108]	2006	J Clin Dent	18	HIGH	UNCLEAR	LOW	LOW	LOW
Fernandez et al.[109]	2016	Oper Dent	30	LOW	LOW	LOW	LOW	LOW
Ferrari et al.[110]	2004	Am J Dent	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Gallagher et al.[111]	2002	J Clin Dent	15	UNCLEAR	UNCLEAR	HIGH	LOW	LOW
Gallo et al.[112]	2009	Quintessence Int	14	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Garcia-Godoy et al.[113]	2004	Comp Cont Educ Dent	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Gerlach et al.[114]	2000	Comp Cont Educ Dent	20	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Gerlach et al.[115]	2001	Am J Dent	18	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Gerlach et al.[116]	2002	Comp Cont Educ Dent	16	HIGH	UNCLEAR	LOW	LOW	LOW
Gerlach et al.[117]	2004	J Clin Dent	15	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Gerlach et al.[118]	2005	Comp Cont Educ Dent	15	HIGH	UNCLEAR	LOW	LOW	LOW
Gerlach, Barker[119]	2003	Am J Dent	20	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Gerlach, Sagel[120]	2004	JADA	15	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Gerlach et al.[121]	2002	Am J Dent	20	HIGH	UNCLEAR	UNCLEAR	LOW	LOW
Gerlach, Zhou[121]	2004	Comp Cont Educ Dent	20	HIGH	UNCLEAR	UNCLEAR	LOW	LOW
Giachetti et al.[122]	2010	JADA	23	LOW	LOW	UNCLEAR	UNCLEAR	LOW
Giniger et al.[123]	2005	J Clin Dent	15	HIGH	UNCLEAR	UNCLEAR	LOW	LOW
Giniger et al.[124]	2005	JADA	21	HIGH	UNCLEAR	LOW	LOW	LOW
Gomes et al.[13]	2008	R Dent Press Estet	10	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Goodson et al.[125]	2005	J Clin Dent	11	LOW	UNCLEAR	LOW	LOW	UNCLEAR
Grobler et al.[126]	2011	Int J Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Guênes et al.[127]	2015	RFO UPF		UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Guerrero et al.[128]	2007	Am J Dent	20	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Gurgan et al.[129]	2010	Lasers Med Sci	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Hanning et al.[130]	2007	Clin Oral Investig	18	UNCLEAR	UNCLEAR	LOW	LOW	LOW

Henry et al.[131]	2013	Int J Dent Hyg	18	UNCLEAR	UNCLEAR	LOW	HIGH	LOW
Hyland et al.[132]	2015	Clin Oral Investig	11	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Ishikawa-Nagai et al.[133]	2004	J Esthet Restor Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Jadad et al.[134]	2011	Am J Orthod Dentofacial Orthop	9	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Javaheri, Janis[135]	2000	Oper Dent	6	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Karpina et al.[136]	2002	Am J Dent	14	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Karpina et al.[137]	2003	J Prosthodont	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Kihn et al.[138]	2000	JADA	17	HIGH	UNCLEAR	LOW	LOW	LOW
Kihn et al.[139]	2002	Comp Cont Educ Dent	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Knosel et al.[140]	2007	Angle Orthod	10	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Knosel et al.[141]	2008	Quintessence Int	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Kose et al.[142]	2011	Am J Dent	20	LOW	UNCLEAR	LOW	LOW	LOW
Kose et al.[62]	2016	Oper Dent	28	LOW	LOW	LOW	LOW	LOW
Kossatz et al.[143]	2011	Oper Dent	17	LOW	UNCLEAR	LOW	LOW	LOW
Kossatz et al.[144]	2012	JADA	25	LOW	UNCLEAR	LOW	LOW	LOW
Kozlovsky et al.[145]	1996	Oral Health	10	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH
Krause et al.[146]	2008	Quintessence Int	13	HIGH	UNCLEAR	LOW	LOW	UNCLEAR
Kugel et al.[147]	2002	Comp Cont Educ Dent	11	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Kugel et al.[148]	2006	Comp Cont Educ Dent	12	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Kugel et al.[149]	2004	Comp Cont Educ Dent	19	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Kugel et al.[150]	2009	J Esthet Restor Dent	19	HIGH	UNCLEAR	LOW	LOW	LOW
Kugel, Kastali[151]	2000	Comp Cont Educ Dent	18	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Leonard et al.[152]	1999	J Esthet Restor Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Leonard et al.[153]	2001	J Esthet Restor Dent	18	HIGH	UNCLEAR	LOW	UNCLEAR	LOW
Leonard et al.[154]	2004	J Esthet Restor Dent	12	UNCLEAR	UNCLEAR	HIGH	LOW	UNCLEAR

Lewgoy et al.[155]	2011	Rev ABO Nac	6	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Li et al.[156]	2003	Comp Cont Educ Dent	18	HIGH	UNCLEAR	LOW	LOW	LOW
Li et al.[156]	2004	J Clin Dent	16	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Lo et al.[157]	2007	Am J Dent	21	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Lo Giudice et al.[158]	2016	Open Dent J	6	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Loguercio et al.[159]	2015	Braz Oral Res	30	LOW	LOW	LOW	LOW	LOW
Loyola-Rodriguez et al.[160]	2003	J Clin Pediatr Dent	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Luo et al.[161]	2007	J Dent	16	HIGH	UNCLEAR	UNCLEAR	LOW	LOW
Machado et al.[162]	2013	Quintessence Int	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Machado et al.[163]	2016	Int J Periodontics Restorative Dent	16	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Maghaireh et al.[164]	2014	Oper Dent	16	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Marson et al.[165]	2008	Oper Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Martín et al.[166]	2015	J Dent	30	LOW	UNCLEAR	LOW	LOW	LOW
Martins et al.[167]	2011	Rev Assoc Paul Cir Dent	12	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Matis et al.[168]	1998	Quintessence Int	15	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Matis et al.[169]	2000	Quintessence Int	17	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Matis et al.[170]	2002	Oper Dent	17	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Matis et al.[171]	2002	Quintessence Int	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Matis et al.[172]	2005	Oper Dent	15	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Matis et al.[173]	2006	Oper Dent	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Matis et al.[174]	2007	Oper Dent	11	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Matis et al.[175]	2009	Oper Dent	15	LOW	UNCLEAR	LOW	LOW	LOW
Medeiros, de Lima[176]	2008	J Can Dent Assoc	17	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Mehta et al.[177]	2013	Eur J Oral Sci	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Meireles et al.[178]	2008	J Dent	22	LOW	UNCLEAR	LOW	LOW	LOW

Meireles et al.[179]	2008	Oper Dent	21	LOW	UNCLEAR	LOW	LOW	LOW
Meireles et al.[180]	2009	JADA	21	LOW	UNCLEAR	LOW	LOW	LOW
Meireles et al.[181]	2010	J Dent	21	LOW	UNCLEAR	LOW	LOW	LOW
Meireles et al.[182]	2014	J Dent	22	LOW	UNCLEAR	LOW	LOW	LOW
Mena Serrano et al.[58]	2016	Oper Dent	30	LOW	LOW	LOW	LOW	LOW
Miller et al.[183]	2000	Pract Proced Aesthet Dent	4	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Moghadam et al.[184]	2013	Eur J Dent	20	LOW	UNCLEAR	LOW	LOW	LOW
Mohan et al.[185]	2008	J Dent	19	HIGH	UNCLEAR	LOW	LOW	LOW
Mokhlis et al.[186]	2000	JADA	16	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Mondelli et al.[187]	2012	J Appl Oral Sci	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Montenegro-Arana et al.[188]	2016	Oper Dent	25	LOW	LOW	LOW	UN	LOW
Morgan et al.[189]	2015	Br Dent J	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Myers et al.[190]	2003	J Esthet Restor Dent	14	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Nathoo et al.[191]	2001	Comp Cont Educ Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Nathoo et al.[192]	2003	J Clin Dent	17	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Navarra et al.[193]	2014	Int J Dent Hyg	11	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR
Nutter et al.[194]	2013	J Dent	14	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Ontiveros, Paravina[195]	2009	J Dent	13	LOW	UNCLEAR	LOW	LOW	LOW
Palé et al.[196]	2014	Odontology	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Paphatanasiou et al.[197]	2001	Comp Cont Educ Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Paphatanasiou et al.[198]	2002	Comp Cont Educ Dent	17	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Perry et al.[199]	2013	Comp Cont Educ Dent	9	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH
Polydorou et al.[200]	2013	Oper Dent	15	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Posso Moreno et al.[201]	2010	Univ Odontol	15	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Reis et al.[202]	2011	Oper Dent	24	LOW	LOW	LOW	LOW	LOW
Reis et al.[203]	2011	Oper Dent	24	LOW	LOW	LOW	LOW	LOW

Reis et al.[204]	2013	Oper Dent	31	LOW	LOW	LOW	LOW	LOW
Rezende et al.[205]	2014	Rev Assoc Paul Cir Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Rezende et al.[206]	2013	Oper Dent	23	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Rezende et al.[207]	2016	Oper Dent	25	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Rezende et al.[61]	2016	Oper Dent	30	LOW	LOW	LOW	LOW	LOW
Rosenstiel et al.[208]	1996	Quintessence Int	11	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Santana et al.[209]	2014	Braz Dent Journal	24	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Shahidi et al.[210]	2005	J Clin Dent	17	HIGH	UNCLEAR	LOW	LOW	LOW
Shanbhag et al.[211]	2013	J Contemp Dent Pract	14	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Sielski et al.[212]	2003	Comp Cont Educ Dent	18	HIGH	UNCLEAR	LOW	LOW	LOW
Silva et al.[213]	2012	Rev Odontol Bras Central	10	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH
Simon et al.[214]	2014	J Clin Dent	16	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Soares et al.[215]	2006	Rev Odont UNESP	8	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH
Strobl et al.[216]	2010	Lasers Med Sci	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Sundfeld et al.[217]	2015	Indian J Dent Res	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Swift et al.[218]	1997	J Esthet Restor Dent	15	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Swift et al.[219]	1999	J Esthet Restor Dent	14	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Swift et al.[220]	2004	Comp Cont Educ Dent	18	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW
Swift et al.[221]	2009	J Dent	19	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Tavares et al.[222]	2003	JADA	19	LOW	UNCLEAR	LOW	LOW	LOW
Tay et al.[6]	2009	JADA	24	LOW	LOW	LOW	LOW	LOW
Tay et al.[223]	2012	Am J Dent	29	LOW	LOW	LOW	LOW	LOW
Tsubura[224]	2010	Odontology	10	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Tsubura ,Yamaguchi[225]	2005	Odontology	12	UNCLEAR	UNCLEAR	UNCLEAR	LOW	HIGH
Türkün et al.[226]	2010	J Esthet Restor Dent	12	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH
Vano et al.[227]	2015	Int J Dent Hyg	24	UNCLEAR	LOW	UNCLEAR	LOW	LOW

Ward, Felix[228]	2012	Comp Cont Educ Dent	13	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Wetter et al.[229]	2009	Lasers Med Sci	14	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Xu et al.[230]	2007	Am J Dent	17	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Yudhira et al.[231]	2007	Am J Dent	22	HIGH	LOW	LOW	LOW	LOW
Zantner et al.[232]	2006	Quintessence Int	23	LOW	UNCLEAR	LOW	LOW	LOW
Zekonis et al.[233]	2003	Oper Dent	18	LOW	UNCLEAR	UNCLEAR	LOW	LOW
Zhao et al.[234]	2013	Quintessence Int	15	LOW	LOW	UNCLEAR	UNCLEAR	LOW
Ziebolz et al.[235]	2007	Clin Oral Investig	18	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	LOW
Ziemba et al.[236]	2005	J Clin Dent	19	LOW	LOW	UNCLEAR	UNCLEAR	LOW

Figure 4.6-1. PRISMA Flow chart diagram.

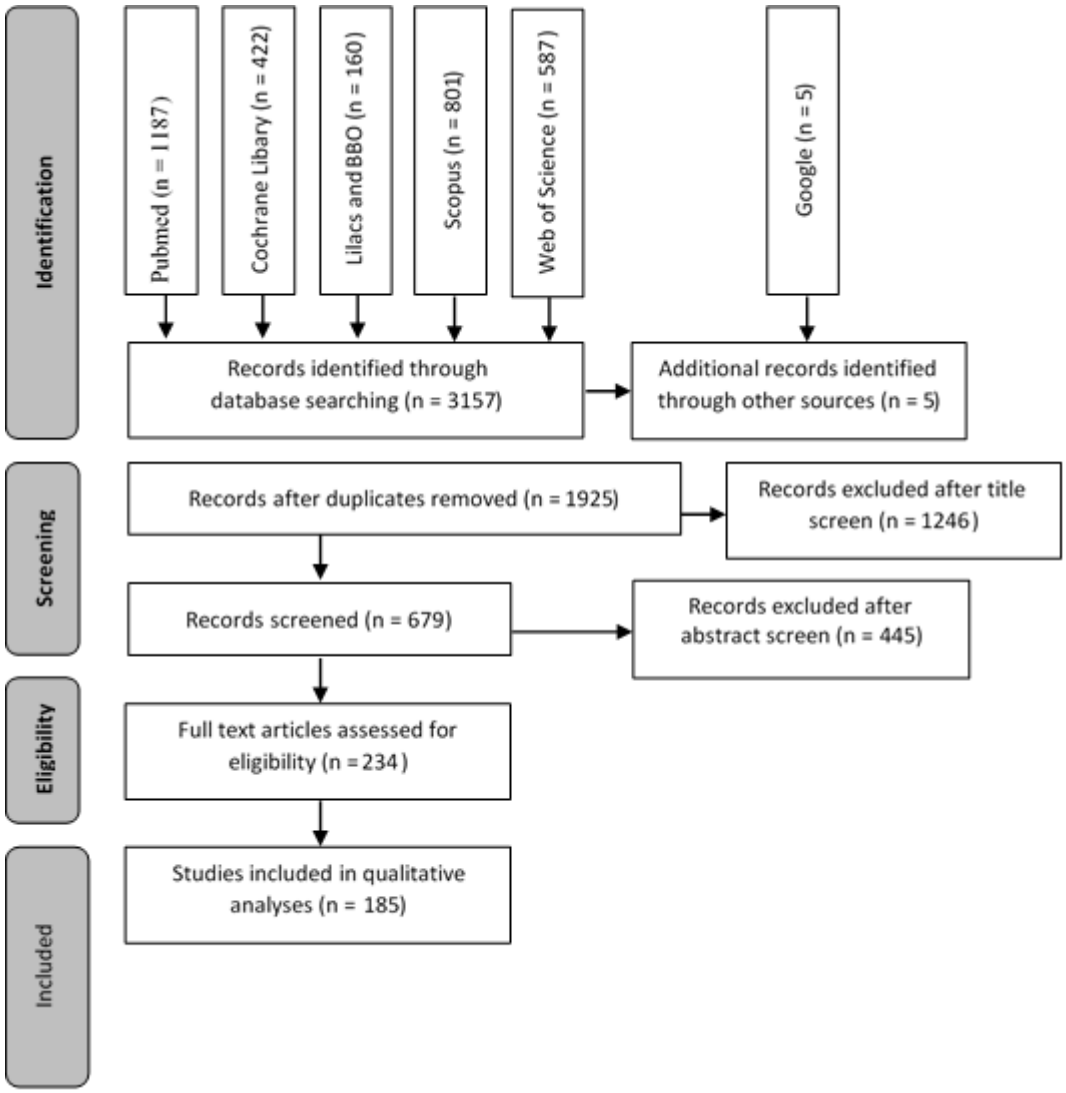


Figure 4.6-2. Percentage of studies per CONSORT score for each CONSORT item analyzed.

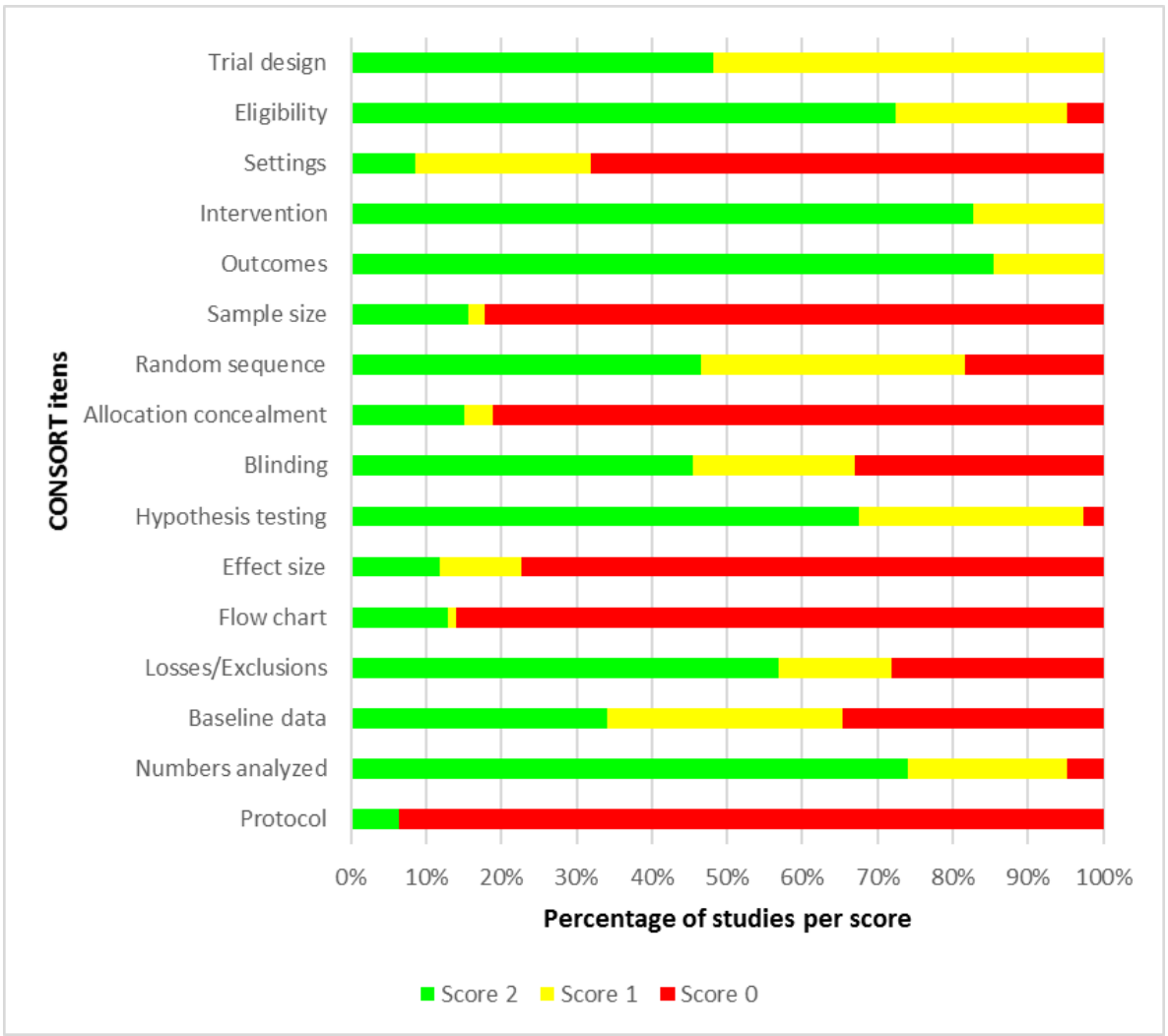


Figure 4.6-3. Linear regression between Impact Factor and Consort Score.

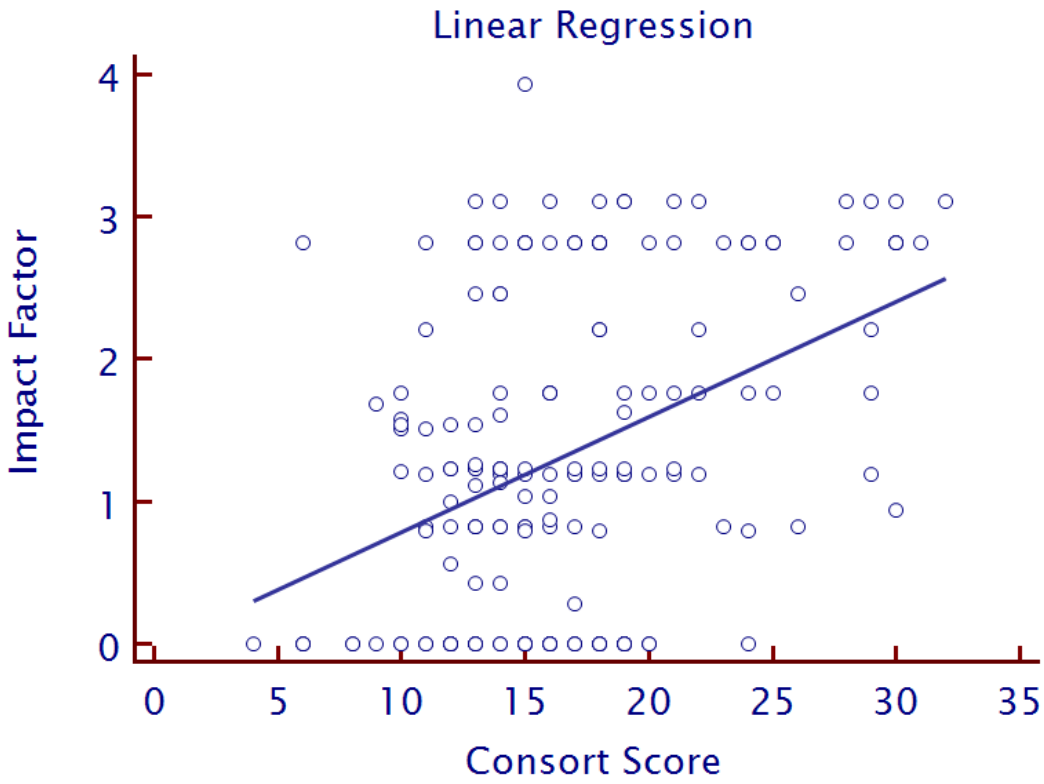
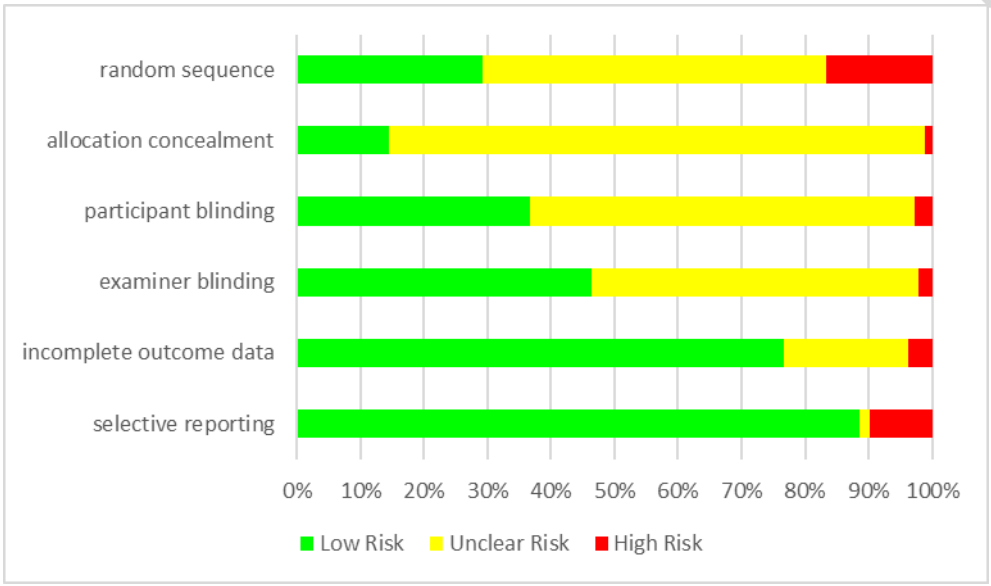


Figure 4.6-4. Methodological risk of bias chart.



REFERENCES

[1] B.K. Al-Zarea, Satisfaction with appearance and the desired treatment to improve aesthetics, Int J Dent, 2013 (2013) 912368.
[2] Z.Z. Akarslan, B. Sadik, H. Erten, E. Karabulut, Dental esthetic satisfaction, received and desired dental treatments for improvement of esthetics, Indian J Dent Res, 20 (2009) 195-200.
[3] E. Fernandez, C. Bersezio, J. Bottner, F. Avalos, I. Godoy, D. Inda, et al., Longevity, esthetic perception, and psychosocial impact of teeth bleaching by low (6%) hydrogen peroxide concentration for in-office treatment: A randomized clinical trial, Oper Dent, 42 (2017) 41-52.
[4] J.L. De Geus, M.B. De Lara, T.A. Hanzen, E. Fernandez, A.D. Loguercio, S. Kossatz, et al., One-year follow-up of at-home bleaching in smokers before and after dental prophylaxis, J Dent, 43 (2015) 1346-1351.
[5] G. Moncada, D. Sepulveda, K. Elphick, M. Contente, J. Estay, V. Bahamondes, et al., Effects of light activation, agent concentration, and tooth thickness on dental sensitivity after bleaching, Oper Dent, 38 (2013) 467-476.
[6] L.Y. Tay, C. Kose, A.D. Loguercio, A. Reis, Assessing the effect of a desensitizing agent used before in-office tooth bleaching, The Journal of the American Dental Association, 140 (2009) 1245-1251.
[7] J.F. Kina, C. Huck, H. Riehl, T.C. Martinez, N.T. Sacono, A.P. Ribeiro, et al., Response of human pulps after professionally applied vital tooth bleaching, Int Endod J, 43 (2010) 572-580.
[8] D.G. Soares, F.G. Basso, J. Hebling, C.A. De Souza Costa, Concentrations of and application protocols for hydrogen peroxide bleaching gels: Effects on pulp cell viability and whitening efficacy, J Dent, 42 (2014) 185-198.
[9] D.G. Soares, F.G. Basso, E.C.V. Pontes, L.D.F.R. Garcia, J. Hebling, C.A. De Souza Costa, Effective tooth-bleaching protocols capable of reducing h2o2 diffusion through enamel and dentine, J Dent, 42 (2014) 351-358.
[10] C. Hanks, J. Fat, J.C. Wataha, J. Corcoran, Cytotoxicity and dentin permeability of carbamide peroxide and hydrogen peroxide vital bleaching materials, in vitro, J Dent Res, 72 (1993) 931-938.
[11] D.A. Roderjan, R. Stanislawczuk, J. Hebling, C.A. Costa, A. Reis, A.D. Loguercio, Response of human pulps to different in-office bleaching techniques: Preliminary findings, Braz Dent J, 26 (2015) 242-248.
[12] E.A. De Paula, S. Kossatz, D. Fernandes, A.D. Loguercio, A. Reis, Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: A randomized triple-blind clinical trial, Oper Dent, 39 (2014) 128-135.
[13] R.S. Gomes, F.B.D. Souza, C.M. Lacerda, C.F.F. Brambilla, R.C. Pascotto, Avaliação clínica da eficiência do uso do sistema led-laser, led e luz halógena na ativação do agente clareador em dentes vitalizados, Rev dental press estét, 5 (2008) 62-77.
[14] A.P. Mena-Serrano, S.O. Parreiras, E.M. Do Nascimento, C.P. Borges, S.B. Berger, A.D. Loguercio, et al., Effects of the concentration and composition of in-office bleaching gels on hydrogen peroxide penetration into the pulp chamber, Oper Dent, 40 (2015) E76-82.
[15] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[16] P.B. Burns, R.J. Rohrich, K.C. Chung, The levels of evidence and their role in evidence-based medicine, Plastic and reconstructive surgery, 128 (2011) 305-310.
[17] P. Jüni, D.G. Altman, M. Egger, Assessing the quality of controlled clinical trials, BMJ, 323 (2001) 42-46.
[18] K.F. Schulz, D.A. Grimes, Allocation concealment in randomised trials: Defending against deciphering, The Lancet, 359 (2002) 614-618.
[19] D. Rennie, Consort revised—improving the reporting of randomized trials, JAMA, 285 (2001) 2006-2007.
[20] K.F. Schulz, D.G. Altman, D. Moher, C. Group, Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials, BMC Med, 8 (2010) 18.
[21] D. Moher, K.F. Hopewell S Fau - Schulz, V. Schulz Kf Fau - Montori, P.C. Montori V Fau - Gotzsche, P.J. Gotzsche Pc Fau - Devereaux, D. Devereaux Pj Fau - Elbourne, et al., Consort 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials,

[22] A. Reis, D.G. J., Wambier L., Schroeder M, L. Ad., Compliance of randomized clinical trials in non-carious cervical lesions with the consort statement: A methodology systematic review., Oper Dent, (2017)
[23] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ, 343 (2011) d5928.
[24] I. Cioffi, M. Farella, Quality of randomised controlled trials in dentistry, International dental journal, 61 (2011) 37-42.
[25] L. Shamseer, M. Sampson, C. Bukutu, C.H. Schmid, J. Nikles, R. Tate, et al., Consort extension for reporting n-of-1 trials (cent) 2015: Explanation and elaboration, Journal of clinical epidemiology, 76 (2016) 18-46.
[26] D. Moher, S. Hopewell, K.F. Schulz, V. Montori, P.C. Gotzsche, P.J. Devereaux, et al., Consort 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials, J Clin Epidemiol, 63 (2010) e1-37.
[27] K.F. Schulz, D.G. Altman, D. Moher, C. Group, Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials, Trials, 11 (2010) 32.
[28] H.E. Flint, J.E. Harrison, How well do reports of clinical trials in the orthodontic literature comply with the consort statement?, J Orthod, 37 (2010) 250-261.
[29] D. Kloukos, S.N. Papageorgiou, I. Doulis, H. Petridis, N. Pandis, Reporting quality of randomised controlled trials published in prosthodontic and implantology journals, J Oral Rehabil, 42 (2015) 914-925.
[30] E. Lempesi, D. Koletsi, P.S. Fleming, N. Pandis, The reporting quality of randomized controlled trials in orthodontics, J Evid Based Dent Pract, 14 (2014) 46-52.
[31] R. Montenegro, I. Needleman, D. Moles, M. Tonetti, Quality of rcts in periodontology--a systematic review, J Dent Res, 81 (2002) 866-870.
[32] S.N. Papageorgiou, D. Kloukos, H. Petridis, N. Pandis, An assessment of the risk of bias in randomized controlled trial reports published in prosthodontic and implant dentistry journals, Int J Prosthodont, 28 (2015) 586-593.
[33] S. Rajasekharan, J. Vandenbulcke, L. Martens, An assessment of the quality of reporting randomised controlled trials published in paediatric dentistry journals, Eur Arch Paediatr Dent, 16 (2015) 181-189.
[34] A.P. Acosta Gómez, G.M. Henao Giraldo, L.G. Henao Arango, Peróxido de hidrógeno al 35 por ciento y peróxido de carbamida al 10 por ciento para el blanqueamiento dental, Univ odontol, 19 (1999) 14-20.
[35] D.R. Bearn, F. Alharbi, Reporting of clinical trials in the orthodontic literature from 2008 to 2012: Observational study of published reports in four major journals, J Orthod, 42 (2015) 186-191.
[36] L. Turner, L. Shamseer, D.G. Altman, L. Weeks, J. Peters, T. Kober, et al., Consolidated standards of reporting trials (consort) and the completeness of reporting of randomised controlled trials (rcts) published in medical journals, Cochrane Database Syst Rev, 11 (2012) MR000030.
[37] N. Pandis, L. Shamseer, V.G. Kokich, P.S. Fleming, D. Moher, Active implementation strategy of consort adherence by a dental specialty journal improved randomized clinical trial reporting, J Clin Epidemiol, 67 (2014) 1044-1048.
[38] R. Sarkis-Onofre, V. Poletto-Neto, M.S. Cenci, T. Pereira-Cenci, D. Moher, Impact of the consort statement endorsement in the completeness of reporting of randomized clinical trials in restorative dentistry, J Dent, (2017)
[39] C. Barbui, A. Cipriani, L. Malvini, M. Tansella, Validity of the impact factor of journals as a measure of randomized controlled trial quality, The Journal of clinical psychiatry, 67 (2006) 37-40.
[40] P. Sjögren, A. Halling, Quality of reporting randomised clinical trials in dental and medical research, British dental journal, 192 (2002) 100-103.
[41] D.G. Altman, Endorsement of the consort statement by high impact medical journals: Survey of instructions for authors, BMJ, 330 (2005) 1056-1057.
[42] S. Hopewell, D.G. Altman, D. Moher, K.F. Schulz, Endorsement of the consort statement by high impact factor medical journals: A survey of journal editors and journal'instructions to authors', Trials, 9 (2008) 20.
[43] G. Scimago. Sjr—scimago journal & country rank. 2007.

[44] A.W. Chan, D.G. Altman, Epidemiology and reporting of randomised trials published in pubmed journals, Lancet, 365 (2005) 1159-1162.
[45] J.P. Higgins, Green, S., Cochrane handbook for systematic reviews of interventions: Wiley-Blackwell; 2014.
[46] S.J. Pocock, M.D. Hughes, R.J. Lee, Statistical problems in the reporting of clinical trials. A survey of three medical journals, N Engl J Med, 317 (1987) 426-432.
[47] M. Borenstein, Hypothesis testing and effect size estimation in clinical trials, Ann Allergy Asthma Immunol, 78 (1997) 5-11; quiz 12-16.
[48] T.T. Houle, D.A. Stump. Statistical significance versus clinical significance. Seminars in Cardiothoracic and Vascular Anesthesia; 2008: SAGE Publications; 2008. p. 5-6.
[49] K.F. Schulz, I. Chalmers, R.J. Hayes, D.G. Altman, Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials, JAMA, 273 (1995) 408-412.
[50] N. Pandis, A. Polychronopoulou, T. Eliades, An assessment of quality characteristics of randomised control trials published in dental journals, J Dent, 38 (2010) 713-721.
[51] F. Cairo, I. Sanz, P. Matesanz, M. Nieri, U. Pagliaro, Quality of reporting of randomized clinical trials in implant dentistry. A systematic review on critical aspects in design, outcome assessment and clinical relevance, J Clin Periodontol, 39 Suppl 12 (2012) 81-107.
[52] M. Egger, P. Juni, C. Bartlett, C. Group, Value of flow diagrams in reports of randomized controlled trials, JAMA, 285 (2001) 1996-1999.
[53] C. De Angelis, J.M. Drazen, F.A. Frizelle, C. Haug, J. Hoey, R. Horton, et al., Clinical trial registration: A statement from the international committee of medical journal editors, Lancet, 364 (2004) 911-912.
[54] G.H. Guyatt, A.D. Oxman, H.J. Schünemann, P. Tugwell, A. Knottnerus, Grade guidelines: A new series of articles in the journal of clinical epidemiology, Journal of clinical epidemiology, 64 (2011) 380-382.
[55] A.O. Oginni, A.A. Adeleke, Comparison of pattern of failure of resin composite restorations in non-carious cervical lesions with and without occlusal wear facets, J Dent, 42 (2014) 824-830.
[56] A. Correa, T. Santana, F. Nahsan, A. Loguercio, A. Faria-E-Silva, The impact of a customized tray on in-office bleaching tooth sensitivity: A randomized clinical trial, Oper Dent, 41 (2016) 15-22.
[57] M. Rezende, E. Bonafe, L. Vochikovski, P.V. Farago, A.D. Loguercio, A. Reis, et al., Pre- and postoperative dexamethasone does not reduce bleaching-induced tooth sensitivity: A randomized, triple-masked clinical trial, J Am Dent Assoc, 147 (2016) 41-49.
[58] A.P. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A.D. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, 41 (2016) 455-464.
[59] E.A. De Paula, J.A. Nava, C. Rosso, C.M. Benazzi, K.T. Fernandes, S. Kossatz, et al., In-office bleaching with a two- and seven-day intervals between clinical sessions: A randomized clinical trial on tooth sensitivity, J Dent, 43 (2015) 424-429.
[60] J.L. De Geus, C. Bersezio, J. Urrutia, T. Yamada, E. Fernández, A.D. Loguercio, et al., Effectiveness of and tooth sensitivity with at-home bleaching in smokers: A multicenter clinical trial, The Journal of the American Dental Association, 146 (2015) 233-240.
[61] M. Rezende, L. Ferri, S. Kossatz, A.D. Loguercio, A. Reis, Combined bleaching technique using low and high hydrogen peroxide in-office bleaching gel, Oper Dent, 41 (2016) 388-396.
[62] C. Kose, A.L. Calixto, J. Bauer, A. Reis, A.D. Loguercio, Comparison of the effects of in-office bleaching times on whitening and tooth sensitivity: A single blind, randomized clinical trial, Oper Dent, 41 (2016) 138-145.
[63] E.A. De Paula, A.D. Loguercio, D. Fernandes, S. Kossatz, A. Reis, Perioperative use of an anti-inflammatory drug on tooth sensitivity caused by in-office bleaching: A randomized, triple-blind clinical trial, Clin Oral Investig, 17 (2013) 2091-2097.
[64] J.L. De Geus, M. Rezende, L.S. Margraf, M.C. Bortoluzzi, E. Fernandez, A.D. Loguercio, et al., Evaluation of genotoxicity and efficacy of at-home bleaching in smokers: A single-blind controlled clinical trial, Oper Dent, 40 (2015) E47-55.

[65] S. Al Shethri, B. Matis, M. Cochran, R. Zekonis, M. Stropes, A clinical evaluation of two in-office bleaching products, Oper Dent, 28 (2003) 488-495.
[66] L.C.D.A. De Almeida, H. Riehl, P.H. Dos Santos, M.L.M.M. Sundfeld, A.L.F. Briso, Clinical evaluation of the effectiveness of different bleaching therapies in vital teeth, International Journal of Periodontics & Restorative Dentistry, 32 (2012)
[67] Q. Alomari, E.D. E., A randomized clinical trial of in-office dental bleaching with or without light activation, The Journal of Contemporary Dental Practice, 11 (2010)
[68] V.A. De La Peña, O.B. Cabrita, Comparison of the clinical efficacy and safety of carbamide peroxide and hydrogen peroxide in at-home bleaching gels, Quintessence Int, 37 (2006)
[69] V. Alonso De La Pena, M. Lopez Raton, Randomized clinical trial on the efficacy and safety of four professional at-home tooth whitening gels, Oper Dent, 39 (2014) 136-143.
[70] T. Auschill, E. Hellwig, S. Schmidale, A. Sculean, N. Arweiler, Efficacy, side-effects and patients' acceptance of different bleaching techniques (otc, in-office, at-home), Oper Dent, 30 (2005) 156-163.
[71] T. Auschill, T. Savio, E. Hellwig, N. Arweiler, Randomized clinical trial of the efficacy, tolerability, and long-term color stability of two bleaching techniques: 18-month follow-up, Quintessence Int, 43 (2012) 683–694.
[72] A. Barlow, R. Gerlach, K. Brennan, I. Struzycka, A. Kwiatkowska, M. Wierzbicka, Clinical response of two brush-applied peroxide whitening systems, The Journal of clinical dentistry, 14 (2002) 59-63.
[73] D. Barnes, P. Kihn, E. Romberg, D. George, L. Depaola, E. Medina, Clinical evaluation of a new 10% carbamide peroxide tooth-whitening agent, Compendium of continuing education in dentistry, 19 (1998) 968-980.
[74] R.T. Basting, F.L. Amaral, F.M. Franca, F.M. Florio, Clinical comparative study of the effectiveness of and tooth sensitivity to 10% and 20% carbamide peroxide home-use and 35% and 38% hydrogen peroxide in-office bleaching materials containing desensitizing agents, Oper Dent, 37 (2012) 464-473.
[75] A.B. Caballero, L.F. Navarro, J.A. Lorenzo, At-home vital bleaching: A comparison of hydrogen peroxide and carbamide peroxide treatments, Med Oral Patol Oral Cir Bucal, 11 (2006) E94-E99.
[76] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G.C. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[77] J.K. Bernardon, P. Ferrari, L.N. Baratieri, G.B. Rauber, Comparison of treatment time versus patient satisfaction in at-home and in-office tooth bleaching therapy, J Prosthet Dent, 114 (2015) 826-830.
[78] J.K. Bernardon, M. Vieira Martins, G. Branco Rauber, S. Monteiro Junior, L.N. Baratieri, Clinical evaluation of different desensitizing agents in home-bleaching gels, J Prosthet Dent, 115 (2016) 692-696.
[79] M. Bizhang, M. Mueller, J.-H. Phark, M.L. Barker, R.W. Gerlach, Clinical trial of long-term color stability of hydrogen peroxide strips and sodium percarbonate film, Am J Dent, 20 (2007) 23A-27A.
[80] M. Bizhang, Y.H. Chun, K. Damerau, P. Singh, W.H. Raab, S. Zimmer, Comparative clinical study of the effectiveness of three different bleaching methods, Oper Dent, 34 (2009) 635-641.
[81] E. Bonafe, A.D. Loguercio, A. Reis, S. Kossatz, Effectiveness of a desensitizing agent before in-office tooth bleaching in restored teeth, Clin Oral Investig, 18 (2014) 839-845.
[82] J.F. Bortolatto, T.C. Trevisan, P.S. Bernardi, E. Fernandez, L.N. Dovigo, A.D. Loguercio, et al., A novel approach for in-office tooth bleaching with 6% h2o2/tio_n and led/laser system-a controlled, triple-blinded, randomized clinical trial, Lasers Med Sci, 31 (2016) 437-444.
[83] A. Braun, S. Jepsen, F. Krause, Spectrophotometric and visual evaluation of vital tooth bleaching employing different carbamide peroxide concentrations, Dent Mater, 23 (2007) 165-169.
[84] W.D. Browning, S.D. Cho, E.J. Deschepper, Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity, J Esthet Restor Dent, 24 (2012) 268-276.
[85] W.D. Browning, D.C. Chan, M.L. Myers, W.W. Brackett, M.G. Brackett, D.H. Pashley, Comparison of traditional and low sensitivity whiteners, Oper Dent, 33 (2008) 379-385.
[86] A.M. Bruhn, M.L. Darby, G.B. Mccombs, C.M. Lynch, Vital tooth whitening effects on oral health–related quality of life in older adults, American Dental Hygienists Association, 86 (2012) 239-247.

[87] R.S. Callan, W.D. Browning, M.C. Downey, M.G. Brackett, Comparison of two low sensitivity whiteners, Am J Dent, 21 (2008) 17-20.
[88] P.C. Cardoso, A. Reis, A. Loguercio, L.C. Vieira, L.N. Baratieri, Clinical effectiveness and tooth sensitivity associated with different bleaching times for a 10 percent carbamide peroxide gel, The Journal of the American Dental Association, 141 (2010) 1213-1220.
[89] B.C.F.D. Carvalho, R.C.S.R. Leite, M.B. Ferreira, E.M.O.F.D. Carvalho, Avaliação da sensibilidade dentinária e manutenção da cor após clareamento, Rev Assoc Paul Cir Dent, 59 (2006) 45-48.
[90] R.R.D. Cerqueira, F.L. Hofstaetter, M. Rezende, G.C. Martins, A.D. Loguercio, A. Reis, et al., Efeito do uso de agente dessensibilizante na efetividade do clareamento e na sensibilidade dental, Revista da Associacao Paulista de Cirurgioes Dentistas, 67 (2013) 64-67.
[91] R.M. Cibirka, M. Myers, M.C. Downey, S.K. Nelson, W.D. Browning, I.K. Hawkins, et al., Clinical study of tooth shade lightening from dentist-supervised, patient-applied treatment with two 10% carbamide peroxide gels, Journal of Esthetic and Restorative Dentistry, 11 (1999) 325-331.
[92] L.Z. Collins, B. Maggio, A. Gallagher, M. York, F. Schäfer, Safety evaluation of a novel whitening gel, containing 6% hydrogen peroxide and a commercially available whitening gel containing 18% carbamide peroxide in an exaggerated use clinical study, J Dent, 32 (2004) 47-50.
[93] S. Corbella, M. Basso, E. Roci, F. De Siena, L. Francetti, Sbiancamento dentale domiciliare e ambulatoriale a confronto, DENTAL CADMOS, 77 (2009)
[94] M. Cronin, C. Charles, Q. Zhao, W. Dembling, Comparison of two over-the-counter tooth whitening products using a novel system, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 26 (2005) 140, 142, 144-148.
[95] J.B. Da Costa, R. Mcpharlin, R.D. Paravina, J.L. Ferracane, Comparison of at-home and in-office tooth whitening using a novel shade guide, Oper Dent, 35 (2010) 381-388.
[96] J. Da Costa, E. Lubisich, J. Ferracane, T. Hilton, Comparison of efficacy of an in-office whitening system used with and without a whitening priming agent, J Esthet Restor Dent, 23 (2011) 97-104.
[97] P.F. Dawson, M.O. Sharif, A.B. Smith, P.A. Brunton, A clinical study comparing the efficacy and sensitivity of home vs combined whitening, Oper Dent, 36 (2011) 460-466.
[98] P.B. De Almeida Farhat, F.A. Santos, J.C. Gomes, O.M. Gomes, Evaluation of the efficacy of led-laser treatment and control of tooth sensitivity during in-office bleaching procedures, Photomed Laser Surg, 32 (2014) 422-426.
[99] P.M. De Freitas, A.N. Menezes, A.C. Da Mota, A. Simoes, F.M. Mendes, A.D. Lago, et al., Does the hybrid light source (led/laser) influence temperature variation on the enamel surface during 35% hydrogen peroxide bleaching? A randomized clinical trial, Quintessence Int, 47 (2016) 61-73.
[100] J.L. De Geus, C. Bersezio, J. Urrutia, T. Yamada, E. Fernandez, A.D. Loguercio, et al., Effectiveness of and tooth sensitivity with at-home bleaching in smokers: A multicenter clinical trial, J Am Dent Assoc, 146 (2015) 233-240.
[101] E. Delgado, P.L. Hernandez-Cott, B. Stewart, M. Collins, W. De Vizio, Tooth-whitening efficacy of custom tray-delivered 9% hydrogen peroxide and 20% carbamide peroxide during daytime use: A 14-day clinical trial, Puerto Rico health sciences journal, 26 (2009)
[102] S. Deliperi, D.N. Bardwell, A. Papathanasiou, Clinical evaluation of a combined in-office and take-home bleaching system, The Journal of the American Dental Association, 135 (2004) 628-634.
[103] Donly, Tooth whitening in children, Compendium / Special Issue, 23 (2002)
[104] K.J. Donly, P. Kennedy, A. Segura, R.W. Gerlach, Effectiveness and safety of tooth bleaching in teenagers, Pediatric Dentistry, 27 (2005) 298-302.
[105] K. Donly, T. Henson, D. Jamison, R. Gerlach, Clinical trial evaluating two peroxide whitening strips used by teenagers, Gen Dent, 54 (2005) 110-112.
[106] K. Donly, A. Segura, T. Henson, M. Barker, R. Gerlach, Randomized controlled trial of professional at-home tooth whitening in teenagers, Gen Dent, 55 (2007) 669-674.
[107] K.J. Donly, A controlled clinical trial to evaluate the safety and whitening efficacy of a 9.5% hydrogen peroxide high-adhesion whitening strip in a teen population, American Journal of DCllIis (f), 23 (2010)

[108] S. Farrell, M.L. Barker, P.A. Sagel, R.W. Gerlach, Use of a physical barrier to improve efficacy of a paint-on whitening gel: A seven-day randomized clinical trial, The Journal of clinical dentistry, 17 (2005) 117-121.
[109] E. Fernández, Efficacy and tooth sensitivity of at-home bleaching in smokers: A two-center clinical trial, Journal of the American Dental Association, (2016)
[110] M. Ferrari, G. Kugel, M. Cagidiaco, M. Barker, R. Gerlach, Clinical trial evaluating the peroxide concentration response of whitening strips over 28 days, Am J Dent, 17 (2004) 291-294.
[111] A. Gallagher, B. Maggio, J. Bowman, L. Borden, S. Mason, H. Felix, Clinical study to compare two in-office (chairside) whitening systems, The Journal of clinical dentistry, 13 (2001) 219-224.
[112] J.R. Gallo, J.O. Burgess, A.H. Ripps, M.J. Bell, D.E. Mercante, J.M. Davidson, Evaluation of 30% carbamide peroxide at-home bleaching gels with and without potassium nitrate—a pilot study, Quintessence Int, 40 (2009)
[113] F. Garcia-Godoy, P. Villalta, M. Barker, R. Gerlach, Placebo-controlled, 6-week clinical trial on the safety and efficacy of a low-gel, 14% hydrogen-peroxide whitening strip, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 25 (2004) 21-26.
[114] R. Gerlach, R. Gibb, P. Sagel, A randomized clinical trial comparing a novel 5.3 percent hydrogen peroxide whitening strip to 10 percent, 15 percent, and 20 percent carbamide peroxide tray-based bleaching systems, Compend Contin Educ Dent, 29 (2000) S22-S28.
[115] R. Gerlach, M. Barker, P. Sagel, Comparative efficacy and tolerability of two direct-to-consumer tooth whitening systems, Am J Dent, 14 (2001) 267-272.
[116] R.W. Gerlach, X. Zhou, Comparative clinical efficacy of two professional bleaching systems, Compend Contin Educ Dent, 23 (2002) 35-41; quiz 50.
[117] R. Gerlach, P. Sagel, M. Barker, K. Karpinia, I. Magnusson, Placebo-controlled clinical trial evaluating a 10% hydrogen peroxide whitening strip, The Journal of clinical dentistry, 15 (2003) 118-122.
[118] R.W. Gerlach, X. Zhou, S.F. Mcclanahan, Comparative response of whitening strips to a low peroxide and potassium nitrate bleaching gel, Am J Dent, 15 Spec No (2002) 19A-23A.
[119] R.W. Gerlach, M.L. Barker, Randomized clinical trial comparing overnight use of two self-directed peroxide tooth whiteners, American Journal of Dentistry, 16 (2003) 17B-21B.
[120] R.W. Gerlach, P.A. Sagel, Vital bleaching with a thin peroxide gel: The safety and efficacy of a professional-strength hydrogen peroxide whitening strip, J Am Dent Assoc, 135 (2004) 98-100.
[121] R.W. Gerlach, Clinical trial comparing two daytime hydrogen-peroxide professional vital-bleaching systems, Compendium, 25 (2004)
[122] L. Giachetti, F. Bertini, C. Bambi, M. Nieri, D.S. Russo, A randomized clinical trial comparing at-home and in-office tooth whitening techniques, The Journal of the American Dental Association, 141 (2010) 1357-1364.
[123] M. Giniger, J. Macdonald, M. Spaid, H. Felix, A 180-day clinical investigation of the tooth whitening efficacy of a bleaching gel with added amorphous calcium phosphate, Journal of Clinical Dentistry, 16 (2005) 11-16.
[124] M. Giniger, J. Macdonald, S. Ziemba, H. Felix, The clinical performance of professionally dispensed bleaching gel with added amorphous calcium phosphate, The Journal of the American Dental Association, 136 (2005) 383-392.
[125] J. Goodson, M. Tavares, M. Sweeney, J. Stultz, M. Newman, V. Smith, et al., Tooth whitening: Tooth color changes following treatment by peroxide and light, The Journal of clinical dentistry, 16 (2004) 78-82.
[126] S.R. Grobler, A. Majeed, R. Hayward, R.J. Rossouw, M.H. Moola, W.K.T.J. Van, A clinical study of the effectiveness of two different 10% carbamide peroxide bleaching products: A 6-month followup, Int J Dent, 2011 (2011) 167525.
[127] G.M.T. Guênes, A.M.a.D. Lima, L.a.D.M.D. Medeiros, E.S.D. Penha, W.T. Pinto, R.L.D. Santos, Avaliação de diferentes sistemas de clareamento dental de consultório, RFO UPF, 20 (2015) 281-286.
[128] J. Guerrero, M. Jiménez-Farfán, A. Lopez-Salgado, M.L. Barker, R.W. Gerlach, Professional whitening strips in a university population, Am J Dent, 20 (2007) 15A-18A.
[129] S. Gurgan, F.Y. Cakir, E. Yazici, Different light-activated in-office bleaching systems: A clinical evaluation, Lasers Med Sci, 25 (2010) 817-822.

[130] C. Hannig, D. Lindner, T. Attin, Efficacy and tolerability of two home bleaching systems having different peroxide delivery, Clin Oral Investig, 11 (2007) 321-329.
[131] R.K. Henry, S.M. Bauchmoyer, W. Moore, R.G. Rashid, The effect of light on tooth whitening: A split-mouth design, Int J Dent Hyg, 11 (2013) 151-154.
[132] B.W. Hyland, A. Mcdonald, N. Lewis, C. Tredwin, A. Petrie, S. Hall, et al., A new three-component formulation for the efficient whitening of teeth (carbamide plus), Clin Oral Investig, 19 (2015) 1395-1404.
[133] S. Ishikawa-Nagai, T. Terui, K. Ishibashi, H.P. Weber, M. Ferguson, Comparison of effectiveness of two 10% carbamide peroxide tooth-bleaching systems using spectrophotometric measurements, Journal of Esthetic and Restorative Dentistry, 16 (2004) 368-375.
[134] E. Jadad, J. Montoya, G. Arana, L.A. Gordillo, R.M. Palo, A.D. Loguercio, Spectrophotometric evaluation of color alterations with a new dental bleaching product in patients wearing orthodontic appliances, Am J Orthod Dentofacial Orthop, 140 (2011) e43-47.
[135] D. Javaheri, J. Janis, The efficacy of reservoirs in bleaching trays, Oper Dent, 25 (2000) 149-151.
[136] K. Karpinia, I. Magnusson, P. Sagel, X. Zhou, R. Gerlach, Vital bleaching with two at-home professional systems, Am J Dent, 15 (2002) 13A-18A.
[137] K. Karpinia, I. Magnusson, M.L. Barker, R.W. Gerlach, Clinical comparison of two self-directed bleaching systems, Journal of Prosthodontics, 12 (2003) 242-248.
[138] P. Kihn, D.M. Barnes, E. Romberg, K. Peterson, A clinical evaluation of 10 percent vs. 15 percent carbamide peroxide tooth-whitening agents, The Journal of the American Dental Association, 131 (2000) 1478-1484.
[139] P. Kihn, D.M. Barnes, E. Romberg, E. Adachi, D. George, Clinical evaluation of a 15% in-office hydrogen peroxide tooth-whitening touch-up agent, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 23 (2002) 939-942, 944, 946 passim; quiz 950.
[140] M. Knosel, R. Attin, K. Becker, T. Attin, External bleaching effect on the color and luminosity of inactive white-spot lesions after fixed orthodontic appliances, Angle Orthod, 77 (2007) 646-652.
[141] M. Knosel, R. Attin, K. Becker, T. Attin, A randomized cie l*a*b* evaluation of external bleaching therapy effects on fluorotic enamel stains, Quintessence Int, 39 (2008) 391–399.
[142] C. Kose, A. Reis, L.N. Baratieri, A.D. Loguercio, Clinical effects of at-home bleaching along with desensitizing agent application, Am J Dent, 24 (2011) 379-382.
[143] S. Kossatz, A.P. Dalanhol, T. Cunha, A. Loguercio, A. Reis, Effect of light activation on tooth sensitivity after in-office bleaching, Oper Dent, 36 (2011) 251-257.
[144] S. Kossatz, G. Martins, A.D. Loguercio, A. Reis, Tooth sensitivity and bleaching effectiveness associated with use of a calcium-containing in-office bleaching gel, The Journal of the American Dental Association, 143 (2012) e81-e87.
[145] A. Kozlovsky, A. Sintov, Z. Artzi, H. Tal, Clinical efficacy of a degradable film-forming product containing carbamide peroxide to reduce tooth discolouration, Oral health, 86 (1996) 47-49, 53-46.
[146] F. Krause, S. Jepsen, A. Braun, Subjective intensities of pain and contentment with treatment outcomes during tray bleaching of vital teeth employing different carbamide peroxide concentrations, Quintessence Int, 39 (2008)
[147] G. Kugel, A. Aboushala, X. Zhou, R. Gerlach, Daily use of whitening strips on tetracycline-stained teeth: Comparative results after 2 months, Compendium of continuing education in dentistry, 23 (2002) 29-34.
[148] G. Kugel, A. Papathanasiou, A. Williams 3rd, C. Anderson, S. Ferreira, Clinical evaluation of chemical and light-activated tooth whitening systems, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 27 (2006) 54-62.
[149] G. Kugel, A. Aboushala, S. Sharma, S. Ferreira, C. Anderson, Maintenance of whitening with a power toothbrush after bleaching treatment, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 25 (2004) 119-131; quiz 132.
[150] G. Kugel, S. Ferreira, S. Sharma, M.L. Barker, R.W. Gerlach, Clinical trial assessing light enhancement of in-office tooth whitening, J Esthet Restor Dent, 21 (2009) 336-347.
[151] G. Kugel, S. Kastali, Tooth-whitening efficacy and safety: A randomized and controlled clinical trial, Compendium of continuing education in dentistry, (1999) S16-21; quiz S42.

[152] R.H. Leonard, Jr., V.B. Haywood, J.C. Eagle, G.E. Garland, D.J. Caplan, K.P. Matthews, et al., Nightguard vital bleaching of tetracycline-stained teeth: 54 months post treatment, J Esthet Dent, 11 (1999) 265-277.
[153] R.H. Leonard Jr, C. Bentley, J.C. Eagle, G.E. Garland, M.C. Knight, C. Phillips, Nightguard vital bleaching: A long-term study on efficacy, shade retention. Side effects, and patients' perceptions, Journal of esthetic and restorative dentistry : official publication of the American Academy of Esthetic Dentistry [et al], 13 (2001) 357-369.
[154] R.H. Leonard, Jr., L.R. Smith, G.E. Garland, D.J. Caplan, Desensitizing agent efficacy during whitening in an at-risk population, J Esthet Restor Dent, 16 (2004) 49-55; discussion 56.
[155] H.R. Lewgoy, R. Amore, R.C.B. Alonso, V. Di Hipólito, C. Anauate Netto, D.A. Barros Filho, et al., Estudo in vivo do manchamento dental causado pela ingestão de café associada ao clareamento profissional, Rev ABO nac, (2011) 108-113.
[156] Y. Li, S.S. Lee, S.L. Cartwright, A.C. Wilson, Comparison of clinical efficacy and safety of three professional at-home tooth whitening systems, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 24 (2003) 357-360, 362, 364 passim; quiz 378.
[157] E. Lo, A. Wong, C. Mcgrath, A randomized controlled trial of home tooth-whitening products, Am J Dent, 20 (2007) 315-318.
[158] R. Lo Giudice, G. Pantaleo, A. Lizio, U. Romeo, G. Castiello, G. Spagnuolo, et al., Clinical and spectrophotometric evaluation of led and laser activated teeth bleaching, Open Dent J, 10 (2016) 242-250.
[159] A.D. Loguercio, L.Y. Tay, D.R. Herrera, J. Bauer, A. Reis, Effectiveness of nano-calcium phosphate paste on sensitivity during and after bleaching: A randomized clinical trial, Braz Oral Res, 29 (2015) 1-7.
[160] J.P. Loyola-Rodriguez, A. De Jesus Pozos-Guillen, F. Hernandez-Hernandez, R. Berumen-Maldonado, N. Patiño-Marin, Effectiveness of treatment with carbamide peroxide and hydrogen peroxide in subjects affected by dental fluorosis: A clinical trial, Journal of Clinical Pediatric Dentistry, 28 (2004) 63-67.
[161] W. Luo, S. Westland, P. Brunton, R. Ellwood, I.A. Pretty, N. Mohan, Comparison of the ability of different colour indices to assess changes in tooth whiteness, J Dent, 35 (2007) 109-116.
[162] L.S. Machado, F.G. De Oliveira, E.P. Rocha, P.H. Dos Santos, A.L. Briso, M.L. Sundefeld, et al., Clinical trial evaluating color change and tooth sensitivity throughout and following in-office bleaching, Int J Periodontics Restorative Dent, 33 (2013) 209-215.
[163] L.S. Machado, R.B. Anchieta, P.H. Dos Santos, A.L. Briso, N. Tovar, M.N. Janal, et al., Clinical comparison of at-home and in-office dental bleaching procedures: A randomized trial of a split-mouth design, Int J Periodontics Restorative Dent, 36 (2016) 251-260.
[164] G.A. Maghaireh, H. Alzraikat, A. Guidoum, Assessment of the effect of casein phosphopeptide-amorphous calcium phosphate on postoperative sensitivity associated with in-office vital tooth whitening, Oper Dent, 39 (2014) 239-247.
[165] F.C. Marson, L.G. Sensi, L.C. Vieira, E. Araujo, Clinical evaluation of in-office dental bleaching treatments with and without the use of light-activation sources, Oper Dent, 33 (2008) 15-22.
[166] J. Martín, N. Ovies, P. Cisternas, E. Fernández, O.B. Oliveira Junior, M.F. De Andrade, et al., Can an led-laser hybrid light help to decrease hydrogen peroxide concentration while maintaining effectiveness in teeth bleaching?, Laser Physics, 25 (2015) 025608.
[167] G.C. Martins, A.C.S.D.A. Izidoro, L.M.B. Meister, S. Kossatz, O.M. Gomes, A. Loguercio, et al., Efeito do uso prévio de um dessensibilizante na sensibilidade do clareamento de consultório, Associação Paulista de CirurgiõesDentistas, (2010)
[168] B.A. Matis, M.A. Cochran, G. Eckert, T.J. Carlson, The efficacy and safety of a 10% carbamide peroxide bleaching gel, Quintessence International, 29 (1998)
[169] B.A. Matis, H.N. Mousa, M.A. Cochran, G.J. Eckert, Clinical evaluation of bleaching agents of different concentrations, Quintessence Int, 31 (2000)
[170] B. Matis, Y. Hamdan, M. Cochran, G. Eckert, A clinical evaluation of a bleaching agent used with and without reservoirs, Oper Dent, 27 (2002) 5-11.
[171] B.A. Matis, Y. Wang, T. Jiang, G.J. Eckert, Extended at-home bleaching of tetracycline-stained teeth with different concentrations of carbamide peroxide, Quintessence Int, 33 (2002)

[172] B. Matis, M. Cochran, G. Wang, M. Franco, G. Eckert, R. Carlotti, et al., A clinical evaluation of bleaching using whitening wraps and strips, Operative Dentistry-University of Washington, 30 (2005) 588.
[173] B.A. Matis, Y. Wang, G.J. Eckert, M.A. Cochran, T. Jiang, Extended bleaching of tetracycline-stained teeth: A 5-year study, Oper Dent, 31 (2006) 643-651.
[174] B.A. Matis, M.A. Cochran, G.J. Eckert, J.I. Matis, In vivo study of two carbamide peroxide gels with different desensitizing agents, Oper Dent, 32 (2007) 549-555.
[175] B.A. Matis, M.A. Cochran, G. Wang, G.J. Eckert, A clinical evaluation of two in-office bleaching regimens with and without tray bleaching, Oper Dent, 34 (2009) 142-149.
[176] M.C.D.S. Medeiros, K.C. De Lima, Effectiveness of nightguard vital bleaching with 10% carbamide peroxide - a clinical study, JCDA • wwwcda-adcca/jcda •, 74 (2008)
[177] D. Mehta, S. Venkata, M. Naganath, U. Lingareddy, H. Ishihata, W.J. Finger, Clinical trial of tooth desensitization prior to in-office bleaching, Eur J Oral Sci, 121 (2013) 477-481.
[178] S.S. Meireles, S.S. Heckmann, I.S. Santos, A. Della Bona, F.F. Demarco, A double blind randomized clinical trial of at-home tooth bleaching using two carbamide peroxide concentrations: 6-month follow-up, Journal of Dentistry, 36 (2008) 878-884.
[179] S.S. Meireles, S.S. Heckmann, F.L. Leida, S. Dos Santos Ida, A. Della Bona, F.F. Demarco, Efficacy and safety of 10% and 16% carbamide peroxide tooth-whitening gels: A randomized clinical trial, Oper Dent, 33 (2008) 606-612.
[180] S.S. Meireles, S. Dos Santos Ida, A. Della Bona, F.F. Demarco, A double-blind randomized controlled clinical trial of 10 percent versus 16 percent carbamide peroxide tooth-bleaching agents: One-year follow-up, J Am Dent Assoc, 140 (2009) 1109-1117.
[181] S.S. Meireles, I.S. Santos, A.D. Bona, F.F. Demarco, A double-blind randomized clinical trial of two carbamide peroxide tooth bleaching agents: 2-year follow-up, Journal of Dentistry, 38 (2010) 956-963.
[182] S.S. Meireles, M.L. Goettems, R.V. Dantas, A.D. Bona, I.S. Santos, F.F. Demarco, Changes in oral health related quality of life after dental bleaching in a double-blind randomized clinical trial, J Dent, 42 (2014) 114-121.
[183] M. Miller, I. Castellanos, M. Rieger, Efficacy of home bleaching systems with and without tray reservoirs, Practical periodontics and aesthetic dentistry: PPAD, 12 (2000) 611-614.
[184] F.V. Moghadam, S. Majidinia, J. Chasteen, M. Ghavamnasiri, The degree of color change, rebound effect and sensitivity of bleached teeth associated with at-home and power bleaching techniques: A randomized clinical trial, Eur J Dent, 7 (2013) 405-411.
[185] N. Mohan, S. Westland, P. Brunton, R. Ellwood, I.A. Pretty, W. Luo, A clinical study to evaluate the efficacy of a novel tray based tooth whitening system, J Dent, 36 (2008) 21-26.
[186] G.R. Mokhlis, B.A. Matis, M.A. Cochran, G.J. Eckert, A clinical evaluation of carbamide peroxide and hydrogen peroxide whitening agents during daytime use, The Journal of the American Dental Association, 131 (2000) 1269-1277.
[187] R.F.L. Mondelli, A.C. Francisconi, C.M.D. Almeida, S.K. Ishikiriama, Comparative clinical study of the effectiveness of different dental bleaching methods-two year follow-up, Journal of Applied Oral Science, 20 (2012) 435-443.
[188] A. Montenegro-Arana, L.A. Arana-Gordillo, D. Farana, A. Davila-Sanchez, E. Jadad, U. Coelho, et al., Randomized double-blind clinical trial of bleaching products in patients wearing orthodontic devices, Oper Dent, 41 (2016) 379-387.
[189] S. Morgan, A.A. Jum'ah, P. Brunton, Assessment of efficacy and post-bleaching sensitivity of home bleaching using 10% carbamide peroxide in extended and non-extended bleaching trays, Br Dent J, 218 (2015) 579-582.
[190] M.L. Myers, W.D. Browning, M.C. Downey, S.T. Hackman, Clinical evaluation of a 3% hydrogen peroxide tooth-whitening gel, Journal of Esthetic and Restorative Dentistry, 15 (2003) 50-56.
[191] S. Nathoo, E. Santana 3rd, Y. Zhang, N. Lin, M. Collins, K. Klimpel, et al., Comparative seven-day clinical evaluation of two tooth whitening products, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 22 (2001) 599-604, 606; quiz 608.

[192] S. Nathoo, B. Stewart, M. Petrone, P. Chaknis, Y. Zhang, W. Devizio, et al., Comparative clinical investigation of the tooth whitening efficacy of two tooth whitening gels, The Journal of clinical dentistry, 14 (2002) 64-69.
[193] C.O. Navarra, B. Reda, M. Diolosa, I. Casula, R. Di Lenarda, L. Breschi, et al., The effects of two 10% carbamide peroxide nightguard bleaching agents, with and without desensitizer, on enamel and sensitivity: An in vivo study, Int J Dent Hyg, 12 (2014) 115-120.
[194] B.J. Nutter, M.O. Sharif, A.B. Smith, P.A. Brunton, A clinical study comparing the efficacy of light activated in-surgery whitening versus in-surgery whitening without light activation, J Dent, 41 Suppl 5 (2013) e3-7.
[195] J.C. Ontiveros, R.D. Paravina, Color change of vital teeth exposed to bleaching performed with and without supplementary light, J Dent, 37 (2009) 840-847.
[196] M. Palé, J.R. Mayoral, J. Llopis, M. Vallès, J. Basilio, M. Roig, Evaluation of the effectiveness of an in-office bleaching system and the effect of potassium nitrate as a desensitizing agent, Odontology, 102 (2014) 203-210.
[197] A. Papathanasiou, D. Bardwell, G. Kugel, A clinical study evaluating a new chairside and take-home whitening system, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 22 (2001) 289-294, 296, 298; quiz 300.
[198] A. Papathanasiou, S. Kastali, R.D. Perry, G. Kugel, Clinical evaluation of a 35% hydrogen peroxide in-office whitening system, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 23 (2002) 335-338, 340, 343-334 passim; quiz 348.
[199] R. Perry, E. Conde, S. Farrell, R. Gerlach, J. Towers, Comparative performance of two whitening systems in a dental practice, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 34 (2012) 15-18.
[200] O. Polydorou, M. Wirsching, M. Wokewitz, P. Hahn, Three-month evaluation of vital tooth bleaching using light units-a randomized clinical study, Oper Dent, 38 (2013) 21-32.
[201] S.L. Posso Moreno, D.X. Ramírez Ramírez, J.A. Rosas Jaimes, E.H. Güiza Cristancho, Comparación del blanqueamiento dental con peróxido de hidrógeno al 25 percent en consultorio, utilizando o no activación con lámpara de luz halógena, Univ odontol, (2010) 19-25.
[202] A. Reis, L.Y. Tay, D.R. Herrera, S. Kossatz, A.D. Loguercio, Clinical effects of prolonged application time of an in-office bleaching gel, Operative Dentistry, 36 (2011) 590-596.
[203] A. Reis, A.P. Dalanhol, T.S. Cunha, S. Kossatz, A.D. Loguercio, Assessment of tooth sensitivity using a desensitizer before light-activated bleaching, Operative Dentistry, 36 (2011) 12-17.
[204] A. Reis, S. Kossatz, G.C. Martins, A.D. Loguercio, Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: A randomized clinical trial, Oper Dent, 38 (2013) 386-393.
[205] M. Rezende, S.H. Siqueira, S. Kossatz, Clareamento dental-efeito da técnica sobre a sensibilidade dental e efetividade, Revista da Associacao Paulista de Cirurgioes Dentistas, 68 (2014) 208-212.
[206] M. Rezende, A.D. Loguercio, A. Reis, S. Kossatz, Clinical effects of exposure to coffee during at-home vital bleaching, Oper Dent, 38 (2013) E229-236.
[207] M. Rezende, J.L. De Geus, A.D. Loguercio, A. Reis, D. Kossatz, Clinical evaluation of genotoxicity of in-office bleaching, Oper Dent, 41 (2016) 578-586.
[208] S.F. Rosenstiel, A.G. Gegauff, W.M. Johnston, Randomized clinical trial of the efficacy and safety of a home bleaching procedure, Quintessence Int, 27 (1996)
[209] M.a.P. Santana, F.P.S. Nahsan, A.H.D.A. Oliveira, A.D. Loguércio, A.L. Faria-E-Silva, Randomized controlled trial of sealed in-office bleaching effectiveness, Braz Dent J, 25 (2014) 207-211.
[210] H. Shahidi, M. Barker, P. Sagel, R. Gerlach, Randomized controlled trial of 10% hydrogen peroxide whitening strips, The Journal of clinical dentistry, 16 (2004) 91-95.
[211] R. Shanbhag, R. Veena, G. Nanjannawar, J. Patil, S. Hugar, H. Vagrali, Use of clinical bleaching with 35% hydrogen peroxide in esthetic improvement of fluorotic human incisors in vivo, The journal of contemporary dental practice, 14 (2013) 208.
[212] C. Sielski, N. Conforti, B. Stewart, P. Chaknis, M.E. Petrone, W. Devizio, et al., A clinical investigation of the efficacy of a tooth-whitening gel, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 24 (2003) 612-614, 616-618.

[213] F.M. Silva, L.G. Nacano, E.C.G. Pizi, Avaliação clínica de dois sistemas de clareamento dental, Revista Odontológica do Brasil Central, 21 (2012)
[214] J.F. Simon, L. Powell, M.S. Hollis, M.K. Anastasia, B.R.W. Gerlach, M.S. Farrell, Placebo-controlled clinical trial evaluating 9.5% hydrogen peroxide high-adhesion whitening strips, The Journal of clinical dentistry, 25 (2014) 49.
[215] C.J. Soares, N.R.D. Silva, P.S. Quagliatto, R.E. Campos, Avaliação clínica de clareamento caseiro com gel de peróxido de carbamida industrializado e manipulado em farmácia, Revista de Odontologia da UNESP, 35 (2006) 69-74.
[216] A. Strobl, N. Gutknecht, R. Franzen, R.D. Hilgers, F. Lampert, J. Meister, Laser-assisted in-office bleaching using a neodymium:Yttrium-aluminum-garnet laser: An in vivo study, Lasers Med Sci, 25 (2010) 503-509.
[217] R.H. Sundfeld, D. Sundfeld Neto, L.S. Machado, F.G. De Oliveira, R.S. De Alexandre, R.M. Palo, et al., Dental bleaching with a 10% hydrogen peroxide product: A six-month clinical observation, Indian J Dent Res, 25 (2014) 4-8.
[218] E.J. Swift, K.N. May, A.D. Wilder, H.O. Heymann, R.S. Wilder, S.C. Bayne, Six-month clinical evaluation of a tooth whitenin system using an innovate experimental design, Journal of Esthetic and Restorative Dentistry, 9 (1997) 265-275.
[219] E.J. Swift, K.N. May, A.D. Wilder, H.O. Heymann, S.C. Bayne, Two-year clinical evaluation of tooth whitening using an at-home bleaching system, Journal of Esthetic and Restorative Dentistry, 11 (1999) 36-42.
[220] E.J. Swift Jr, Three-week clinical trial of a 14% hydrogen-peroxide, strip-based bleaching system, Compendium, 25 (2004)
[221] E.J. Swift, Jr., H.O. Heymann, A.D. Wilder, Jr., M.L. Barker, R.W. Gerlach, Effects of duration of whitening strip treatment on tooth color: A randomized, placebo-controlled clinical trial, J Dent, 37 Suppl 1 (2009) e51-56.
[222] M. Tavares, J. Stultz, M. Newman, V. Smith, R. Kent, E. Carpino, et al., Light augments tooth whitening with peroxide, The Journal of the American Dental Association, 134 (2003) 167-175.
[223] L.Y. Tay, C. Kose, D.R. Herrera, A. Reis, A.D. Loguercio, Long-term efficacy of in-office and at-home bleaching: A 2-year double-blind randomized clinical trial, Am J Dent, 25 (2012) 199.
[224] S. Tsubura, Clinical evaluation of three months' nightguard vital bleaching on tetracycline-stained teeth using polanight 10% carbamide gel: 2-year follow-up study, Odontology, 98 (2010) 134-138.
[225] S. Tsubura, R. Yamaguchi, Clinical evaluation of a new bleaching product "polanight" in a japanese population, Odontology, 93 (2005) 52-55.
[226] M. Turkun, E.U. Celik, A. Aladag, N. Gokay, One-year clinical evaluation of the efficacy of a new daytime at-home bleaching technique, J Esthet Restor Dent, 22 (2010) 139-146.
[227] M. Vano, G. Derchi, A. Barone, A. Genovesi, U. Covani, Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: A 9-month follow-up randomized clinical trial, Int J Dent Hyg, 13 (2015) 301-307.
[228] M. Ward, H. Felix, A clinical evaluation comparing two h2o2 concentrations used with a light-assisted chairside tooth whitening system, Compendium of continuing education in dentistry (Jamesburg, NJ: 1995), 33 (2012) 286-291.
[229] N.U. Wetter, E.P. Branco, A.M. Deana, J.E. Pelino, Color differences of canines and incisors in a comparative long-term clinical trial of three bleaching systems, Lasers Med Sci, 24 (2009) 941-947.
[230] X. Xu, L. Zhu, Y. Tang, Y. Wang, K. Zhang, S. Li, et al., Randomized clinical trial comparing whitening strips, paint-on gel and negative control, Am J Dent, 20 (2007) 28A-31A.
[231] R. Yudhira, M. Peumans, M.L. Barker, R.W. Gerlach, Clinical trial of tooth whitening with 6% hydrogen peroxide whitening strips and two whitening dentifrices, American journal of dentistry, 20 (2007) 32A-36A.
[232] C. Zantner, F. Derdilopoulou, P. Martus, A.M. Kielbassa, Randomized clinical trial on the efficacy of 2 over-the-counter whitening systems, Quintessence Int, 37 (2006)
[233] R. Zekonis, B. Matis, M. Cochran, S.A. Shetri, G. Eckert, T. Carlson, Clinical evaluation of in-office and at-home bleaching treatments, Oper Dent, 28 (2003) 114-121.
[234] K. Zhao, L. Zong, Q. Zhang, W. Att, Clinical comparison between two bleaching techniques: A 180-day follow-up study, Quintessence Int, 44 (2013) 601-607.

[235] D. Ziebolz, K. Helms, C. Hannig, T. Attin, Efficacy and oral side effects of two highly concentrated tray-based bleaching systems, Clin Oral Investig, 11 (2007) 267-275.
[236] S. Ziemba, H. Felix, J. Macdonald, M. Ward, Clinical evaluation of a novel dental whitening lamp and light-catalyzed peroxide gel, The Journal of clinical dentistry, 16 (2004) 123-127.

5 DISCUSSÃO

O processo de randomização equilibra fatores prognósticos conhecidos e desconhecidos na atribuição de tratamentos, mantendo as características basais dos grupos semelhantes na linha de base. Isto é o que faz os ECRs e seus desenhos serem o mais amplamente aceitos e poderosos para avaliar os verdadeiros benefícios dos cuidados na saúde [33]. Assim como a ocultação de alocação, que é tão importante quanto a geração de sequências no processo de randomização, pois protege o processo de randomização, de modo que o tratamento a ser alocado não seja conhecido antes que o paciente esteja inscrito no estudo. Dessa forma, gerar uma sequência aleatória, e deixa-la aberta para o conhecimento, não tem validade [34].

Infelizmente, este é um problema muito comum em ECRs de clareamento, pois o processo de randomização e ocultação da sequência é consistentemente mal executado e incompletamente relatado, como vimos neste trabalho.

Ainda, uma revisão sistemática recente da literatura feita por nosso próprio grupo de pesquisa [35], que avaliou o clareamento caseiro com e sem agente dessensibilizante incorporado ao gel, mostrou que dos oito artigos encontrados ao final [12,13,18-20,36-39], todos foram julgados como incertos no risco de viés. Ou seja, há uma falta de dados confiáveis nos estudos. Ressaltando, mais uma vez a importância de estudos clínicos randomizados seguirem um controle rigoroso de randomização, ocultação da sequência aleatória e cegamento.

Dessa forma, um dos objetivos deste trabalho foi além de estudar a incorporação de um agente dessensibilizante ao gel, especificamente o nitrato de potássio 3% e fluoreto de sódio 0,2% no clareamento caseiro, fazer um ECR rigoroso com os critérios do CONSORT. E o resultado desse estudo mostrou que o agente dessensibilizante não reduziu o risco e a intensidade da sensibilidade dental induzida pelo clareamento. No entanto, esses agentes foram eficazes na minimização da SD, reduzindo a excitabilidade das fibras nervosas pulpares (nitrato de potássio) e/ou ocluindo os túbulos dentinários pela precipitação de cristais de fluoreto de cálcio ou cristais de hidroxiapatita (fluoreto de sódio) [10,19], quando aplicados previamente à aplicação do gel clareador em outros estudos [8,10,40-43].

Já no estudo de clareamento em consultório deste trabalho, a incorporação do agente dessensibilizante ao gel, nitrato de potássio 5%, gerou baixa intensidade de SD nas primeiras 24 horas, e isto está em acordo com os estudos que reportaram que a SD após clareamento ocorre nas primeiras 24 horas [31,40,44], em acordo ainda com uma revisão sistemática recente da literatura que concluiu que o nitrato de potássio e fluoreto de sódio podem reduzir a SD comparado a placebos [10].

Em relação a eficácia, o resultado do procedimento do clareamento vai depender da concentração do agente clareador, da idade do paciente, da capacidade do agente oxidar o componente orgânico da dentina, do número de vezes que o agente está em contato com o tecido dentário e da duração do contato [11,45]. E nos estudos clínicos presentes, a presença ou ausência do agente dessensibilizante no gel clareador não comprometeu a eficácia do clareamento.

Outra característica importante neste trabalho foi a escolha dos caninos para avaliação da cor, a vantagem dessa escolha é que facilita o recrutamento de pacientes, pois é muito difícil encontrar participantes com incisivos mais escuros do que A2 que também atendam aos critérios de inclusão [46-49].

Acrescenta-se ainda, a escolha do desenho dos estudos clínicos serem boca-divida, isso auxilia ao fato de ser o mesmo paciente, ou seja, remove características relacionadas ao dente e hábitos, caso fosse em diferentes indivíduos [31,50,51], permitindo assim, metódos estatísticos de análise que tiram proveito de medidas repetidas dentro de um sujeito com redução da variabilidade [52].

Já a revisão sistemática que avaliou a utilização da luz no clareamento em consultório, o resultado mostrou que a luz não aumenta a eficácia do clareamento. Teoricamente, fontes de calor e luz podem acelerar a decomposição de HP para formar radicais livres de oxigênio e peridroxila, aumentando a eficácia do clareamento [4,53]. No entanto, este aumento não leva a uma maior eficácia clareadora, devido à presença de passos desconhecidos determinantes da taxa no mecanismo de oxidação do clareamento dental [46].

Em acordo com a revisão sistemática acima, a qual mesclou as fontes de luz para compará-las com um grupo controle de clareamento em consultório sem ativação da luz; a outra revisão sistemática deste trabalho com o mesmo objetivo, porém com uma diferença importante, avaliou diferentes tipos de ativação luminosa sobre a eficácia do clareamento por meio de uma abordagem bayesiana de MTC, ou seja, uma combinação direta e indireta dos dados, devido a presença de diferentes fontes de luz presentes no mercado, as quais variam significativamente em espectro de luz, intensidade e potência; sendo um interesse comum entre os profissionais em identificar o tratamento mais eficaz ou classificar os tratamentos entre uma variedade de alternativas clínicas disponíveis.

No entanto, com essa revisão, podemos confirmar mais uma vez de que a ativação com luz, independentemente de sua fonte, não afetou a eficácia do clareamento em termos de mudança de cor, o que de fato confirma os resultados da metanálise tradicional apresentada na

revisão sistemática anterior. Mesmo assim, as variações observadas nos protocolos de clareamento devem ser consideradas, as quais também podem explicar a similaridade entre os grupos.

Em relação à SD com o uso da luz no clareamento em consultório, a primeira revisão sistemática, mostrou que não houve diferença significativa no risco de SD em nenhuma das comparações. No entanto, maior intensidade de SD foi observada quando o clareamento foi realizado usando produtos com baixa concentração de PH com ativação de luz [46,48,54]. A taxa aumentada de radicais livres de PH liberados pela ativação da luz pode aumentar o número de radicais livres que atingem a polpa, levando a uma resposta inflamatória mais intensa e desencadeamento da dor [55]. Na análise de MTC, a SD não foi avaliada, entretanto está sob investigação através de outra análise comparativa de tratamento.

Na revisão sistemática para avaliar o clareamento combinado versus clareamento isolado, foi observada uma menor intensidade da SD no clareamento caseiro quando realizado isoladamente, isso era esperado, devido ao uso de agentes clareadores em concentrações muito maiores no clareamento combinado do que o usado no protocolo caseiro [56-58].

No estudo sobre a adesão dos ECRs de clareamento ao CONSORT, embora as diretrizes tenham sido incluídas nas instruções para autores de alguns periódicos, a conformidade ativa está longe de ser alcançada. Os resultados deste trabalham indicam que a aderência de ECRs de sistemas de clareamento à Declaração CONSORT requer melhorias, além do que, a adesão fará com que os leitores os leitores repensem sua metodologia e, em última instância, reduzam o alto risco de viés dos estudos na área.

Em relação ao risco de viés, embora os resultados incompletos e o relato seletivo tenham sido pouco descritos, principalmente na geração de sequências inadequadas, ocultação de alocação e cegamento do examinador e/ou participantes, nos outros domínios do risco de viés a porcentagem dos estudos com “baixo risco de viés” foi maior.

Ainda, as limitações deste trabalho devem ser relatadas. Em relação aos estudos clínicos, foram avaliados dois produtos de clareamento, cada um em um estudo, dessa forma variações na acidez do gel, concentração e outros aditivos também podem ter um impacto na SD induzida pelo clareamento. Estudos futuros devem se concentrar na incorporação de mais de um agente dessensibilizante ou no aumento da concentração do nitrato de potássio no gel clareador.

Outros ECRs comparando variáveis no protocolo de clareamento, fontes de luz e aplicação devem ser realizados para fornecer uma avaliação mais abrangente das variáveis envolvidas nas técnicas de clareamento.

Por fim, nos adesão ao CONSORT e análise dos riscos de viés nos ECRs de clareamento, embora uma pesquisa muito abrangente em termos de diferentes bancos de dados com vocabulário específico e palavras-chave tenha sido realizada, alguns estudos podem não terem sido encontrados na pesquisa.

6 CONCLUSÕES

Estudos clínicos randomizados

(1) A incorporação do agente dessensibilizante no gel clareador 10% PC não afetou a cor e não reduziu a SD no clareamento caseiro.

(2) A incorporação do agente dessensibilizante no gel clareador 35% PH não afetou a cor e o risco de SD, porém diminuiu a intensidade da SD no clareamento em consultório.

Revisões sistemáticas

(3) A ativação com luz no clareamento em consultório não melhorou a cor nem afetou a SD, mas em baixas concentrações houve uma menor SD sem o uso da luz.

(4) Nenhuma fonte de luz foi melhor na alteração da cor comparada a ausência da mesma no clareamento em consultório independente da concentração de PH utilizada.

(5) O clareamento combinado produziu uma maior intensidade de SD comparado ao clareamento caseiro isolado, sem qualquer benefício adicional em termos de mudança de cor. Já na comparação do clareamento combinado versus o clareamento em consultório isolado, produziu uma mudança de cor semelhante, mas não foram obtidas informações sobre a SD entre essas duas abordagens de clareamento.

(6) A adesão ao CONSORT em ECRs de diferentes técnicas de clareamento é baixa e com alto risco de viés.

7 REFERÊNCIAS

[1] C.M. Carey, Tooth whitening: What we now know Journal of Evidence-Based Dental Practice, 14 (2014) 70-76.
[2] S.S. Meireles, M.L. Goettems, R.V. Dantas, D. Bona Á, I.S. Santos, F.F. Demarco. Changes in oral health related quality of life after dental bleaching in a double-blind randomized clinical trial. Journal of Dentistry; 2014. p. 114-121.
[3] J. Martin, L. Moncada, O.B. Oliveira Junior, J.R.C. Saad, E. Fernandez, V. Rivas, et al., Personality style in patients looking for tooth bleaching and its correlation with treatment satisfaction, Braz Dent J, 27 (2016) 60-65.
[4] M. Kashima-Tanaka, Y. Tsujimoto, K. Kawamoto, N. Senda, K. Ito, M. Yamazaki, Generation of free radicals and/or active oxygen by light or laser irradiation of hydrogen peroxide or sodium hypochlorite, J Endod, 29 (2003) 141-143.
[5] D. Nathanson, Vital tooth bleaching: Sensitivity and pulpal considerations, J Am Dent Assoc, 128 (1997) 41S-44S.
[6] C. Turssi, R. Schiavoni, M. Serra, I. Froner, Permeability of enamel following light-activated power bleaching, General Dentistry, 54 (2006) 323-326.
[7] A.P. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A.D. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, (2016)
[8] E. Bonafe, A.D. Loguercio, A. Reis, S. Kossatz, Effectiveness of a desensitizing agent before in-office tooth bleaching in restored teeth, Clin Oral Investig, 18 (2014) 839-845.
[9] S.O. Parreiras, P. Vianna, S. Kossatz, A.D. Loguercio, A. Reis, Effects of light activated in-office bleaching on permeability, microhardness, and mineral content of enamel, Oper Dent, 39 (2014) E225-230.
[10] Y. Wang, J. Gao, T. Jiang, S. Liang, Y. Zhou, B.A. Matis, Evaluation of the efficacy of potassium nitrate and sodium fluoride as desensitizing agents during tooth bleaching treatment - a systematic review and meta-analysis, J Dent, 43 (2015) 913-923.
[11] M. Rezende, A.D. Loguercio, S. Kossatz, A. Reis, Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis, J Dent, 45 (2016) 1-6.
[12] J.R. Gallo, J.O. Burgess, A.H. Ripps, M.J. Bell, D.E. Mercante, J.M. Davidson, Evaluation of 30% carbamide peroxide at-home bleaching gels with and without potassium nitrate--a pilot study, Quintessence Int, 40 (2009)
[13] C. Navarra, B. Reda, M. Diolosà, I. Casula, R. Di Lenarda, L. Breschi, et al., The effects of two 10% carbamide peroxide nightguard bleaching agents, with and without desensitizer, on enamel and sensitivity: An in vivo study, Int J Dent Hyg, 12 (2014) 115-120.
[14] L.Y. Tay, C. Kose, A.D. Loguercio, A. Reis, Assessing the effect of a desensitizing agent used before in-office tooth bleaching, The Journal of the American Dental Association, 140 (2009) 1245-1251.
[15] A. Reis, S. Kossatz, G.C. Martins, A.D. Loguercio. Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: A randomized clinical trial. Operative Dentistry; 2013. p. 386-393.
[16] E.A. De Paula, S. Kossatz, D. Fernandes, A.D. Loguercio, A. Reis, Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: A randomized tripleblind clinical trial, Oper Dent, 39 (2014) 128-135.
[17] S.J. Padayatty, H. Sun, Y. Wang, H.D. Riordan, S.M. Hewitt, A. Katz, et al., Vitamin c pharmacokinetics: Implications for oral and intravenous use, Annals of internal medicine, 140 (2004) 533-537.
[18] M. Giniger, J. Macdonald, S. Ziemba, H. Felix. The clinical performance of professionally dispensed bleaching gel with added amorphous calcium phosphate. J Am Dent Assoc; 2005. p. 383-392.
[19] W.D. Browning, D.C. Chan, M.L. Myers, W.W. Brackett, M.G. Brackett, D.H. Pashley, Comparison of traditional and low sensitivity whiteners, Oper Dent, 33 (2008) 379-385.

[20] J.B. Da Costa, R. Mcpharlin, T. Hilton, J.L. Ferracane, M. Wang, Comparison of two at-home whitening products of similar peroxide concentration and different delivery methods, Oper Dent, 37 (2012) 333-339.
[21] J.C. Ontiveros, In-office vital bleaching with adjunct light, Dent Clin North Am, 55 (2011) 241-253.
[22] M. Sulieman, M. Addy, J.S. Rees, Development and evaluation of a method in vitro to study the effectiveness of tooth bleaching, Journal of Dentistry, 31 (2003) 415-422.
[23] G. Moncada, D. Sepulveda, K. Elphick, M. Contente, J. Estay, V. Bahamondes, et al., Effects of light activation, agent concentration, and tooth thickness on dental sensitivity after bleaching, Oper Dent, 38 (2013) 467-476.
[24] L.B. He, M.Y. Shao, K. Tan, X. Xu, J.Y. Li, The effects of light on bleaching and tooth sensitivity during in-office vital bleaching: A systematic review and meta-analysis, J Dent, 40 (2012) 644-653.
[25] R.K. Henry, S.M. Bauchmoyer, W. Moore, R.G. Rashid, The effect of light on tooth whitening: A split-mouth design, Int J Dent Hyg, 11 (2013) 151-154.
[26] G. Lu, A. Ades, Combination of direct and indirect evidence in mixed treatment comparisons, Statistics in medicine, 23 (2004) 3105-3124.
[27] P.F. Dawson, M.O. Sharif, A.B. Smith, P.A. Brunton. A clinical study comparing the efficacy and sensitivity of home vs combined whitening. Operative Dentistry; 2011. p. 460-466.
[28] S. Deliperi, D.N. Bardwell, A. Papathanasiou, Clinical evaluation of a combined in-office and take-home bleaching system, J Am Dent Assoc, 135 (2004) 628-634.
[29] B.A. Matis, M.A. Cochran, G. Wang, G.J. Eckert, A clinical evaluation of two in-office bleaching regimens with and without tray bleaching, Operative Dentistry, 34 (2009) 142-149.
[30] M. Rezende, L. Ferri, S. Kossatz, A.D. Loguercio, A. Reis, Combined bleaching technique using low and high hydrogen peroxide in-office bleaching gel, Oper Dent, 41 (2016) 388-396.
[31] J.K. Bernardon, N. Sartori, A. Ballarin, J. Perdigao, G. Lopes, L.N. Baratieri, Clinical performance of vital bleaching techniques, Oper Dent, 35 (2010) 3-10.
[32] G. Kugel, R.D. Perry, E. Hoang, W. Scherer, Effective tooth bleaching in 5 days: Using a combined in-office and at-home bleaching system, Compend Contin Educ Dent, 18 (1997) 378, 380-373.
[33] C. Begg, M. Cho, S. Eastwood, Et Al., Improving the quality of reporting of randomized controlled trials: The consort statement, JAMA, 276 (1996) 637-639.
[34] K.F. Schulz, D.A. Grimes, Allocation concealment in randomised trials: Defending against deciphering, Lancet, 359 (2002) 614-618.
[35] M. Rezende, F. Coppla, K. Chemin, A.C. Chibinski, A.D. Loguercio, A. Reis, Tooth sensitivity after dental bleaching with a desensitizing-containing and a desensitizing-free bleaching gel: A systematic review and meta-analysis, Oper Dent, (2018)
[36] V. Alonso De La Peña, O. Balboa Cabrita. Comparison of the clinical efficacy and safety of carbamide peroxide and hydrogen peroxide in at-home bleaching gels. Quintessence Int; 2006. p. 551-556.
[37] M. Giniger, J. Macdonald, M. Spaid, H. Felix, A 180-day clinical investigation of the tooth whitening efficacy of a bleaching gel with added amorphous calcium phosphate, J Clin Dent, 16 (2005) 11-16.
[38] D. Ziebolz, K. Helms, C. Hannig, T. Attin. Efficacy and oral side effects of two highly concentrated tray-based bleaching systems. Clin Oral Investig; 2007. p. 267-275.
[39] L. Tam, Effect of potassium nitrate and fluoride on carbamide peroxide bleaching, Quintessence Int, 32 (2001)
[40] L.Y. Tay, C. Kose, A.D. Loguercio, A. Reis, Assessing the effect of a desensitizing agent used before in-office tooth bleaching, J Am Dent Assoc, 140 (2009) 1245-1251.
[41] S. Kossatz, G. Martins, A.D. Loguercio, A. Reis. Tooth sensitivity and bleaching effectiveness associated with use of a calcium-containing in-office bleaching gel. J Am Dent Assoc; 2012. p. e81-87.
[42] G.C. Martins, A.C.S.D.A. Izidoro, L.M.B. Meister, S. Kossatz, O.M.M. Gomes, A.D. Loguercio, et al., Avaliação clínica do uso de um dessensibilizante antes do clareamento de consultório, Rev Assoc Paul Cir Dent, 65 (2011) 119-123.

[43] M. Pale, J.R. Mayoral, J. Llopis, M. Valles, J. Basilio, M. Roig, Evaluation of the effectiveness of an in-office bleaching system and the effect of potassium nitrate as a desensitizing agent, Odontol, 102 (2014) 203-210.
[44] L.Y. Tay, C. Kose, D.R. Herrera, A. Reis, A.D. Loguercio, Long-term efficacy of in-office and at-home bleaching: A 2-year double-blind randomized clinical trial, Am J Dent, 25 (2012) 199-204.
[45] J.E. Dahl, U. Pallesen, Tooth bleaching - a critical review of the biological aspects, Critical Reviews in Oral Biology & Medicine, 14 (2003) 292-304.
[46] A. Mena-Serrano, E. Garcia, I. Luque-Martinez, R. Grande, A. Loguercio, A. Reis, A single-blind randomized trial about the effect of hydrogen peroxide concentration on light-activated bleaching, Oper Dent, 41 (2016) 455-464.
[47] N.U. Wetter, E.P. Branco, A.M. Deana, J.E. Pelino, Color differences of canines and incisors in a comparative long-term clinical trial of three bleaching systems, Lasers Med Sci, 24 (2009) 941-947.
[48] J.C. Ontiveros, R.D. Paravina, Color change of vital teeth exposed to bleaching performed with and without supplementary light, J Dent, 37 (2009) 840-847.
[49] O. Polydorou, M. Wirsching, M. Wokewitz, P. Hahn. Three-month evaluation of vital tooth bleaching using light units-a randomized clinical study. Oper Dent; 2013. p. 21-32.
[50] S. Al Shethri, B.A. Matis, M.A. Cochran, R. Zekonis, M. Stropes. A clinical evaluation of two in-office bleaching products. Oper Dent; 2003. p. 488-495.
[51] E. Lesaffre, B. Philstrom, I. Needleman, H. Worthington, The design and analysis of split-mouth studies: What statisticians and clinicians should know, Stat Med, 28 (2009) 3470-3482.
[52] A.A. Antczak-Bouckoms, J. Tulloch, C.S. Berkey, Split-mouth and cross-over designs in dental research, J Clin Periodontol, 17 (1990) 446-453.
[53] A. Joiner, The bleaching of teeth: A review of the literature, J Dent, 34 (2006) 412-419.
[54] S.L. Ziemba, H. Felix, J. Macdonald, M. Ward, Clinical evaluation of a novel dental whitening lamp and light-catalyzed peroxide gel, J Clin Dent, 16 (2005) 123-127.
[55] L. Markovic, K. Fotouhi, H. Lorenz, R.A. Jordan, P. Gaengler, S. Zimmer, Effects of bleaching agents on human enamel light reflectance, Oper Dent, 35 (2010) 405-411.
[56] F. Krause, S. Jepsen, A. Braun, Subjective intensities of pain and contentment with treatment outcomes during tray bleaching of vital teeth employing different carbamide peroxide concentrations, Quintessence International, 39 (2008) 203-209.
[57] C. Kose, A. Reis, L.N. Baratieri, A.D. Loguercio. Clinical effects of at-home bleaching along with desensitizing agent application. Am J Dent; 2011. p. 379-382.
[58] S.S. Meireles, S.S. Heckmann, I.S. Santos, A. Della Bona, F.F. Demarco, A double blind randomized clinical trial of at-home tooth bleaching using two carbamide peroxide concentrations: 6-month follow-up, Journal of Dentistry, 36 (2008) 878-884.

8 ANEXOS

8.1 Escala de Sensibilidade Dental

8.1.1 Escala Visual Analógica

8.1.2 Escala de Classificação Numérica

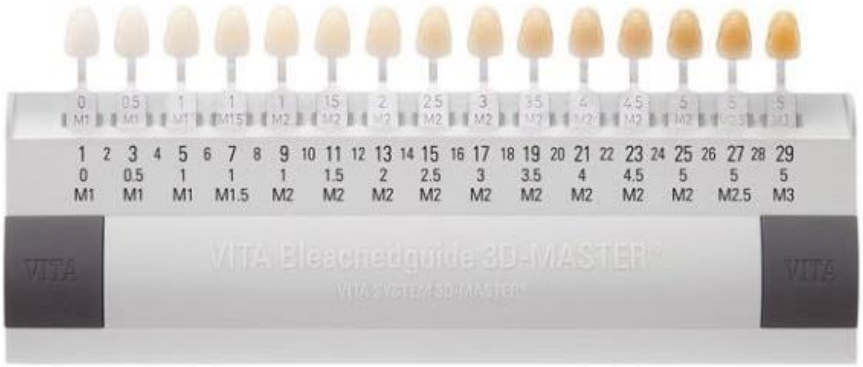
NRS

0 – Nenhuma		1 – Leve		2 – Moderada		3-Considerável		4 – Severa	
D	E	D	E	D	E	D	E	D	E

8.2 Escala de Cor

8.2.1 Vita Classical (Vita Classical Shade, Vita Zahnfabrik, Bad Säckingen, Alemanha)

8.2.2 Vita Bleachedguide 3D-Master (BG, VITA Zahnfabrik, Bad Säckingen, Alemanha)



8.2.3 Espectrofotômetro Vita Easyshade (VITA Zahnfabrik, Bad Säckingen, Alemanha)

8.3 ARTIGO 1

8.3.1 Parecer final

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO DA SENSIBILIDADE PÓS CLAREAMENTO DENTAL AT HOME APLICANDO GEL CLAREADOR COM E SEM AGENTE DESSENSIBILIZANTE ¿ ESTUDO CLÍNICO RANDOMIZADO, TRIPLO CEGO

Pesquisador: Alessandra Reis

Área Temática:

Versão: 2

CAAE: 60047516.1.0000.0105

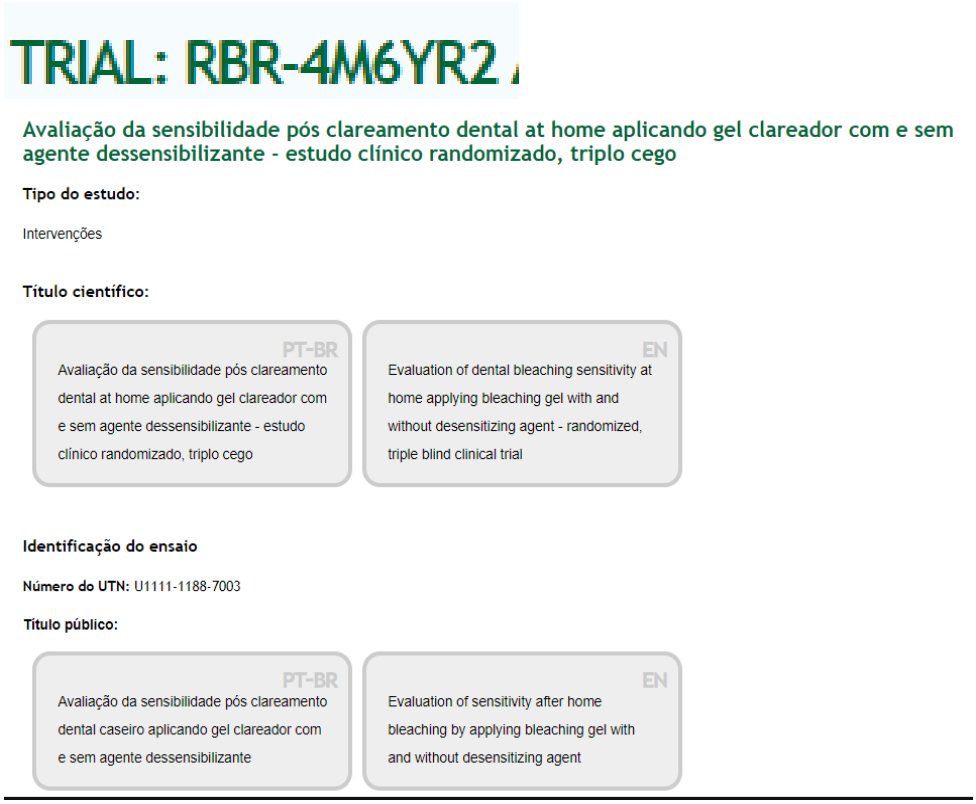
Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.762.164

8.3.2 Registro de Ensaios Clínicos



TRIAL: RBR-4M6YR2

Avaliação da sensibilidade pós clareamento dental at home aplicando gel clareador com e sem agente dessensibilizante - estudo clínico randomizado, triplo cego

Tipo do estudo:

Intervenções

Titulo cientifico:

PT-BR
Avaliação da sensibilidade pós clareamento dental at home aplicando gel clareador com e sem agente dessensibilizante - estudo clínico randomizado, triplo cego

EN
Evaluation of dental bleaching sensitivity at home applying bleaching gel with and without desensitizing agent - randomized, triple blind clinical trial

Identificação do ensaio

Número do UTN: U1111-1188-7003

Titulo público:

PT-BR
Avaliação da sensibilidade pós clareamento dental caseiro aplicando gel clareador com e sem agente dessensibilizante

EN
Evaluation of sensitivity after home bleaching by applying bleaching gel with and without desensitizing agent

8.4 ARTIGO 2

8.4.1 Parecer final

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO DA SENSIBILIDADE PÓS CLAREAMENTO DENTAL IN OFFICE APLICANDO GEL CLAREADOR COM E SEM AGENTE DESSENSIBILIZANTE ¿ ESTUDO CLÍNICO RANDOMIZADO, TRIPLO CEGO

Pesquisador: Alessandra Reis

Área Temática:

Versão: 1

CAAE: 60046016.0.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.756.984

8.4.2 Registro de Ensaios Clínicos

TRIAL: RBR-4TKYS8

Avaliação da sensibilidade pós clareamento dental in office aplicando gel clareador com e sem agente dessensibilizante - estudo clínico randomizado, triplo cego

Tipo do estudo:

Intervenções

Titulo científico:

PT-BR
Avaliação da sensibilidade pós clareamento dental in office aplicando gel clareador com e sem agente dessensibilizante - estudo clínico randomizado, triplo cego

EN
Evaluation of tooth sensitivity after in office dental bleaching applying whitening gel with and without desensitizing agent - randomized clinical trial, triple blind

Identificação do ensaio

Número do UTN: U1111-1188-6972

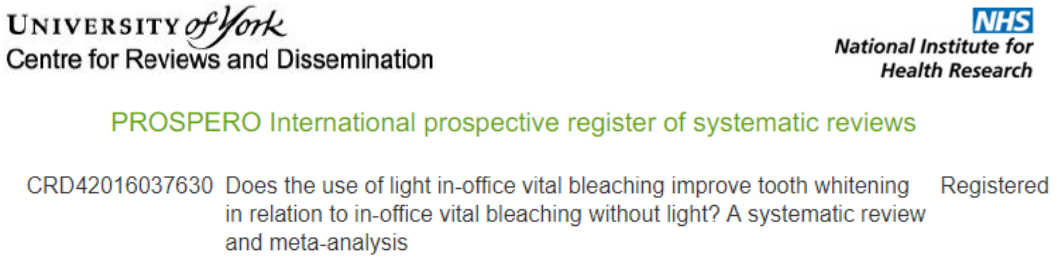
Título público:

PT-BR
Avaliação da sensibilidade pós clareamento dental de consultório com gel clareador com e sem agente dessensibilizante

EN
Evaluation of dental office bleaching sensitivity with bleaching gel with and without desensitizing agent

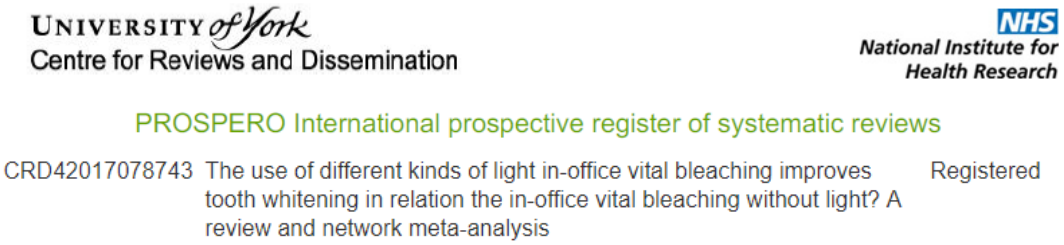
8.5 ARTIGO 3

8.5.1 PROSPERO



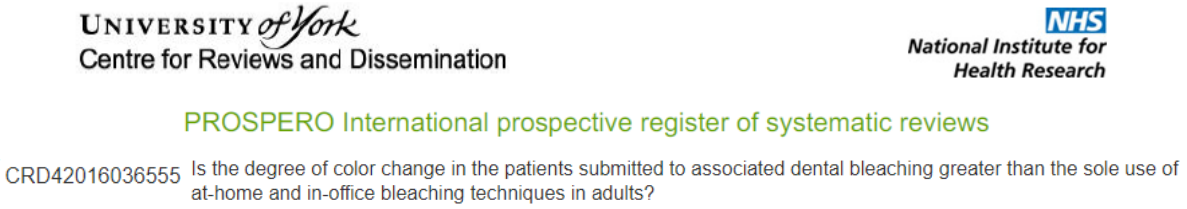
8.6 ARTIGO 4

8.6.1 PROSPERO



8.7 ARTIGO 5

8.7.1 PROSPERO



9 APÊNDICES

9.1 ARTIGO 1

9.1.1 TCLE

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

A pesquisa intitulada "Avaliação da sensibilidade pós clareamento dental *at home* aplicando gel clareador com e sem agente dessensibilizante – estudo clínico randomizado, triplo cego" tem como objetivo avaliar o grau de sensibilidade dos dentes após a realização do clareamento dental com e sem o agente dessensibilizante dental presente no gel clareador, bem como o grau de coloração. A resposta da pesquisa pode trazer benefício clínico aos pacientes que desejarem clarear seus dentes, pois se espera que os efeitos adversos como sensibilidade dental sejam menores. Esta pesquisa clínica será realizada nas clínicas odontológicas da Universidade Estadual de Ponta Grossa, pela aluna do doutorado Bianca Medeiros Maran e pela professora Alessandra Reis Silva Loguercio. Para execução da pesquisa serão necessários 60 voluntários que atendam aos critérios de seleção e concordem em participar de livre e espontânea vontade.

No início do tratamento clareador, será feita uma limpeza nos dentes, e os voluntários receberão uma moldeira de silicone para aplicação do gel clareador para uso caseiro. Que deverá ser utilizada três horas por dia durante 21 dias, de tal forma que de um lado será aplicado um gel com dessensibilizante e do outro lado um gel sem o agente dessensibilizante. Todos os materiais empregados no tratamento já apresentam eficácia comprovada e serão fornecidos pelos pesquisadores sem nenhum custo para os voluntários. Durante todo o período da pesquisa os voluntários serão acompanhados pelos pesquisadores para verificação de qualquer efeito adverso como sensibilidade dental. Caso ocorra, os voluntários serão imediatamente tratados e acompanhados, se necessário, o paciente será medicado com analgésicos e/ou anti-inflamatórios. Para o tratamento de reações adversas, os custos estão previstos no orçamento do projeto.

Quanto aos benefícios, os indivíduos da pesquisa terão seus dentes clareados e receberão gratuitamente o tratamento. Os indivíduos terão a garantia de que receberão esclarecimento a qualquer dúvida, acerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa. Os pesquisadores responsáveis assumem o compromisso de proporcionar informação atualizada obtida durante o estudo, ainda que esta possa afetar a vontade do indivíduo em continuar participando dele.

Os voluntários têm a liberdade de se recusar a participar da pesquisa ou de retirar seu consentimento a qualquer momento, sem sofrer qualquer tipo de prejuízo, ou represálias de qualquer natureza. Os pesquisadores se comprometem a resguardar todas as informações individuais, tratando-as com impessoalidade e não revelando a identidade do sujeito que as originou.

Eu, _____, certifico que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Bianca Medeiros Maran e pela professora Alessandra Reis Silva Loguercio, estou plenamente de acordo com a realização do experimento voluntário do trabalho de pesquisa, exposto acima. Certifico também ter recebido uma cópia deste Termo de Consentimento Livre e Esclarecido.

Ponta Grossa, _____ de _____ de 2016.

Nome:_____
Assinatura:_____
Pesquisador Responsável:_____
1ª via da instituição, 2ª via do sujeito da pesquisa.
Para entrar em contato com os pesquisadores:
Bianca Medeiros Maran (42) 9925-6046
Alessandra Reis Silva Loguercio (42) 3220-3741
ATENÇÃO: A sua participação em qualquer tipo de pesquisa é voluntária. Em caso de dúvida quanto aos seus direitos, entre em contato com a Comissão de Ética em Pesquisa da UEPG. Endereço – Av. Carlos Cavalcanti, n.4748, Bloco M, Sala 100, CEP- 84030-900 – Ponta Grossa – PR. Fone: (42) 3220-3108. email: coep@uepg.br

9.2 ARTIGO 2

9.2.1 TCLE

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

A pesquisa intitulada "Avaliação da sensibilidade pós clareamento dental *in office* aplicando gel clareador com e sem agente dessensibilizante – estudo clínico randomizado, triplo cego" tem como objetivo avaliar o grau de sensibilidade dos dentes após a realização do clareamento dental com e sem o agente dessensibilizante dental presente no gel clareador, bem como o grau de coloração. A resposta da pesquisa pode trazer benefício clínico aos pacientes que desejarem clarear seus dentes, pois se espera que os efeitos adversos como sensibilidade dental sejam menores. Esta pesquisa clínica será realizada nas clínicas odontológicas da Universidade Estadual de Ponta Grossa, pela aluna do doutorado Bianca Medeiros Maran e pela professora Alessandra Reis Silva Loguercio. Para execução da pesquisa serão necessários 60 voluntários que atendam aos critérios de seleção e concordem em participar de livre e espontânea vontade.

No início do tratamento clareador, será feita uma limpeza nos dentes, e os voluntários serão submetidos a uma barreira gengival para evitar o extravasamento do gel na cavidade oral. Posteriormente será feita a aplicação do gel clareador, de tal forma que de um lado será aplicado um gel com dessensibilizante e do outro lado um gel sem o agente dessensibilizante. Os voluntários receberão 1 aplicação única do gel por 50 minutos. Todos os materiais empregados no tratamento já apresentam eficácia comprovada e serão fornecidos pelos pesquisadores sem nenhum custo para os voluntários. Durante todo o período da pesquisa os voluntários serão acompanhados pelos pesquisadores para verificação de qualquer efeito adverso como sensibilidade dental. Caso ocorra, os voluntários serão imediatamente tratados e acompanhados, se necessário, o paciente será medicado com analgésicos e/ou anti-inflamatórios. Para o tratamento de reações adversas, os custos estão previstos no orçamento do projeto.

Quanto aos benefícios, os indivíduos da pesquisa terão seus dentes clareados e receberão gratuitamente o tratamento. Os indivíduos terão a garantia de que receberão esclarecimento a qualquer dúvida, acerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa. Os pesquisadores responsáveis assumem o compromisso de proporcionar informação atualizada obtida durante o estudo, ainda que esta possa afetar a vontade do indivíduo em continuar participando dele.

Os voluntários têm a liberdade de se recusar a participar da pesquisa ou de retirar seu consentimento a qualquer momento, sem sofrer qualquer tipo de prejuízo, ou represálias de qualquer natureza. Os pesquisadores se comprometem a resguardar todas as informações individuais, tratando-as com impessoalidade e não revelando a identidade do sujeito que as originou.

Eu, _____, certifico que tendo lido as informações acima e suficientemente esclarecido de todos os itens, pelos pesquisadores clínicos responsáveis: Bianca Medeiros Maran e pela professora Alessandra Reis Silva Loguercio, estou plenamente de acordo com a realização do experimento voluntário do trabalho de pesquisa, exposto acima. Certifico também ter recebido uma cópia deste Termo de Consentimento Livre e Esclarecido.

Ponta Grossa, _____ de _____ de 2016.

Nome:_____

Assinatura:_____

Pesquisador Responsável:_____

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

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