Murilo Navarro de Oliveira

Análise Comparativa de alteração de cor em protocolos de clareamento dental: Revisão Sistemática e network metanálise

Comparative analysis of tooth color change -in dental bleaching protocols: a systematic review and network meta-analysis

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia para obtenção de Título de Mestre em Clínica Odontológica.

Uberlândia, 2020

Murilo Navarro de Oliveira

Análise Comparativa de alteração de cor em protocolos de clareamento dental: Revisão Sistemática e network metanálise.

Comparative analysis of tooth color change -in dental bleaching protocols: a systematic review and network meta-analysis

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia para obtenção de Título de Mestre em Clínica Odontológica.

Uberlândia, 2020

UNIVERSIDADE FEDERAL DE UBERLÂNDIA
Coordenação do Programa de Pós-Graduação em Odontologia
Av. Pará, 1720, Bloco 4L, Anexo B, Sala 35 - Bairro Umuarama, Uberlândia-MG, CEP 38400-902 Telefone: (34) 3225-8115/8108 - www.ppgoufu.com - copod@umuarama.ufu.br

ATA DE DEFESA - PÓS-GRADUAÇÃO

Programa de Pós-Graduação em:	Odontologia				
Defesa de:	Dissertação de Mestrado Acadêmico, número 366, sigla do PPGO				
Data:	Doze de fevereiro de dois mil e vinte	Hora de início:	09:00	Hora de encerramento:	12:20hs
Matrícula do Discente:	11812ODO011				
Nome do Discente:	Murilo Navarro de Oliveira				
Título do Trabalho:	Análise Comparativa de alteração de cor em protocolos de clareamento dental: Revisão Sistemática e network metanálise				
Área de concentração:	Clínica Odontológica Integrada				
Linha de pesquisa:	Propriedades Físicas e Biológicas dos materiais Odontológicos e das estruturas dentais				
Projeto de Pesquisa de vinculação:	Propriedades Físicas e Biológicas dos materiais Odontológicos e das estruturas dentais				

Reuniu-se no Anfiteatro/Sala 23, Bloco 4L Anexo A, Campus Umuarama, da Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Odontologia, assim composta: Professores Doutores: Carlos José Soares (UFU); Gustavo Giacomelli Nascimento (Aarhus University) e Paulo Cesar de Freitas Santos Filho orientador(a) do(a) candidato(a). O Prof. Dr. Gustavo Giacomelli Nascimento participou da defesa de Dissertação por meio de vídeo-conferência desde a cidade de Ãrhus- Dinamarca ; e os demais membros da Banca participaram *in loco.*

Iniciando os trabalhos o(a) presidente da mesa, Dr(a). Paulo Cesar de Freitas Santos Filho, apresentou a Comissão Examinadora e o candidato(a), agradeceu a presença do público, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

A seguir o senhor(a) presidente concedeu a palavra, pela ordem sucessivamente, aos(às) examinadores(as), que passaram a arguir o(a) candidato(a). Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu o resultado final, considerando o(a) candidato(a):

Aprovado.

Esta defesa faz parte dos requisitos necessários à obtenção do titulo de Mestre.

O competente diploma será expedido após cumprimento dos demais requisitos, conforme as normas do Programa, a legislação pertinente e a regulamentação interna da UFU.

Nada mais havendo a tratar foram encerrados os trabalhos. Foi lavrada a presente ata que após lida e achada conforme foi assinada pela Banca Examinadora.

ocumento assinado eletronicamente por **Paulo César de Freitas Santos Filho**, **Professor(a) do agistério Superior**, em 12/02/2020, às 12:21, conforme horário oficial de Brasília, com fundamento no . 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

ocumento assinado eletronicamente por **Carlos José Soares**, **Professor(a) do Magistério Superior**, em /02/2020, às 12:21, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do ecreto nº 8.539, de 8 de outubro de 2015.

ocumento assinado eletronicamente por **Gustavo Giacomellli Nascimento**, **Usuário Externo**, em /02/2020, às 12:23, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do ecreto nº 8.539, de 8 de outubro de 2015.

autenticidade deste documento pode ser conferida no site h s://www.sei.ufu.br/sei/controlador_externo.php? ao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **1866395** e o digo CRC **12F0379D**.

Ficha Catalográfica Online do Sistema de Bibliotecas da UFU
com dados informados pelo(a) próprio(a) autor(a).

O48
2020

Oliveira, Murilo Navarro de, 1991-
Análise Comparativa de alteração de cor em protocolos de clareamento dental: Revisão Sistemática e network metanálise [recurso eletrônico] / Murilo Navarro de Oliveira. - 2020.

Orientador: Paulo Cesar Freitas Santos Filho.
Coorientador: Luiz Renato Paranhos.
Dissertação (Mestrado) - Universidade Federal de Uberlândia, Pós-graduação em Odontologia.
Modo de acesso: Internet.
Disponível em: http://doi.org/10.14393/ufu.di.2020.195
Inclui bibliografia.
Inclui ilustrações.

1. Odontologia. I. Santos Filho, Paulo Cesar Freitas, 1983-, (Orient.). II. Paranhos, Luiz Renato,1975-, (Coorient.). III. Universidade Federal de Uberlândia. Pós-graduação em Odontologia. IV. Título.

CDU: 616.314

Bibliotecários responsáveis pela estrutura de acordo com o AACR2:
Gizele Cristine Nunes do Couto - CRB6/2091
Nelson Marcos Ferreira - CRB6/3074

SUMÁRIO

RESUMO

Objetivo: Buscar ensaios clínicos randomizados que comparam diferentes protocolos de clareamento dental, para se avaliar quais técnicas apresentam os melhores resultados de alteração de cor.

Material e métodos: Foram utilizadas nove bases de dados, incluindo parte da "literatura cinzenta". Os protocolos clareadores foram divididos em quatro grupos (*In-Office*, *At-Home*, Combinados e *Whitestrips*) e agrupados de acordo com o agente clareador, concentração do material e tempo de atuação. A extração de dados e avaliação do risco de viés foi realizada e os valores de ΔEab foram coletados em quatro tempos de tratamento (Imediatamente após, sete dias, 30 dias e 180 dias). A network foi realizada para se comparar indiretamente a alteração de cor dos protocolos clareadores. Diferentes análises foram executadas para cada follow-up, e as comparações não eram iguais para os diferentes tempos de avaliação.

Resultados: 19 ensaios clínicos com ao menos um grupo em comum com outros estudos foram incluídos na metanálise. Os resultados imediatamente após foram divididos em duas análises sem um comparador em comum entre eles e os protocolos exclusivamente *in-office* apresentaram resultados piores quando comparados as outras técnicas. Após sete dias, a análise apresentou melhores valores de ΔEab para técnicas combinadas. A análise de 30 dias após o tratamento clareador foi dividida em três partes sem relação entre elas e protocolos combinados ou at-home apresentaram maior índice de alteração de cor, técnicas *in-office* não apresentam diferença estatística entre elas. Os resultados de 180 dias foram limitados a quatro protocolos, e uma técnica *at-home* foi melhor do que três métodos *in-office*.

Conclusões: Protocolos exclusivamente In-Office apresentaram resultados piores em alteração de cor quando comparadas as outras técnicas.

PALAVRAS-CHAVE: manchamento dental, clareamento dental, agentes clareadores, network metanálise

ABSTRACT

Objectives: Looking after clinical randomized trials that compare different protocols of teeth whitening, to evaluate which methods presents the best results of color change.

Methods: Nine databases were used, including part of the gray literature". The whitening methods were divided in four groups (In-Office, At-home, Combined and Whitestrips) and grouped according to each whitening agent, material concentration and action time. Data extraction and risk of bias assessment were performed and the values of ΔEab were collected in four times after treatment (immediately after, seven days, 30 days and 180 days). Network was performed to indirectly compare color change of bleaching protocols. Different analyses were performed for each follow-up, and the comparisons were not equal over the different time points.

Results: 19 clinical trials with at least one common group with other studies were included in the meta-analysis. The results immediately after were divided in two analysis with no common comparator and the exclusively in-office protocols presents worse results of color change compared to other techniques. After seven days, the analysis shows better values of ΔEab for a combined technique. The 30 days after analysis were divided in three parts with no relation between them and at-home or combined protocols related higher degree of color change, in-office techniques did not show statistical difference among them. And the results of 180 days were limited to four protocols, and an at-home technique were better than other three in-office methods.

Conclusions: Exclusively In-Office techniques presented worse results of color change compared to other techniques.

KEYWORDS: tooth staining, dental bleaching, bleaching agents, network metanalysis

INTRODUÇÃO E REFERENCIAL TEÓRICO

A cor dos dentes é um fator que influencia diretamente a autopercepção de estética facial, afetando a qualidade de vida dos pacientes. (Hofel *et al.*, 2007; Al-Zarea, 2013) Essa busca por estética vem levando a um crescente aumento na procura por procedimentos de clareamento dental em clínicas odontológicas nas últimas décadas, essa procura é influenciada também pelo fato desses procedimentos serem minimamente invasivos, e apresentarem resultados satisfatórios em um curto intervalo de tempo. (Kihn, 2007; Brunton *et al.*, 2008)

O tratamento clareador mais comumente utilizado é realizado utilizando-se como agente principal o peróxido de hidrogênio (H_2O_2), uma molécula altamente instável que se quebra liberando radicais hidroxila, responsáveis pela quebra dos cromófilos, fato que causa a alteração de cor buscada durante o tratamento. (Féliz-Matos *et al*., 2014) O peróxido de carbamida, também utilizado para o clareamento dental é uma molécula maior e mais estável, que se divide em peróxido de hidrogênio e ureia, que atua como mantenedor de pH, o que faz com que o produto consiga uma eficácia maior em longos períodos de utilização. (Junior *et al.*, 2018; Peixoto *et al.*, 2018)

Os tratamentos de clareamento dental podem ser divididos entre técnicas de aplicação profissional, ou sob supervisão de um cirurgião-dentista. (Serraglio et *al.*, 2016) Esse tipo de clareamento pode ser realizado em consultório (in-office) ou com prescrição para utilização caseira (at-home), com aplicação do agente clareador em uma moldeira adaptada as superfícies dentais. (Machado *et al.*, 2016; Silva *et al.*, 2018)

Há também uma grande variedade de produtos disponibilizados comercialmente, que podem ser comprados em farmácias e/ou supermercados sem a indicação de um cirurgião-dentista e que podem atuar como agente clareador (tiras, bochechos, gomas, dentifrícios). (Serraglio *et al.*, 2016) Porém, alguns desses produtos não possuem peróxido de hidrogênio em sua composição, atuando somente na remoção de manchas extrínsecas, logo, não atuam na alteração da

escala de cor. (Demarco *et al.*, 2009)

A grande busca por tratamentos clareadores também leva a uma grande variedade de produção de produtos clareadores por parte das empresas. O que leva a uma gama de produtos de diferentes concentrações e com a presença de diversos agentes secundários na sua formula, como dessensibilizantes, mantenedores de pH, catalisadores e flavorizantes. (Bruhn *et al.*, 2012; Silva *et al.*, 2018) Esses fatores são geradores de confusão, dificultando o cirurgião-dentista a uma conclusão durante o planejamento do tratamento, baseando a escolha do protocolo clareador em experiências prévias. (Luque-Martínez *et al.*, 2016; De Geus *et al.*, 2018)

O planejamento do método clareador a ser utilizado deve visar a eficácia do tratamento, nesse caso, o índice de alteração de cor é apenas um dos fatores, não sendo o único resultado a ser avaliado. (Markowitz, 2010) O cirurgião-dentista deve visar a satisfação do paciente, e sabendo disso, mesmo levando-se em consideração que procedimentos clareadores são minimamente invasivos, há uma série de efeitos adversos que devem ser considerados, afim de não exercer influência negativa sobre a experiencia do paciente sobre o clareamento. (Goldberg *et al.*, 2009; Cartagena *et al.*, 2014)

Dentre os efeitos adversos mais comuns, incluem-se irritação e inflamação gengival e da mucosa oral, muitas vezes causada por desadaptação da moldeira em tratamentos at-home, ou proteção inadequada em procedimentos in-office. (Majeed *et al.*, 2015) Alteração de morfologia das estruturas (microdureza e rugosidade) dentais, relacionadas a superexposição ao peróxido de hidrogênio e possibilidade de danos a polpa. (Pinto *et al.*, 2004; Soares *et al.*, 2013)

Porém, o efeito adverso mais relatado na literatura é a hipersensibilidade dentinária causada pela reação inflamatória dos tecidos pulpares pela proximidade dos radicais hidroxila liberados pelo agente clareador durante o tratamento. (Darriba *et al.*, 2017) Estudos mostram que a chance e a intensidade da sensibilidade dental estão diretamente relacionadas com a concentração do agente clareador e o tempo de ação do peróxido de hidrogênio sobre as estruturas dentais. (Moncada *et al.*, 2013; Rezende *et al.*, 2018)

Portanto, durante a escolha do protocolo clareador a ser utilizado, o cirurgião dentista deve avaliar, dentre as técnicas clareadoras que apresentem melhor resultado na escala de alteração de cor, por métodos que priorizem a utilização de agentes clareadores de baixa concentração e com a utilização dos mesmos por um menor período de tempo. (Cardoso *et al.*, 2010; Nie *et al.*, 2017)

Devido as propriedades estéticas dos dentes, a forma de avaliação de cor é um desafio na odontologia afim de se representar a real alteração de cor obtida pelo procedimento clareador. (Stephen, 2003) Atualmente as duas metodologias mais estabelecidas na literatura são, de forma subjetiva, através do escore numerado pela escala de cores, onde as cores presentes na escala visual são classificadas de 1 a 15, da mais clara pra mais escura, e avaliada antes e depois do tratamento clareados, o resultado final é dado pelo ΔSGU. (Cho *et al.*, 2007)

Outro método bem relatado em estudos clínicos é baseado na escala de cores CIELAB, onde são levados em consideração os valores iniciais e finais de L* (translucidez), a* (variação de cor do verde ao vermelho) e b* (variação de cor do amarelo ao azul). (Pérez *et al.*, 2015) A avaliação é realizada de maneira objetiva, por instrumentos como espectrofotômetro, colorímetro ou por softwares de análise de imagens e o resultado final é dado em forma de ΔEab. A literatura mostra uma melhor reprodutibilidade na avaliação realizada por meio de instrumentos de avaliação objetiva. (Paul *et al.*, 2002)

Diversos estudos científicos apresentados na literatura realizam ensaios clínicos afim de se comparar a alteração de cor de diferentes técnicas clareadoras. (Loguercio *et al*., 2017; Maran *et al*., 2019) Também são reportadas revisões que avaliam esses ensaios de forma mais ampla, porém sempre de forma dicotômica (por exemplo, técnicas caseiras e de consultório, peróxido de hidrogênio e peróxido de carbamida, ausência ou presença de fontes de luz). (Mokhlis *et al*., 2000; Lu & Ades, 2004) A avaliação por meio de uma network metanalise permite a análise indireta de técnicas que foram realizadas em diferentes estudos, desde que haja um comparador em comum entre elas. Por exemplo, caso um estudo tenha comparado os protocolos A e B, e outro ensaio clínico, os protocolos B e C, a network permite uma comparação indireta entre as técnicas A e C.

(Hutton *et al*., 2015)

Levando isso em consideração, o objetivo desse trabalho foi de se realizar uma revisão sistemática da literatura, buscando ensaios clínicos randomizados que comparavam diferentes protocolos de clareamento dental, afim de se obter avaliações diretas e indiretas da alteração de cor obtida pelo tratamento clareador. Deve-se ressaltar que o objetivo desse estudo, não é criar um "protocolo universal", já que a escolha da técnica a ser utilizada envolve uma série de variáveis. Mas sim realizar a comparação da alteração de cor para que não sejam indicados métodos que vão levar a uma superexposição das estruturas dentais ao agente clareador, aumentando a chance de ocorrência de efeitos adversos

CAPÍTULO ÚNICO – ARTIGO

Comparative analysis of tooth color change -in bleaching protocols: a systematic review and network meta-analysis

Abstract

Objectives: Looking after clinical randomized trials that compare different protocols of teeth whitening, to evaluate which methods presents the best results of color change.

Methods: Nine databases were used, including part of the gray literature". The whitening methods were divided in four groups (In-Office, At-home, Combined and Whitestrips) and grouped according to each whitening agent, material concentration and action time. Data extraction and risk of bias assessment were performed and the values of ΔEab were collected in four times after treatment (immediately after, seven days, 30 days and 180 days). Network was performed to indirectly compare color change of bleaching protocols. Different analyses were performed for each follow-up, and the comparisons were not equal over the different time points.

Results: 19 clinical trials with at least one common group with other studies were included in the meta-analysis. The results immediately after were divided in two analysis with no common comparator and the exclusively in-office protocols presents worse results of color change compared to other techniques. After seven days, the analysis shows better values of ΔEab for a combined technique. The 30 days after analysis were divided in three parts with no relation between them and at-home or combined protocols related higher degree of color change, in-office techniques did not show statistical difference among them. And the results of 180 days were limited to four protocols, and an at-home technique were better than other three in-office methods.

Conclusions: Exclusively In-Office techniques presented worse results of color change compared to other techniques.

KEYWORDS: bleaching agents, dental bleaching, network metanalysis, tooth staining

1 INTRODUCTION

The tooth bleaching professionally applied techniques are primarily divided between in-office and at-home, still having the possibility of combining those techniques.[1,2] Also, consumer-purchased/over-the-counter products applied by the patients such as whitening strips are available in supermarkets and pharmacies.[3] Moreover, a range of bleaching agents and their concentration are available on the market resulting in different bleaching possibilities and protocols which hinders the professional to achieve a clear clinical decision, basing this decision on previous clinical experiences.[4-7]

In order to achieve the patient satisfaction the dentist must to consider possible adverse effects that the procedure may lead to, like dental hypersensitivity, caused by the inflammatory reaction of the dental pulp to the hydroxyl radicals action.[8-10] The literature shows that factors like the bleaching agent concentration and the duration of the treatment directly affects the risk and the intensity of dental sensitivity during the whitening protocol.[11-13]

Therefore, to improve the bleaching efficacy and the patient satisfaction, if different protocols present similar results for color change, it is recommendated the chose of techniques that can reduce the chance of dental sensitivity whenever is possible.[14,15] Besides the dental hypersensitivity, the overexposure to hydrogen peroxide can lead to other undesirable adversal effects like alterations on dental structures. The literature shows that the action of bleaching agents can lead to alterations on roughness, microhardness and morphology of enamel surfaces.[16,17]

The color change analysis can be performed by several different methods, the most reported on the literature are, using the Shade Guide Unit score (ΔSGU), or using objective instruments, such as spectrophotometer, colorimeter, or digital image analysis, based on the CIELAB color space system (ΔEab).[18-20] Despite the importance of results obtained using visual shade guides, which can be applied to compare different bleaching techniques,[21] the literature presents more reliable and reproducible results when this evaluation was performed using objective

techniques.[22,23]

Diverse amounts of clinical research have been compared bleaching techniques for presenting the color change results of them to professionals.[23,24] The literature presents scientific evidences that evaluate different methods, however, always comparing a unique result (for example, at-home and in-office, hydrogen peroxide and carbamide peroxide).[4,5,7] The evaluation through meta-analysis network allows that an indirect evaluation could be made between studies that used different procedures, since there is one common comparator group between them.[7,24]

Taking it in consideration, the objective of this article was to perform a systematic review, looking after randomized clinical trials that compare different bleaching protocols evaluating in direct and indirect forms the effectiveness to tooth color change. It should be reinforced that is not possible to determine an "universal protocol", due to each patient needs, the objective is to compare the color change to avoid the indication of unnecessary high concentration agents or excessive chair time that may lead to adversal effects such as dental sensitivity.

2 METHODS AND MATERIALS

2.1 Protocol and registration

This systematic review was performed according to the list of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations[25] and the Cochrane guidelines[26]. The systematic review protocol was registered in the PROSPERO (CRD 42019119802).

2.2 Study design and eligibility criteria

This study was a systematic review that aimed to answer the following guiding question: "Which bleaching protocols presents the best color alteration results?"

The inclusion criteria were only randomized controlled studies that

compare different bleaching protocols, without constraints of year, language and publication status.

Exclusion criteria were: 1) Studies in children and adolescents; 2) Studies in patients with tetracycline staining; 3) Studies that compare the same protocol, using masking substances of only commercial variations; 4) Studies that not clearly described the bleaching protocols used.

2.3 Sources of information and search

The PubMed (including MedLine), Scopus, Latin-American and Caribbean Health Sciences Literature (LILACS), SciELO, Cochrane Library, Embase and Web of Science databases were used as primary study sources. OpenGrey and OpenThesis were used to partially capture the "gray literature". All steps were performed to minimize selection and publication biases.

The MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Embase Subject Headings) resources were used to select the search descriptors. The Boolean operators "AND" and "OR" were used to enhance the research strategy through several combinations. The main terms used on the search were related to the population (“tooth staining”, “stained teeth”), the comparator (“tooth bleaching”, “bleaching agents”) and to the study design (“randomized clinical trials”, “in vivo studies”). The bibliographic research was performed in January 2019. The results obtained were exported to the EndNote Web™ software (Thomson Reuters, Toronto, Canada), in which duplicates were removed. The remaining results were exported to Microsoft Word™ 2010 (Microsoft™ Ltd, Washington, USA), in which the remaining duplicates were manually removed.

2.4 Study selection

The selection of studies was performed in three moments. A calibration exercise previously the phases was done, which the reviewers discussed the

eligibility criteria and applied them to a sample of 10% of the studies retrieved to determine inter-examiner agreement (Kappa ≥0.81). In all moments, two eligibility reviewers [*MNO and MSP*] performed the reading of each phase independently and then the disagreements between of inter-examiners were discussed with a third reviewer [*LRP*] to have a consensus.

Thus, in the first moment a methodical analysis of the titles of the studies was done. The reviewers were not blind to the names of authors and journals. Titles not related to the topic were eliminated in this phase. In the second moment, the abstracts were read for the initial application of the exclusion criteria afore mentioned. The titles met the objectives of the study but did not have abstracts available were fully analyzed in the moment three. In the third moment, preliminary eligible studies had their full texts obtained and evaluated to verify whether they fulfilled the eligibility criteria. The studies rejected were registered separately, explaining the reasons for exclusion.

2.5 Data collection

After selected, the studies were analyzed and two reviewers [*MNO and MSP*] extracted their data for the following information: Identification of the study (author, year and study design), sample characteristics (number of patients in each study and distribution by sex, average age), characteristics of sample collection and processing (protocols used, time of patient monitoring and color evaluation method) and main results (initial evaluation of color and bleaching effectiveness).

In order to ensure the consistency among reviewers, a calibration exercise was performed with both reviewers [*MNO and MSP*], in which information were extracted jointly from an eligible study. Any disagreement between the reviewers was solved through discussions, and when both reviewers disagreed, a third one [*LRP*] was consulted to make a final decision.

2.6 Risk of individual bias of the studies

The Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for randomized controlled trials assessed the risk of bias and the individual quality of the studies selected.[27] Two authors [*MNO and LRP*] assessed independently each domain regarding their potential risk of bias, as recommended by the PRISMA statement.[25]

Each study was categorized according to the percentage of positive answers to the questions corresponding to the assessment tool. Risk of bias was considered ***High*** when the study obtained 49% of "yes" answers, ***Moderate*** when the study obtained 50% to 69% of "yes" answers, and ***Low*** when the study reached more than 70% of "yes" score.

2.7 Summary measures and syntheses of results

In order to perform network meta-analyses, studies were grouped in four groups (at-home, in office, over-the counter Whitestrips or combined bleaching methods), and subgroups within each group to identify the different treatment protocols. Network meta-analysis was performed to indirectly comparing the effectiveness of the different bleaching protocols. A key feature of this approach is the ability to combine direct and indirect evidence of multiple studies. When comparing different treatments, the network meta-analysis is only able to compare studies that are either directly or indirectly connected. Thus, disconnected studies cannot be computed by this analysis. For instance, to compare treatments A, B and C, a study must include at least one comparison that involves either treatment A, B or C. Thus, if a study includes treatment D and E, such a study could not be included in the network meta-analysis, and be compared with studies A, B and C. The main outcome of this analysis was the ΔE_{ab}. Different analyses were performed for each follow-up, but due to the requirements of the network meta-analysis, comparisons might not have been equal over the different time points.

3 RESULTS

3.1 Study selection

During the first phase of study selection, 14.107 results were found distributed in nine electronic databases, including the "gray literature". The repeated/duplicate results were excluded, remaining 9.519 articles for the analysis of titles and abstracts. After a detailed analysis, 103 studies were eligible for the full text analysis. Then, the full text was read, and 25 studies did not fulfill the inclusion criteria and were eliminated. Appendix 1 shows the studies eliminated and the reasons for exclusion. Thus, 93 studies were selected for qualitative analysis and 19 for meta-analysis. Figure 1 reproduces the process of search, identification, inclusion, and exclusion of articles.

3.2 Study characteristics of eligible studies

For the statistical evaluation of the studies, the bleaching protocols were grouped according to bleaching agent, material concentration and action time on the dental surface. It was founded 25 different whitening protocols exclusively in-office, 42 at-home, 15 combined, and 7 protocols using Whitestrips. Resulting in a total of 89 different techniques of dental bleaching which described in the Table 1.

The studies were published between the years of 1999 and 2019 and they were performed in 14 different countries, being 35 of them made in Brazil[2,13,15,23,28-58], 24 in USA[59-82] and 10 in Germany[83-92]; there was also studies in Chile[93-97]; United Kingdom[98-100];Turkey [101-103]; Italy[104,105]; Spain1[12,106]; Jordan[107,108]; China[14,109]; South Africa[110]; Japan[111]; Kuwait[112]; and Puerto Rico[113]. Beyond a multicenter study made in Brazil and Chile [114].Other sources of information regarding demographic and clinical characteristics of the population

were informed. Without the exception of 11 articles [33,61-63,66,69,70,83,90,111.113], all the other articles included related the respect of ethical criteria and reported about informed consent prior to the start of the study with the patients. Only 22 studies declared that they followed the CONSORT guideline for clinical trials. [12,13,34,42,47-54,58,64,86,91,93-97,115] In the Table 2 shows more details of the eligible study characteristics.

3.3 Risk of individual bias of the studies

Only 15[23,28,29,39,35,49,50,57,70,78,80,91,98,99,101] studies presented a moderated risk of bias, while the remanescents showed low risk. Table 3 shows detailed information on the risk of bias of the studies included. The questions 4 and 5 were considered appliable in 18 [5,22,26,35,46,53,53,56,58,73,75,78,81,88,94,98,103,104] and 36 [5,16,18-20,22,23,26,31,32,34-36,41,43,46,53,55-58,70,73,75,78,81,83,85-88,91,94,97,99,105] respectively studies, due to impossibility of blinding the operator or the patient. The question number 6, related to blinding the evaluator, presented a "No" response in 37articles. [6,17,21,27-29,34,42,45,48-51,53,55-58,62-64,70,71,73,76-81,88-90,94,96,99,101] Question 9 was considered "Yes" in 19 studies because CONSORT recommends statistical analysis of ITT and only these studies made detailed and specific analysis for losses. [19,26,30,31,38-42,44,56,73,81,86,87,98,99,103,105]

3.4 Network Meta-Evidence

Among the 94 eligible studies, only 19 had a comparator group between them, in at least one evaluation time,[7,22,29,38,39,43,45,54,57,60,66,83,84,86,91,93,96,97,105] and were included in the network metanalysis. The results of ΔE_{ab} used for the statistical analysis are described in the Table 4. The results were analyzed in four evaluations time (Immediately after bleaching, seven days, 30 days and 180 days), and those who had a common comparator were evaluated used mean difference between the values of ΔE_{ab}. The results of the statistical analysis are presented on

the Appendix 2.

3.5 Network Meta-Evidence

3.5.1 – Immediately after

The results for the ΔE_{ab} immediately after bleaching were showed in 20 studies [7,22,29,33,35,43,45,54,57,60,66,69,72,83,85,92,93,96,97,100], in which 7 were excluded in the meta-analysis, [33,35,69,72,85,92,100] because those evaluated bleaching protocols that had no common comparison with the other ones. (Figure 2a) The remanescents made 22 different protocols that were divided in two groups, without a common comparison between them. In the first part, the protocols that showed better effectiveness were H6, M1 e W2 (Figure 2b), and in the second part was noted a better effectiveness in M7, M8 e H30 (Figure 2c). Quantitative analysis is presented at Appendix 2: Table I.

3.5.2 – 7 days

A total of 15studies registered values of ΔE_{ab} 7 days after bleaching.[18,29,39,45,47,53,60,66,67,83-86,91,100] In which 11 used protocols without common comparisons, [18,39,47,53,60,67,83-86,100] being consequently excluded from the network. Between the others, 7 different protocols were evaluated, between then, the best results were obtained with M7 (Figures 3). Quantitative analysis is presented at Appendix 2: Tables II and III.

3.5.3 – 30 days

The effectiveness evaluation of (ΔE_{ab}) after 30 days of the treatment being done was made in 17 studies[7,29,34,38,39,43-45,48,60,83-87,100,105], 7 from them had not presented a common comparison, [34,43,44,48,85,87,100] that resulted in the exclusion of those. (Figure 4a) Counting that 13 different protocols were compared; those were divided in three parts without one comparison between then. In the first part there

was no statistical difference, between the protocols H6, O10, M1, only in the treatments O17 and O2 showed worst results than the others (Figure 4b). In the second part, there was no statistical different between 4 techniques (O1, O9, O19 and O20) (Figure 4c). In the third group, the best results were from H30 (Figure 4d). Quantitative analysis is presented at Appendix 2: Tables IV, V and VI

3.5.4 – 180 days

Only 6 studies demonstrated ΔE_{ab} values,[18,29,35,45,47,100] being that just 2 of them had any comparison in common.[29,45] The two studies did comparisons between 4 different protocols, (O3, O15, H30 e O21), being that in all the comparisons the value of p was >0.05 (Figure 5). Quantitative analysis is presented at Appendix 2: Table VII

3 DISCUSSION

This systematic review of the literature aimed to investigate through a meta-analysis network which bleaching protocols presented best results of tooth color alteration. The study evidenced a variety of protocols that had made harder the process of decision for the dentist during the planning of the whitening treatment. Even though there is a grouping, for concentration of the product and for time of its application, it was reported 89 different protocols of whitening. Also, it is highlighted that a variety of companies and commercial names of products were used. This is a factor that could be associated to the commercial appeal for aesthetics procedures, since the literature has been showing a continuous increase in the search for whitening treatments in dentistry offices.[1,115]

There are several over-the counter methods available to realize bleaching treatments (paint-on, gum, rinses), but not all of them contain hydrogen peroxide on their formula, acting only removing extrinsical stains.[116] The whitestrips were selected among them due to their stablished scientific evidence, presenting similar results to at-home techniques using low-concentration peroxide.[3]

Among the best results for color change immediately after the treatment end, it is highlighted the presence of three combined treatments, with the usage of hydrogen peroxide in concentrations varying from 25% to 35%, followed by the carbamide peroxide with lower concentrations (10% to 15%) for the application at-home. Although these protocols present better results, there is a difference on the action time of the bleaching agent over dental structures. While the protocol M1 suggests the use of a tray overnight for at least 14 days after one session, protocols M7 and M8 recommends the at-home using in an interval between 7-13 days, diverging only at the chair time during the in-office session. However, these protocols were related in only one study each. It is suggested the realization of new studies comparing these techniques with other methods decreasing the daily use of the bleaching agent, since the literature shows high risk of dental sensitivity reports using overnight methods.[15,57]

Despite the relevance of the evaluation immediately after the bleaching protocol, is important to reinforce the demineralization and dehydration process that occurs during the whitening treatment, which can lead to instantly results that not represents the real color alteration obtained after the tooth bleaching.[117,118] The rebound effect is a complex mechanism that can be influenced by factors such as tooth remineralization, feeding patterns and the bleaching technique that were used.[119] The literature shows follow-ups after in-office bleaching treatments with a variation of translucency (L*) seven days after the tooth whitening.[120] Low variations on the CELAB scale, however, does not necessarily means lower patient satisfaction, since the bleaching efficacy is related to a 5-unit change of ΔEab.[23,121]

The ΔE_{ab} results 7 days after the treatment showed the best results for two treatments that had already presented good results in the analysis done immediately after the conclusion off the treatment (M7 e H30). The good results obtained from the protocol H30 (carbamide peroxide 11%-15%, 2 hours/day) also raise a discussion about the usage time of the dental tray during the treatments at home. Since, the long term of action of the whitening agent over the dental surface leads to a bigger liberation of free radicals close to the dental pulp, resulting in an

inflammatory process.[49,122] Studies have been showing similar results at color change results in protocols with shorter times of dental tray usage. [15,123]

The analysis of 30 days was harder due to the lack of common comparisons. It took to a division of the network in 3 different analysis, being two with only 4 protocols and another with 5. In one of the analysis, it was compared 4 techniques in-office, (O1, O9, O19, O20), demonstrating that there was no statistical difference between them. The four protocols were realized in two sessions, with a break of 7 days range. Among them, the protocol O19 had the shortest chair time, realizing the sessions less than 20 minutes, the protocol O20 used less agent concentration (10%-20%). Despite the need of more clinical studies to confirm these results, it is suggested the use of shortest sessions or low-concentrating agents to reduce the adversal effects of in-office techniques. While in the other analysis, the at-home and combined protocols presented better results than exclusively in-office techniques.

This study also shows the need for more studies that make the monitoring of long-term patients that were submitted to dental bleaching. Only 6 works described values of ΔE_{ab} after 180 days from the treatment end.[18,29,35,45,47,100] Related to it, only two works from the same author has any comparison group in common.[40,55] These evaluations from the long-term have substantial importance to evaluate the “rebound effect” of the whitening process. In the techniques evaluated during this time, the protocol H30 presented the best results, being compared with 3 techniques in-office, reinforcing results presented in other times and justified by the color maintenance of at-home methods.

This study made a large search on the available literature, and made it possible the indirect color change comparison of several different techniques. However, the variety of whitening techniques also was a factor of limitation for this work, since from the 94 eligible articles, just 19 have any comparison in common and were included in the meta-analysis. It is being suggested a realization of clinical works using at least one the experimental groups, one whitening protocol already well described and established in the literature.

5 CONCLUSIONS

Considering this study limitations, it was possible to conclude that the exclusively in-office techniques presented worse results compared to other methods. However, the heterogeneity of bleaching techniques made it difficult the network mapping. More studies with well stablished protocols are recommended to new metanalyses.

ACKNOWLEDGMENTS

This study was financed in part by the Coordination of Upper Level Personal Improvement (known in Portuguese by the acronym CAPES - translated in Portuguese as Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil) - Finance Code 001.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

[1] Silva FBD, Chisini LA, Demarco FF, Horta BL, Correa MB (2018) Desire for tooth bleaching and treatment performed in Brazilian adults: findings from a birth cohort *Brazilian oral research* **8(32)** e12. https://doi.org/10.1590/1807-3107bor-2018.vol32.0012

[2] Machado L, Anchieta R, dos Santos P, Briso A, Tovar N, Janal M, Coelho P, Sundfeld R (2016) Clinical Comparison of At-Home and In-Office Dental Bleaching Procedures: A Randomized Trial of a Split-Mouth Design *The International journal of periodontics & restorative dentistry* **36(2)** 251-260. https://doi.org/10.11607/prd.2383

[3] Serraglio CR, Zanella L, Dalla-Vecchia KB, Rodrigues-Junior AS (2016) Efficacy and safety of over-the-counter whitening strips as compared to home-whitening with 10 % carbamide peroxide gel--systematic review of RCTs and metanalysis *Clinical oral investigations* **20(1)** 1-14. https://doi.org/10.1007/s00784-015-1547-8

[4] de Geus JL, Wambier LM, Boing TF, Loguercio AD, Reis A (2018) At-home Bleaching With 10% vs More Concentrated Carbamide Peroxide Gels: A Systematic Review and Meta- analysis *Operative dentistry* **43(4)** e210-e222. https://doi.org/10.2341/17-222-L

[5] Luque-Martinez I, Reis A, Schroeder M, Muñoz MA, Loguercio AD, Masterson D, Maia LC (2016) Comparison of efficacy of tray-delivered carbamide and hydrogen peroxide for at- home bleaching: a systematic review and meta-analysis *Clinical oral investigations* **20(7)** 1419- 1433. https://doi.org/10.1007/s00784-016-1863-7

[6] de Geus JL, Wambier LM, Kossatz S, Loguercio AD, Reis A (2016) At-home vs In-office Bleaching: A Systematic Review and Meta-analysis *Operative dentistry* **41(4)** 341-356. https://doi.org/10.2341/15-287-LIT

[7] Lu G & Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons *Statistics in medicine* **23(20)** 3105-3124. https://doi.org/10.1002/sim.1875

[8] Goldberg M, Grootveld M, Lynch E (2010) Undesirable and adverse effects of tooth-whitening products: a review *Clinical oral investigation* **14(1)** 1-10. https://doi.org/10.1007/s00784-009-0302-4

[9] Markowitz K (2010) Pretty painful: why does tooth bleaching hurt? *Medical hypotheses* **74(5)** 835-840. https://doi.org/10.1016/j.mehy.2009.11.044

[10] Cartagena AF, Parreiras SO, Loguercio AD, Reis A, Campanha NH (2014) In-office bleaching effects on the pulp flow and tooth sensitivity - case series *Brazilian oral research* **29(1)** 1-6. https://doi.org/10.1590/1807-3107BOR-2015.vol29.0026

[11] Moncada G, Sepúlveda D, Elphick K, Contente M, Estay J, Bahamondes V, Fernandez E, Oliveira OB, Martin J (2013) Effects of light activation, agent concentration, and tooth thickness on dental sensitivity after bleaching *Operative dentistry* **38(5)** 467-476. https://doi.org/10.2341/12-335-C

[12] Darriba IL, Novoa L, de la Peña VA (2017) Efficacy of different protocols for at-home bleaching: A randomized clinical trial *American journal of dentistry* **30(6)** 329-334

[13] Rezende M, Ferri L, Kossatz S, Loguercio AD, Reis A (2016) Combined Bleaching Technique Using Low and High Hydrogen Peroxide In-Office Bleaching Gel *Operative dentistry* **41(4)** 388-396. https://doi.org/10.2341/15-266-C

[14] Nie J, Tian FC, Wang ZH, Yap AU, Wang XY (2017) Comparison of efficacy and outcome satisfaction between in-office and home teeth bleaching in Chinese patients *Journal of oral science* **59(4)** 527-532. https://doi.org/10.2334/josnusd.16-0636

[15] Cardoso PC, Reis A, Loguercio A, Vieira LC, Baratieri LN (2010) 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(10)** 1213-1220. https://doi.org/10.14219/jada.archive.2010.0048

[16] Pinto CF, Oliveira R, Cavalli V, Giannini M (2004) Peroxide bleaching agent effects on enamel surface microhardness, roughness and morphology *Brazilian Oral Research* **18(4)** 306-311. https://doi.org/10.1590/S1806-83242004000400006

[17] Chu JS (2003) Use of a Reflectance Spectrophotometer in Evaluating Shade Change Resulting from Tooth-Whitening Products *Journal of Esthetic and Restorative Dentistry* **15(Supplementary 1)** S42-S48. https://doi.org/10.1111/j.1708-8240.2003.tb00317.x

[18] Cho BH, Lim YK, Lee YK (2007) Comparison of the color of natural teeth measured by a colorimeter and Shade Vision System *Dental materials* **23(10)** 1307-1312. https://doi.org/10.1016/j.dental.2006.11.008

[19] Pérez MM, Ghinea R, Rivas MJ, Yebra A, Ionescu AM, Paravina RD, Herrera LJ (2016) Development of a customized whiteness index for dentistry based on CIELAB color space *Dental materials* **32(3)** 461-467. https://doi.org/10.1016/j.dental.2015.12.008

[20] Browning WD (2003) Use of shade guides for color measurement in tooth-bleaching studies *Journal of esthetic and restorative dentistry* **15(Supplementary 1)** S13-S20. https://doi.org/10.1111/j.1708-8240.2003.tb00314.x

[21] Paul S, Peter A, Pietrobon N, Hämmerle CH (2002) Visual and spectrophotometric shade analysis of human teeth *Journal of dental research* **81(8)** 578-582. https://doi.org/10.1177/154405910208100815

[22] Rustogi KN & Curtis J (1994) Development of a quantitative measurement to assess the whitening effects of two different oxygenating agents on teeth in vivo Compendium. Supplement **17** 1631-1634

[23] Bernardon JK, Sartori N, Ballarin A, Perdigão J, Lopes GC, Baratieri LN (2010) Clinical performance of vital bleaching techniques *Operative dentistry* **35(1)** 3-10. https://doi.org/10.2341/09-008CR

[24] Maran BM, Ziegelmann PK, Burey A, de Paris Matos T, Loguercio AD, Reis A (2019) Different light-activation systems associated with dental bleaching: a systematic review and a network meta-analysis *Clinical oral investigations* **23(4)** 1499-1512. https://doi.org/10.1007/s00784-019-02835-x

[25] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations *Annals of internal medicine* **162(11)** 777-784. https://doi.org/10.7326/M14-2385

[26] Higgins JPT & Green S (2011) *Cochrane handbook for systematic reviews of interventions Version 5.1.2* Cochrane Collaboration, Oxford (UK)

[27] Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L (2017) Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute.

[28] Soares CJ, Silva NR, Quagliatto OS, Campos RE (2006) Avaliação clínica de clareamento caseiro com gel de peróxido de carbamida industrializado e manipulado em farmácia *Revista de Odontologia da UNESP* **35(1)** 69-74

[29] Marson FC, Sensi LG, Vieira LC, Araújo E. (2008) Clinical evaluation of in-office dental bleaching treatments with and without the use of light-activation sources *Operative dentistry* **33(1)** 15-22. https://doi.org/10.2341/07-57

[30] Meireles SS, Heckmann SS, Leida FL, Santos IS, Della Bona A, Demarco FF (2008) Efficacy and safety of 10% and 16% carbamide peroxide tooth-whitening gels: a randomized clinical trial *Operative dentistry* **33(6)** 606-612. https://doi.org/10.2341/07-150

[31] Meireles SS, Heckmann SS, Santos IS, Della Bona A, Demarco FF (2008) A double blind randomized clinical trial of at-home tooth bleaching using two carbamide peroxide concentrations: 6-month follow-up *Journal of dentistry* **36(11)** 878-884. https://doi.org/10.1016/j.jdent.2008.07.002

[32] Meireles SS, Santos IS, Della Bona A, Demarco FF (2009) A double-blind randomized controlled clinical trial of 10 percent versus 16 percent carbamide peroxide tooth-bleaching agents: one-year follow-up *The Journal of the American Dental Association* **140(9)** 1109-1117. https://doi.org/10.14219/jada.archive.2009.0337

[33] Wetter NU, Branco EP, Deana AM, Pelino JE (2009) Color differences of canines and incisors in a comparative long-term clinical trial of three bleaching systems *Lasers in medical science* **24(6)** 941-947. https://doi.org/10.1007/s10103-008-0575-x

[34] Meireles SS, Santos IS, Della Bona A, Demarco FF (2010) A double-blind randomized clinical trial of two carbamide peroxide tooth bleaching agents: 2-year follow-up *Journal of dentistry* **38(12)** 956-963. https://doi.org/10.1016/j.jdent.2010.08.003

[35] Kossatz S, Dalanhol AP, Cunha T, Loguercio A, Reis A (2011) Effect of light activation on tooth sensitivity after in-office bleaching *Operative dentistry* **36(3)** 251-257. https://doi.org/10.2341/10-289-C

[36] Reis A, Tay LY, Herrera DR, Kossatz S, Loguercio AD (2011) Clinical effects of prolonged application time of an in-office bleaching gel *Operative dentistry* **36(6)** 590-596. https://doi.org/10.2341/10-173-C

[37] Almeida LC, Riehl H, Santos PH, Sundfeld ML, Briso AL (2012) Clinical evaluation of the effectiveness of different bleaching therapies in vital teeth *The International journal of periodontics & restorative dentistry* **32(3)** 303-309

[38] Basting RT, Amaral FL, França FM, Flório FM (2012) 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 *Operative dentistry* **37(5)** 464-473. https://doi.org/10.2341/11-337-C

[39] de Almeida LC, Costa CA, Riehl H, dos Santos PH, Sundfeld RH, Briso AL (2012) Occurrence of sensitivity during at-home and in-office tooth bleaching therapies with or without use of light sources *Acta odontológica latinoamericana: AOL* **25(1)** 3-8

[40] Mondelli RFL, Azevedo JFDG, Francisconi AC, Almeida CM, Ishikiriama SK (2012) Comparative clinical study of the effectiveness of different dental bleaching methods - two year follow-up *Journal of Applied Oral Science* **20(4)** 435-443. https://doi.org/10.1590/S1678-77572012000400008

[41] Tay LY, Kose C, Herrera DR, Reis A, Loguercio AD (2012) Long-term efficacy of in- office and at-home bleaching: a 2-year double-blind randomized clinical trial *American journal of dentistry* **25(4)** 199-204

[42] Reis A, Kossatz S, Martins GC, Loguercio AD (2013) Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: a randomized clinical trial *Operative dentistry* **38(4)** 386-393. https://doi.org/10.2341/12-140-C

[43] Farhat PBA, Santos FA, Gomes JC, Gomes OM (2014) Evaluation of the efficacy of LED- laser treatment and control of tooth sensitivity during in-office bleaching procedures *Photomedicine and laser surgery* **32(7)** 422-426. https://doi.org/10.1089/pho.2014.3729

[44] Bernardon JK, Ferrari P, Baratieri LN, Rauber GB (2015) Comparison of treatment time versus patient satisfaction in at-home and in-office tooth bleaching therapy *The Journal of prosthetic dentistry* **114(6)** 826-830. https://doi.org/10.1016/j.prosdent.2015.05.014

[45] de Paula EA, Nava JA, Rosso C, Benazzi CM, Fernandes KT, Kossatz S, Loguercio AD, Reis A (2015) In-office bleaching with a two- and seven-day intervals between clinical sessions: A randomized clinical trial on tooth sensitivity *Journal of dentistry* **43(4)** 424-429. https://doi.org/10.1016/j.jdent.2014.09.009

[46] Bernardon JK, Martins MV, Rauber GB, Monteiro Junior S, Baratieri LN (2016) Clinical evaluation of different desensitizing agents in home-bleaching gels *The Journal of prosthetic dentistry* **115(6)** 692-696. https://doi.org/10.1016/j.prosdent.2015.10.020

[47] Bortolatto JF, Trevisan TC, Bernardi PS, Fernandez E, Dovigo LN, Loguercio AD, Batista de Oliveira Junior O, Pretel H (2016) 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 in medical science* **31(3)** 437-444. https://doi.org/10.1007/s10103-016-1866-2

[48] de Freitas PM, Menezes AN, da Mota AC, Simões A, Mendes FM, Lago AD, Ferreira LS, Ramos-Oliveira TM (2016) Does the hybrid light source (LED/laser) influence temperature variation on the enamel surface during 35%

hydrogen peroxide bleaching? A randomized clinical trial *Quintessence international* **47(1)** 61-73

[49] Kose C, Calixto AL, Bauer JR, Reis A, Loguercio AD (2016) Comparison of the Effects of In-office Bleaching Times on Whitening and Tooth Sensitivity: A Single Blind, Randomized Clinical Trial *Operative dentistry* **41(2)** 138-145. https://doi.org/10.2341/15-085-C

[50] Mena-Serrano AP, Garcia E, Luque-Martinez I, Grande R, Loguercio AD, Reis A (2016) A Single-Blind Randomized Trial About the Effect of Hydrogen Peroxide Concentration on Light-Activated Bleaching *Operative dentistry* **41(5)** 455-464. https://doi.org/10.2341/15-077-C

[51] Montenegro-Arana A, Arana-Gordillo LA, Farana D, Davila-Sanchez A, Jadad E, Coelho U, Gomes O, Loguercio AD (2016) Randomized Double-blind Clinical Trial of Bleaching Products in Patients Wearing Orthodontic Devices *Operative dentistry* **41(4)** 379-387. https://doi.org/10.2341/15-240-C

[52] Carlos NR, Bridi EC, Amaral F, França F, Turssi CP, Basting RT (2017) Efficacy of Home-use Bleaching Agents Delivered in Customized or Prefilled Disposable Trays: A Randomized Clinical Trial *Operative dentistry* **42(1)** 30-40. https://doi.org/10.2341/15-315-C

[53] Chemin K, Rezende M, Loguercio AD, Reis A, Kossatz S (2018) Effectiveness of and Dental Sensitivity to At-home Bleaching With 4% and 10% Hydrogen Peroxide: A Randomized, Triple-blind Clinical Trial *Operative dentistry* **43(3)** 232-240. https://doi.org/10.2341/16-260-C

[54] Martins I, Onofre S, Franco N, Martins LM, Montenegro A, Arana-Gordillo LA, Reis A, Loguercio AD, da Silva LM (2018) Effectiveness of In-office Hydrogen Peroxide With Two Different Protocols: A Two-center Randomized Clinical Trial *Operative dentistry* **43(4)** 353- 361. https://doi.org/10.2341/17-128-C

[55] Mondelli RFL, de Almeida CM, Rizzante FAP, Sanches Borges AF, Ishikiriama SK, Bombonatti JFS (2018) The effects of hybrid light activation and enamel acid etching on the effectiveness, stability and sensitivity after a single session in-office bleaching: A 12-month clinical trial *Photodiagnosis and photodynamic therapy* **24** 22-26. https://doi.org/10.1016/j.pdpdt.2018.08.009

[56] Peixoto AC, Vaez SC, Pereira NAR, Santana CNS, Soares KDA, Romão

ACTR, Ferreira LF, Martins-Filho PRS, Faria-e-Silva AL (2018) High-concentration carbamide peroxide can reduce the sensitivity caused by in-office tooth bleaching: a single-blinded randomized controlled trial *Journal of Applied Oral Science* **26** e20170573. https://doi.org/10.1590/1678-7757-2017-0573

[57] Rodrigues JL, Rocha PS, Pardim SLS, Machado ACV, Faria-e-Silva AL, Seraidarian, PI (2018) Association Between In-Office And At-Home Tooth Bleaching: A Single Blind Randomized Clinical Trial. *Brazilian Dental Journal* **29(2)** 133-139. https://doi.org/10.1590/0103-6440201801726

[58] Cordeiro D, Toda C, Hanan S, Arnhold LP, Reis A, Loguercio AD, Bandeira MCL (2019) Clinical Evaluation of Different Delivery Methods of At-Home Bleaching Gels Composed of 10% Hydrogen Peroxide *Operative dentistry* **44(1)** 13-23. https://doi.org/10.2341/17-174-C

[59] Mokhlis GR1, Matis BA, Cochran MA, Eckert GJ (2000) A clinical evaluation of carbamide peroxide and hydrogen peroxide whitening agents during daytime use *The Journal of the American Dental Association* **131(9)** 1269-1277. https://doi.org/10.14219/jada.archive.2000.0380

[60] Cibirka RM, Myers M, Downey MC, Nelson SK, Browning WD, Hawkins IK, Dickinson GL (1999) Clinical study of tooth shade lightening from dentist-supervised, patient-applied treatment with two 10% carbamide peroxide gels *Journal of esthetic dentistry* **11(6)** 325-331. https://doi.org/10.1111/j.1708-8240.1999.tb00415.x

[61] Kihn PW, Barnes DM, Romberg E, Peterson K (2000) A clinical evaluation of 10 percent vs. 15 percent carbamide peroxide tooth-whitening agents *The Journal of the American Dental Association* **131(10)** 1478-1484. https://doi.org/10.14219/jada.archive.2000.0061

[62] Matis BA, Mousa HN, Cochran MA, Eckert GJ (2000) Clinical evaluation of bleaching agents of different concentrations *Quintessence international* **31(5)** 303-310

[63] Nathoo S, Santana E 3rd, Zhang YP, Lin N, Collins M, Klimpel K, DeVizio W, Giniger M (2001) Comparative seven-day clinical evaluation of two tooth whitening products The *Compendium of continuing education in dentistry* **22(7)** 599-604, 606; quiz 608

[64] Gerlach RW & Zhou X (2002) Comparative clinical efficacy of two professional bleaching systems *Compendium of continuing education in dentistry*

23(1A) 35-41; quiz 50

[65] Gerlach RW, Sagel PA, Jeffers ME, Zhou X (2002) Effect of peroxide concentration and brushing on whitening clinical response *Compendium of continuing education in dentistry* **23(1A)** 16-21; quiz 49

[66] Al Shethri S, Matis BA, Cochran MA, Zekonis R, Stropes MA (2003) Clinical evaluation of two in-office bleaching products *Operative dentistry* **28(5)** 488-495

[67] Karpinia K, Magnusson I, Barker ML, Gerlach RW (2003) Clinical comparison of two self-directed bleaching systems *Journal of prosthodontics : official journal of the American College of Prosthodontists* **12(4)** 242-248. https://doi.org/10.1016/S1059-941X(03)00102-5

[68] Nathoo S, Stewart B, Petrone ME, Chaknis P, Zhang YP, DeVizio W, Volpe AR (2003) Comparative clinical investigation of the tooth whitening efficacy of two tooth whitening gels *The Journal of clinical dentistry* **14(3)** 64-69

[69] Tavares M, Stultz J, Newman M, Smith V, Kent R, Carpino E, Goodson JM (2003) Light augments tooth whitening with peroxide *The Journal of the American Dental Association* **134(2)** 167-175. https://doi.org/10.14219/jada.archive.2003.0130

[70] Zekonis R, Matis BA, Cochran MA, Al Shetri SE, Eckert GJ, Carlson TJ (2003) Clinical evaluation of in-office and at-home bleaching treatments *Operative dentistry* **28(2)** 114-121

[71] Gerlach RW & Zhou X (2004) Clinical trial comparing two daytime hydrogen-peroxide professional vital-bleaching systems *Compendium of continuing education in dentistry* **25(8 Supplement 2)** 33-40.

[72] Cronin MJ, Charles CA, Zhao Q, Dembling WZ (2005) Comparison of two over-the- counter tooth whitening products using a novel system *Compendium of continuing education in dentistry* **26(2)** 140, 142, 144-148

[73] Matis BA, Cochran M, Wang G, Franco M, Eckert GJ, Carlotti RJ, Bryan C (2005) A clinical evaluation of bleaching using whitening wraps and strips *Operative dentistry* **30(5)** 588- 592

[74] Deliperi S, Bardwell DN, Papathanasiou A (2007) Clinical evaluation of a combined in- office and take-home bleaching system *The Journal of the American Dental Association* **135(5)** 628-634. https://doi.org/10.14219/jada.archive.2004.0252

[75] Kugel G, Ferreira S, Sharma S, Barker ML, Gerlach RW (2009) Clinical trial assessing light enhancement of in-office tooth whitening *Journal of esthetic and restorative dentistry* **21(5)** 336-347. https://doi.org/10.1111/j.1708-8240.2009.00287.x

[76] Matis BA, Cochran MA, Wang G, Eckert GJ (2009) A clinical evaluation of two in-office bleaching regimens with and without tray bleaching *Operative dentistry* **34(2)** 142-149. https://doi.org/10.2341/08-64

[77] Ontiveros JC & Paravina RD (2009) Color change of vital teeth exposed to bleaching performed with and without supplementary light *Journal of dentistry* **37(11)** 840-847. https://doi.org/10.1016/j.jdent.2009.06.015

[78] da Costa JB, McPharlin R, Paravina RD, Ferracane JL (2010) Comparison of at-home and in-office tooth whitening using a novel shade guide *Operative dentistry* **35(4)** 381-388. https://doi.org/10.2341/09-344-C

[79] da Costa JB, McPharlin R, Hilton T, Ferracane JI, Wang M (2012) Comparison of two at- home whitening products of similar peroxide concentration and different delivery methods *Operative dentistry* **37(4)** 333-339. https://doi.org/10.2341/11-053-C

[80] Ward M & Felix H (2012) A clinical evaluation comparing two H2O2 concentrations used with a light-assisted chairside tooth whitening system *Compendium of continuing education in dentistry* **33(4)** 286-291

[81] Henry RK, Bauchmoyer SM, Moore W, Rashid RG (2013) The effect of light on tooth whitening: a split-mouth design *International journal of dental hygiene* **11(2)** 151-154. https://doi.org/10.1111/j.1601-5037.2012.00568.x

[82] Oliveira GM, Miguez PA, Oliveira GB, Swift EJ Jr, Farrell S, Anastasia MK, Conde E, Walter R (2013) Safety and efficacy of a high-adhesion whitening strip under extended wear regimen *Journal of dentistry* **41(Supplement 3)** e46-e52. https://doi.org/10.1016/j.jdent.2012.11.019

[83] Auschill TM1, Hellwig E, Schmidale S, Sculean A, Arweiler NB (2005) Efficacy, side- effects and patients' acceptance of different bleaching techniques (OTC, in-office, at-home) *Operative dentistry* **30(2)** 156-163

[84] Zantner C1, Derdilopoulou F, Martus P, Kielbassa AM (2006) Randomized clinical trial on the efficacy of a new bleaching lacquer for self-application

Operative dentistry **31(3)** 308- 316. https://doi.org/10.2341/05-69

[85] Braun A, Jepsen S, Krause F (2007) Spectrophotometric and visual evaluation of vital tooth bleaching employing different carbamide peroxide concentrations *Dental materials: official publication of the Academy of Dental Materials* **23(2)** 165-169. https://doi.org/10.1016/j.dental.2006.01.017

[86] Hannig C, Lindner D, Attin T (2007) Efficacy and tolerability of two home bleaching systems having different peroxide delivery *Clinical oral investigations* **11(4)** 321-329. https://doi.org/10.1007/s00784-007-0128-x

[87] Ziebolz D, Helms K, Hannig C, Attin T (2007) Efficacy and oral side effects of two highly concentrated tray-based bleaching systems *Clinical oral investigations* **11(3)** 267-275. https://doi.org/10.1007/s00784-007-0108-1

[88] Krause F1, Jepsen S, Braun A (2008) Subjective intensities of pain and contentment with treatment outcomes during tray bleaching of vital teeth employing different carbamide peroxide concentrations *Quintessence international* **39(3)** 203-209

[89] Bizhang M, Chun YH, Damerau K, Singh P, Raab WH, Zimmer S (2009) Comparative clinical study of the effectiveness of three different bleaching methods *Operative dentistry* **34(6)** 635-641. https://doi.org/10.2341/08-069-C

[90] Strobl A, Gutknecht N, Franzen R, Hilgers RD, Lampert F, Meister J (2010) Laser- assisted in-office bleaching using a neodymium:yttrium-aluminum-garnet laser: an in vivo study *Lasers in medical science* **25(4)** 503-509. https://doi.org/10.1007/s10103-009-0675-2

[91] Auschill TM, Schneider-Del Savio T, Hellwig E, Arweiler NB (2013) Randomized clinical trial of the efficacy, tolerability, and long-term color stability of two bleaching techniques: 18- month follow-up *Quintessence international* **43(8)** 683-694

[92] Polydorou O, Wirsching M, Wokewitz M, Hahn P (2013) Three-month evaluation of vital tooth bleaching using light units-a randomized clinical study *Operative dentistry* **38(1)** 21-32. https://doi.org/10.2341/12-041-C

[93] Martín J, Vildósola P, Bersezio C, Herrera A, Bortolatto J, Saad JR, Oliveira OB Jr, Fernández E (2015) Effectiveness of 6% hydrogen peroxide concentration for tooth bleaching—A double-blind, randomized clinical trial *Journal of*

dentistry **42(8)** 965-972. https://doi.org/10.1016/j.jdent.2015.05.011

[94] Fernández E, Bersezio C, Bottner J, Avalos F, Godoy I, Inda D, Vildósola P, Saad J, Oliveira OB Jr, Martín (2017) J Longevity, Esthetic Perception, and Psychosocial Impact of Teeth Bleaching by Low (6%) Hydrogen Peroxide Concentration for In-office Treatment: A Randomized Clinical Trial *Operative dentistry* **42(1)** 41-52. https://doi.org/10.2341/15-335-C

[95] Vildósola P, Vera F, Ramírez J, Rencoret J, Pretel H, Oliveira OB Jr, Tonetto M, Martín J, Fernández E (2017) Comparison of Effectiveness and Sensitivity Using Two In-Office Bleaching Protocols for a 6% Hydrogen Peroxide Gel in a Randomized Clinical Trial *Operative dentistry* **42(3)** 244-252. https://doi.org/10.2341/16-043-C

[96] Vildósola P, Bottner J, Avalos F, Godoy I, Martín J, Fernández E Teeth bleaching with low concentrations of hydrogen peroxide (6%) and catalyzed by LED blue (450 ± 10 nm) and laser infrared (808 ± 10 nm) light for in-office treatment: Randomized clinical trial 1-year follow-up *Journal of esthetic and restorative dentistry* **29(5)** 339-345. https://doi.org/10.1111/jerd.12318

[97] Angel P, Bersezio C, Estay J, Werner A, Retamal H, Araya C, Martin J, Fernández E (2018) Color stability, psychosocial impact, and effect on self-perception of esthetics of tooth whitening using low-concentration (6%) hydrogen peroxide *Quintessence international* 49(7) 557-566

[98] Brunton PA, Ellwood R, Davies R (2004) A six-month study of two self-applied tooth whitening products containing carbamide peroxide *Operative dentistry* **29(6)** 623-626

[99] Dawson PF, Sharif MO, Smith AB, Brunton PA (2011) A clinical study comparing the efficacy and sensitivity of home vs combined whitening *Operative dentistry* **36(5)** 460-466. https://doi.org/10.2341/10-159-C

[100] Nutter BJ1, Sharif MO, Smith AB, Brunton PA (2013) A clinical study comparing the efficacy of light activated in-surgery whitening versus in-surgery whitening without light activation *Journal of dentistry* **41(supplement 5)** e3-e7. https://doi.org/10.1016/j.jdent.2013.03.004

[101] Gurgan S, Cakir FY, Yazici E (2010) Different light-activated in-office bleaching systems: a clinical evaluation *Lasers in medical science* **25(6)** 817-822. https://doi.org/10.1007/s10103-009-0688-x

[102] Türkün M, Celik EU, Aladağ A, Gökay N (2010) One-year clinical

evaluation of the efficacy of a new daytime at-home bleaching technique *Journal of esthetic and restorative dentistry* **22(2)** 139-146. https://doi.org/10.1111/j.1708-8240.2010.00325.x

[103] Firat E, Ercan E, Gurgan S, Yucel OO, Cakir FY, Berker E (2011) The effect of bleachıng systems on the gingiva and the levels of IL-1β and IL-10 in gingival crevicular fluid *Operative dentistry* 36(6) 572-580. https://doi.org/10.2341/10-058-C

[104] Ferrari M, Kugel G, Cagidiaco MC, Barker ML, Gerlach RW (2004) Clinical trial evaluating the peroxide concentration response of whitening strips over 28 days *American journal of dentistry* **17(4)** 291-294

[105] Giachetti L, Bertini F, Bambi C, Nieri M, Scaminaci Russo D (2010) A randomized clinical trial comparing at-home and in-office tooth whitening techniques: A nine-month follow-up The *Journal of the American Dental Association* **141(11)** 1357-1364. https://doi.org/10.14219/jada.archive.2010.0081

[106] de la Peña VA & Ratón ML (2014) Randomized clinical trial on the efficacy and safety of four professional at-home tooth whitening gels *Operative dentistry* **39(2)** 136-143. https://doi.org/10.2341/12-402-C

[107] Al Quran FA, Mansour Y, Al-Hyari S, Al Wahadni A, Mair L (2011) Efficacy and persistence of tooth bleaching using a diode laser with three different treatment regimens *The European journal of esthetic dentistry* **6(4)** 436-445

[108] Al-Omiri MK, Hassan RS, AlZarea BK, Lynch E (2016) Effects of combining ozone and hydrogren peroxide on tooth bleaching: A clinical study *Journal of dentistry* **53** 88-93. https://doi.org/10.1016/j.jdent.2016.08.002

[109] Zhao K, Zong L, Zhang Q, Att W (2013) Clinical comparison between two bleaching techniques: a 180-day follow-up study *Quintessence international* **44(8)** 601-607

[110] Grobler SR, Majeed A, Hayward R, Rossouw RJ, Moola MH, van W Kotze TJ (2011) A clinical study of the effectiveness of two different 10% carbamide peroxide bleaching products: a 6-month followup I*nternational journal of dentistry* 2011:167525. https://doi.org/10.1155/2011/167525

[111] Tsubura S & Yamaguchi R (2005) Clinical evaluation of a new bleaching product "Polanight" in a Japanese population *Odontology / the Society of the Nippon Dental University* **93(1)**52-55. https://doi.org/10.1007/s10266-005-0047-8

[112] Alomari Q & El Daraa E (2010) A randomized clinical trial of in-office dental bleaching with or without light activation *The journal of contemporary dental practice* **11(1)** e17-e24. https://doi.org/10.5005/jcdp-11-1-17

[113] Delgado E, Hernández-Cott PL, Stewart B, Collins M, De Vizio W (2007) 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(4**) 367-372

[114] Loguercio AD, Servat F, Stanislawczuk R, Mena-Serrano A, Rezende M, Prieto MV, Cereño V, Rojas MF, Ortega K, Fernandez E, Reis A (2017) Effect of acidity of in-office bleaching gels on tooth sensitivity and whitening: a two-center double-blind randomized clinical trial *Clinical oral investigations* **21(9)** 2811-2818. https://doi.org/10.1007/s00784-017-2083-5

[115] Bruhn AM, Darby ML, McCombs GB, Lynch CM (2012) Vital tooth whitening effects on oral health-related quality of life in older adults *Journal of dental hygiene* **86(3)** 239-247

[116] Demarco FF, Meireles SS, Masotti AS (2009) Over-the-counter whitening agents: a concise review *Brazilian oral research* **23(Supplementary 1)** 64-70. https://doi.org/10.1590/S1806-83242009000500010

[117] Jiang T, Ma X, Wang Y, Zhu Z, Tong H, Hu J (2007) Effects of hydrogen peroxide on human dentin structure *Journal of dental research* **86(11)** 1040-1045. https://doi.org/10.1177/154405910708601104

[118] Li Q, Xu BT, Li R, Yu H, Wang YN (2010) Quantitative evaluation of colour regression and mineral content change of bleached teeth *Journal of dentistry* **38(3)** 253-260. https://doi.org/10.1016/j.jdent.2009.11.005

[119] Moghadam, F. V., Majidinia, S., Chasteen, J., & Ghavamnasiri, M (2013). The degree of color change, rebound effect and sensitivity of bleached teeth associated with at-home and power bleaching techniques: A randomized clinical trial *European journal of dentistry* **7(4)** 405–411. https://doi.org/10.4103/1305-7456.120655

[120] Salem YM, Osman YI (2011) The effect of in-office vital bleaching and patient perception of the shade change *Journal of the South African Dental Association* **66(2)** 70, 72-76

[121] Bersezio C, Martín J, Mayer C, Rivera O, Estay J, Vernal R, Haidar ZS, Angel P, Oliveira OB Jr, Fernández E (2018) Quality of life and stability of tooth

color change at three months after dental bleaching *Quality of life research* **27(12)** 3199-3207. https://doi.org/10.1007/s11136-018-1972-7

[122] Pugh G Jr, Zaidel L, Lin N, Stranick M, Bagley D (2005) High levels of hydrogen peroxide in overnight tooth-whitening formulas: effects on enamel and pulp *Journal of esthetic and restorative dentistry* **17(1)** 40-45. https://doi.org/10.1111/j.1708-8240.2005.tb00082.x

[123] Matis BA, Gaiao U, Blackman D, Schultz FA, Eckert GJ (1999) In vivo degradation of bleaching gel used in whitening teeth *Journal of the American Dental Association* **130(2)** 227-235. https://doi.org/10.14219/jada.archive.1999.0172

Table 2
Summary of the main characteristics of bleaching protocols.

Bleaching Technique	Deliver Method	Bleaching Agent	Agent Concentration	Bleaching Protocol (Gel time of action over the dental surface)	N of studies that used
O1	In-Office	Hydrogen Peroxide	31% - 40%	Two sessions (21-30 minutes), with 7 days interval between them	6 [32,36,38,56,80,105]
O2	In-Office	Hydrogen Peroxide	31% - 40%	Three sessions (21-30 minutes), with 7 days interval between them	7 [26-28,51,83,84,86]
O3	In-Office	Hydrogen Peroxide	31% - 40%	One session (>40min)	8 [6,29,37,45,46,66,91,103]
O4	In-Office	Hydrogen Peroxide	31% - 40%	One session (≤20min) with ozone application after the therapy	1 [99]
O5	In-Office	Hydrogen Peroxide	31% - 40%	One session (≤20min)	2 [95,99]
O6	In-Office	Hydrogen Peroxide	31% - 40%	Two sessions (31-40 minutes), with 7 days interval between them	4 [25,31,44,87]
O7	In-Office	Hydrogen Peroxide	<10%	Two sessions (31-40 minutes), with 7 days interval between them	1 [87]
O8	In-Office	Hydrogen Peroxide	31% - 40%	A variable number of sessions (≤20min) were performed with 7 days interval, until it reaches 6 less values in the VITA scale, maximum of 3 sessions	1 [73]
O9	In-Office	Hydrogen Peroxide	31% - 40%	Two sessions (>40min), with 7 days interval between them	6 [17,24,30,38,39,47]
O10	In-Office	Hydrogen Peroxide	31% - 40%	Two sessions (>40min), with 15 days interval between them	1 [7]
O11	In-Office	Hydrogen Peroxide	31% - 40%	A variable number of sessions (≤20min) were performed with 7 days interval, until the patient satisfaction	1 [33]
O12	In-Office	Hydrogen Peroxide	10% - 20%	Three sessions (>40min), with 7 days interval between them	1 [79]
O13	In-Office	Hydrogen Peroxide	<10%	Two sessions (21-30 minutes), with 7 days interval between them	1 [36]
O14	In-Office	Hydrogen Peroxide	21% - 30%	One session (>40min)	5 [65,67,68,61,71]
O15	In-Office	Hydrogen Peroxide	31% - 40%	One session (21-30min)	4 [29,37,91,93]
O16	In-Office	Hydrogen Peroxide	31% - 40%	Two sessions (31-40 minutes), with 2 days interval between them	1 [34]
O17	In-Office	Hydrogen Peroxide	<10%	Three sessions (21-30 minutes), with 7 days interval between them	3 [83,84,86]
O18	In-Office	Hydrogen Peroxide	31% - 40%	One session (31-40min)	2 [66,91]
O19	In-Office	Hydrogen Peroxide	31% - 40%	Two sessions (≤20min), with 7 days interval between them	1 [38]
O20	In-Office	Hydrogen Peroxide	10% - 20%	Two sessions (>40min), with 7 days interval between them	3 [25,31,39]
O21	In-Office	Hydrogen Peroxide	31% - 40%	One session (>40min) after acid conditioning	1 [45]

O22	In-Office	Carbamide Peroxide	31% - 40%	One session (31-40min)	1 [46]
O23	In-Office	Hydrogen Peroxide	31% - 40%	One session with variable applications (15min) until it reaches 6 less values in the VITA scale, maximum of 4 applications	1 [82]
O24	In-Office	Hydrogen Peroxide	10% - 20%	One session (>40min)	2 [59,70]
O25	In-Office	Hydrogen Peroxide	<10%	Two sessions (31-40 minutes), with 2 days interval between them	1 [85]
H1	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 4 hours/day [≥21 days]	2 [26,28]
H2	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 8 hours/day until it reaches 6 less values in the VITA scale	1 [73]
H3	At-Home	Hydrogen Peroxide	≤6%	Uses the tray 1 hour/day [14-20 days]	3 [43,62,81]
H4	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 2 hours/day [≥21 days]	6 [18-20,23,27,35]
H5	At-Home	Carbamide Peroxide	16% - 20%	Uses the tray 2 hours/day [≥21 days]	5 [18-20,23,27]
H6	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 8 hours/day or overnight [14-20 days]	11 [7,22,42,50-52,60,79,95,101,102]
H7	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 2 hours/day until patient satisfaction	1 [33]
H8	At-Home	Carbamide Peroxide	21% - 25%	Uses the tray 2 hours/day until patient satisfaction	1 [33]
H9	At-Home	Carbamide Peroxide	11% - 15%	Uses the tray 2 hours/day [≥21 days]	1 [35]
H10	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 2 hours/day [7-13 days]	3 [5,75,78]
H11	At-Home	Carbamide Peroxide	16% - 20%	Uses the tray 2 hours/day [7-13 days]	2 [75,78]
H12	At-Home	Carbamide Peroxide	16% - 20%	Uses the tray 1 hour/day [7-13 days]	3 [5,62,88]
H13	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 15 minutes/day [14-20 days]	1 [22]
H14	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 30 minutes/day [14-20 days]	2 [22,88]
H15	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 1 hour/day [14-20 days]	6 [21,22,57,76,96,97]
H16	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 30 minutes/day [14-20 days]	3 [42,48,97]
H17	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 1 hour/day [14-20 days]	3 [43,96,97]
H18	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 8 hours/day or overnight until patient satisfaction	1 [68]
H19	At-Home	Carbamide Peroxide	≥25%	Uses the tray 1 hour/day [14-20 days]	1 [69]
H20	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 8 hours/day or overnight [14-20 days]	1 [97]
H21	At-Home	Carbamide Peroxide	16% - 20%	Uses the tray 8 hours/day or overnight [14-20 days]	2 [51,89]
H22	At-Home	Carbamide Peroxide	11% - 15%	Uses the tray 1 hour/day [14-20 days]	1 [96]

H23	At-Home	Hydrogen Peroxide	16% - 20%	Uses the tray 30 minutes/day [14-20 days]	1 [104]
H24	At-Home	Carbamide Peroxide	≥25%	Uses the tray 30 minutes/day [14-20 days]	1 [93]
H25	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 2 hours/day [14-20 days]	1 [54]
H26	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 1 hour/day [7-13 days]	2 [61,63]
H27	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 4 hours/day [14-20 days]	2 [2,16]
H28	At-Home	Carbamide Peroxide	11% - 15%	Uses the tray 8 hours/day or overnight [7-13 days]	2 [6,52]
H29	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 30 minutes/day [7-13 days]	2 [63,72]
H30	At-Home	Carbamide Peroxide	11% - 15%	Uses the tray 2 hours/day [7-13 days]	1 [29]
H31	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 45 minutes/day [7-13 days]	1 [40]
H32	At-Home	Carbamide Peroxide	≤6%	Uses the tray 8 hours/day or overnight [7-13 days]	1 [53]
H33	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 8 hours/day or overnight [7-13 days]	2 [53,92]
H34	At-Home	Carbamide Peroxide	21% - 25%	Uses the tray 8 hours/day or overnight [≥21 days]	1 [58]
H35	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 8 hours/day or overnight [≥21 days]	1 [58]
H36	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 2 hours/day [7-13 days]	1 [72]
H37	At-Home	Carbamide Peroxide	16% - 20%	Uses the tray 8 hours/day or overnight [≥21 days]	1 [30]
H38	At-Home	Carbamide Peroxide	≥25%	Uses the tray 20 minutes/day [7-13 days]	1 [92]
H39	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 20 minutes/day [14-20 days]	1 [74]
H40	At-Home	Carbamide Peroxide	7% - 10%	Uses the tray 40 minutes/day [14-20 days]	1 [74]
H41	At-Home	Carbamide Peroxide	16% - 20%	Uses the tray 4 hours/day [7-13 days]	1 [77]
H42	At-Home	Hydrogen Peroxide	7% - 10%	Uses the tray 40 minutes/day [7-13 days]	1 [77]
W1	White strips	Hydrogen Peroxide	5.3% - 6.5%	Uses the strips 1 hours/day until it reaches 6 less values in the VITA scale	1 [73]
W2	White strips	Hydrogen Peroxide	5.3% - 6.5%	Uses the strips 1 hours/day [14 days]	7 [54,55,57,76,79,81,94]
W3	White strips	Hydrogen Peroxide	9% - 10%	Uses the strips 30 minutes/day [14 days]	1 [48]
W4	White strips	Hydrogen Peroxide	14%	Uses the strips 1 hours/day [16 days]	1 [69]
W5	White strips	Hydrogen Peroxide	1.8%	Uses the strips 1 hours/day [28 days]	1 [94]
W6	White strips	Hydrogen Peroxide	3.3%	Uses the strips 1 hours/day [28 days]	1 [94]
W7	White strips	Hydrogen Peroxide	9% - 10%	Uses the strips 1 hour/day [7 days]	2 [61,63]

M1	Combined	Hydrogen Peroxide / Carbamide Peroxide	35% / 10%	One in-office session (>40min), followed by use of a tray 8 hours/day or overnight [14-20 days]	1 [7]
M2	Combined	Carbamide Peroxide / Hydrogen Peroxide	16% / 9%	Uses the tray 7 hours/day or overnight [14-20 days] followed by two in-office sessions (31-40 minutes), with 7 days interval between them	1 [89]
M3	Combined	Carbamide Peroxide / Hydrogen Peroxide	16% / 27%	Uses the tray 7 hours/day or overnight [14-20 days] followed by two in-office sessions (31-40 minutes), with 7 days interval between them	1 [89]
M4	Combined	Hydrogen Peroxide / Carbamide Peroxide	35% / 10%	Three in-office sessions (21-30 minutes) with 24 hours interval between them, followed by use of a tray for 1 hour after each session	1 [64]
M5	Combined	Hydrogen Peroxide / Carbamide Peroxide	38% / 10%	Three in-office sessions (21-30 minutes) with 24 hours interval between them, followed by use of a tray for 1 hour after each session	1 [64]
M6	Combined	Hydrogen Peroxide / Carbamide Peroxide	38% / 10%	Two in-office sessions (21-30 minutes) with 8 days interval between them, followed by use of a tray 4 hours/day for 14 days	1 [2]
M7	Combined	Hydrogen Peroxide / Carbamide Peroxide	36% / 15%	One in-office session (>40min), followed by use of a tray 8 hours/day or overnight for 7 days	1 [66]
M8	Combined	Hydrogen Peroxide / Carbamide Peroxide	36% / 15%	One in-office session (31 - 40min), followed by use of a tray 8 hours/day or overnight for 7 days	1 [66]
M9	Combined	Hydrogen Peroxide / Carbamide Peroxide	25% / 10%	One in-office session (>40min), followed by use of a tray 8 hours/day or overnight for 7 days	1 [90]
M10	Combined	Hydrogen Peroxide / Carbamide Peroxide	35% / 10%	One in-office session (31 - 40min), followed by use of a tray 2 hours/day for 14 days	1 [90]
M11	Combined	Hydrogen Peroxide / Carbamide Peroxide	20% / 10%	One in-office session (31 - 40min), followed by use of a tray 2 hours/day for 14 days	1 [41]
M12	Combined	Hydrogen Peroxide / Carbamide Peroxide	35% / 10%	One in-office session (>40min), followed by use of a tray 4 hours/day for 7 days	1 [41]
M13	Combined	Hydrogen Peroxide / Carbamide Peroxide	35% / 10%	One in-office session (≤20min), followed by use of a tray 1 hour/day for 7 days	1 [47]
M14	Combined	Hydrogen Peroxide	6% / 36%	Uses the tray 1 hours/day for 7 days, followed by one in-office session (21-30min), and using the tray for 7 more days	1 [21]

M15	Combined	Hydrogen Peroxide	36% / 6%	One in-office session (21-30min), followed by use of a tray 1 hour/day for 7 days	1 [21]

Table 2
Summary of the main characteristics of the eligible studies.

Author, year	Study Design	Sample (n)	Participants	Average age ± SD (years)	Bleaching Protocols	Evaluation time	Color Assessment (outcome)
Cibirka et al., 1999 [60]	Parallel	64	48♀ 16♂	n.r.	Group A: H6 Group B: H6	14 days	Vita Shade Guide (ΔSGU)
Kihn et al., 2000 [61]	Parallel	56	n.r	n.r.	Group A: H6 Group B: H21	14 days	Vita Lumin (ΔSGU)
Matis et al., 2000 [62]	Split-Mouth	25	17♀ 8♂	50.4±n.r.	Group A: H6 Group B: H28	6 weeks	Colorimeter (ΔE)
Mokhlis et al., 2000 [59]	Split-Mouth	24	n.r.	n.r.	Group A: H12 Group B: H10	12 weeks	Colorimeter (ΔE)
Nathoo et al., 2001 [63]	Parallel	60	n.r.	n.r.	Group A: H32 Group B: H33	Immediately after	Vita Shade Guide and Spectroscopy (ΔSGU, ΔE)
Gerlach and Zhou, 2002 [64]	Parallel	20	9♀ 11♂	n.r.	Group A: W2 Group B: H25	Immediately after	Chroma Meter (ΔSGU)
Gerlach et al., 2002 [65]	Parallel	36	31♀ 15♂	n.r.	Group A: W2 Group B: W2	Immediately after	Photographic System (ΔE)
Al-Shethri et al., 2003 [66]	Split-Mouth	20	10♀ 10♂	55±n.r	Group A: O1 Group B: O1	10 weeks	Trubyte Bio form Shade Guide and Colorimeter (ΔSGU, ΔE)
Karpinia et al., 2003 [67]	Parallel	56	44♀ 12♂	Group A: 29±9.15 Group B: 33.5±13.09	Group A: W2 Group B: H15	Immediately after	Photographic System (ΔE)
Nathoo et al., 2003 [68]	Parallel	59	29♀ 30♂	Group A: 41.1±n.r. Group B: 36.5±n.r.	Group A: H34 Group B: H35	Immediately after	Vita Shade Guide (ΔSGU)
Tavares et al., 2003 [69]	Parallel	87	49♀ 38♂	44±n.r	Group A: O24 Group B: O24	6 months	Vita Shade Guide (ΔSGU)

Zekonis et al., 2003 [70]	Parallel	20	n.r.	n.r.	Group A: H6 Group B: O2	3 months	Trubyte Bio form Shade Guide and Chroma Meter (ΔSGU, ΔE)
Brunton et al., 2004 [98]	Parallel	93	n.r.	n.r.	Group A: H12 Group B: H14	6 months	Vita Shade Guide (ΔSGU)
Ferrari et al., 2004 [104]	Parallel	33	16♀ 17♂	37.2±11.4	Group A: W5 Group B: W6 Group C: W2	Immediately after	Photographic System (ΔE)
Gerlach and Zhou, 2004 [71]	Parallel	31	19♀ 12♂	40±12.7	Group A: W7 Group B: H26	Immediately after	Photographic System (ΔE)
Auschill et al., 2005 [83]	Parallel	39	n.r.	29.82±n.r.	Group A: W1 Group B: H2 Group C: O8	Immediately after	Vita Shade Guide (ΔSGU)
Cronin et al., 2005 [72]	Parallel	59	49♀ 10♂	42.3±9.12	Group A: H3 Group B: H12	Immediately after	Vita Shade Guide and Shade Vision Color Score (ΔSGU, ΔE)
Matis et al., 2005 [73]	Parallel	78	37♀ 41♂	n.r.	Group A: H26 Group B: H29 Group C: W7	2 weeks	Colorimeter (ΔE)
Tsubura and Yamaguchi, 2005 [111]	Split-Mouth	58	42♀ 16♂	30.4±n.r.	Group A: H6 Group B: H6	2 weeks	Portable Chromameter (ΔE)
Soares et al., 2006 [28]	Parallel	40	19♀ 21♂	n.r.	Group A: H27 Group B: H27	1 week	Vita Shade Guide (ΔSGU)
Zantner et al., 2006 [84]	Parallel	46	35♀ 11♂	29.1±8.5	Group A: H39 Group B: H40	9 months	Chroma cop Complete (ΔSGU)
Braun et al., 2007 [85]	Parallel	30	n.r.	n.r.	Group A: H10 Group B: H11	2 weeks	Spectrophotometer (ΔE)
Delgado et al., 2007 [113]	Parallel	46	28♀ 18♂	n.r.	Group A: H14 Group B: H23	Immediately after	Vita Shade Guide (ΔSGU)
Deliperi et al., 2007 [74]	Split-Mouth	10	5♀ 5♂	n.r.	Group A: M4 Group B: M5	1 week	Vita Shade Guide (ΔSGU)

Hannig et al., 2007 [86]	Parallel	46	22♀ 24♂	Group A: 29.8±10.24 Group B: 28.9±7.69	Group A: W2 Group B: H15	Immediately after	Image Analysis Technology (ΔE)
Ziebolz et al., 2007 [87]	Parallel	60	38♀ 22♂	Group A: 26.9±5.27 Group B: 26.6±4.52	Group A: H41 Group B: H42	Immediately after	Image Analysis Technology (ΔE)
Krause et al., 2008 [88]	Parallel	30	14♀ 16♂	31±4	Group A: H10 Group B: H11	2 weeks	n.r.
Marson et al., 2008 [29]	Parallel	40	n.r.	n.r.	Group A: O9 Group B: O9 Group C: O9 Group D: O9	6 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Meireles et al., 2008 [30]	Parallel	92	61♀ 31♂	Group A: 26.4±9.2 Group B: 24.2±6.2	Group A: H4 Group B: H5	1 week	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Meireles et al., 2008 (2) [31]	Parallel	92	61♀ 31♂	Group A: 26.4±9.2 Group B: 24.2±6.2	Group A: H4 Group B: H5	6 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Bizhang et al., 2009 [89]	Parallel	75	45♀ 30♂	40.87±n.r.	Group A: H6 Group B: O12 Group C: W2	3 months	Colorimeter (ΔE)
Kugel et al., 2009 [75]	Parallel	33	n.r.	30.9±n.r	Group A: O14 Group B: O14	1 month	Image Analysis Technology (ΔE)
Matis et al., 2009 [76]	Split-Mouth	37	23♀ 14♂	n.r.	Group A: O3 Group B: M7 Group C: O18 Group D: M8	3 months	Vita Shade Guide and Chroma Meter (ΔSGU, ΔE)
Meireles et al., 2009 [32]	Parallel	92	61♀ 31♂	Group A: 26.4±9.2 Group B: 24.2±6.2	Group A: H4 Group B: H5	12 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Ontiveros and Paravina, 2009 [77]	Split-Mouth	20	n.r.	n.r.	Group A: O14 Group B: O14	1 week	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Wetter et al., 2009 [33]	Parallel	90	58♀ 32♂	n.r.	Group A: M14 Group B: M15 Group C: H15	3 months	Portable Spectrometer (ΔE)

Alomari and El Daraa, 2010 [112]	Parallel	40	28♀ 12♂	27.8±n.r	Group A: O3 Group B: O3 Group C: O3 Group D: O3	1 month	Vita Shade Guide (ΔSGU)
Bernardon et al., 2010 [23]	Split-Mouth	90	n.r.	n.r.	Group A: H6 Group B: O10 Group C: O10 Group D: M1	4 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Cardoso et al., 2010 [15]	Parallel	60	n.r.	n.r.	Group A: H13 Group B: H14 Group C: H15 Group D: H6	Immediately after	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Da Costa et al., 2010 [78]	Split-Mouth	20	8♀ 12♂	n.r.	Group A: O14 Group B: H18	19 days	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Giachetti et al., 2010 [105]	Split-Mouth	17	7♀ 10♂	22±1.4	Group A: H6 Group B: O5	9 months	Spectrophotometer (ΔE)
Gurgan et al., 2010 [101]	Parallel	40	29♀ 11♂	27.3±n.r.	Group A: O15 Group B: O15 Group C: O3 Group D: O18	1 week	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Meireles et al, 2010 [34]	Parallel	92	61♀ 31♂	Group A: 26.4±9.2 Group B: 24.2±6.2	Group A: H4 Group B: H5	24 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Strobl et al., 2010 [90]	Split-Mouth	20	13♀ 7♂	n.r.	Group A: O1 Group B: O1	Immediately after	Vita Shade Guide and Chromameter (ΔSGU, ΔE)
Turkun et al., 2010 [102]	Parallel	20	n.r.	Group A: 25±n.r. Group B: 28±n.r.	Group A: H38 Group B: H33	12 months	Spectrophotometer (ΔE)
Al-Quran et al., 2011 [107]	Parallel	60	37♀ 23♂	31.5±n.r.	n.r.	6 months	3D-Master VITA Shade Guide (ΔSGU)
Dawson et al., 2011 [99]	Parallel	36	n.r.	29.8±n.r.	Group A: H21 Group B: M2 Group C: M3	1 week	Vita Shade Guide (ΔSGU)

Firat et al., 2011 [103]	Parallel	30	23♀ 7♂	23.7±n.r.	Group A: H24 Group B: O15 Group C: O15	Immediately after	Spectrophotometer (ΔE)
Grobler et al., 2011 [110]	Parallel	34	n.r.	n.r.	Group A: H6 Group B: H6	6 months	Spectrophotometer (ΔE)
Kossatz et al., 2011 [35]	Parallel	30	n.r.	n.r.	Group A: O9 Group B: O9	Immediately after	Vita Shade Guide (ΔSGU)
Reis et al., 2011 [36]	Parallel	30	n.r.	n.r.	Group A: O6 Group B: O20	Immediately after	Vita Shade Guide (ΔSGU)
Almeida et al., 2012 [37]	Parallel	40	n.r.	n.r.	Group A: H1 Group B: O2 Group C: O2 Group D: O2	6 months	Vita Shade Guide (ΔSGU)
Basting et al., 2012 [38]	Parallel	100	76♀ 18♂	n.r.	Group A: H4 Group B: H5 Group C: O2 Group D: O2	3 weeks	Vita Shade Guide (ΔSGU)
Da Costa et al., 2012 [79]	Split-Mouth	25	13♀ 12♂	n.r.	Group A: H19 Group B: W4	2 weeks	VITA Bleached Guide 3D-Master and Spectrophotometer (ΔSGU, ΔE)
De Almeida et al., 2012 [39]	Parallel	40	n.r.	n.r.	Group A: H1 Group B: O2 Group C: O2 Group D: O2	6 months	n.r.
Henry et al., 2012 [81]	Split-Mouth	49	25♀ 24♂	38.39±13.64	Group A: O14 Group B: O14	2 weeks	Vita Shade Guide (ΔSGU)
Mondelli et al., 2012 [40]	Split-Mouth	48	n.r	n.r.	Group A: O15 Group B: O3 Group C: O15 Group D: O3 Group E: H30	24 months	Spectrophotometer (ΔE)

Tay et al., 2012 [41]	Parallel	60	n.r.	Group A: 21±3.8 Group B: 21±3.2	Group A: O9 Group B: H37	24 months	Vita Shade Guide (ΔSGU)
Ward and Felix, 2012 [80]	Split-Mouth	15	n.r.	n.r.	Group A: O24 Group B: O14	1 week	Vita Shade Guide (ΔSGU)
Auschill et al., 2013 [91]	Parallel	30	18♀ 12♂	Group A: 31.3±n.r. Group B: 34.9±n.r.	Group A: H3 Group B: W2	18 months	Vita Shade Guide (ΔSGU)
Nutter et al., 2013 [100]	Parallel	22	n.r.	n.r.	Group A: M9 Group B: M10	2 weeks	Vita Shade Guide (ΔSGU)
Oliveira et al., 2013 [82]	Parallel	29	12♀ 17♂	Group A: 41.6±14.3 Group B: 42.7±12.7	Group A: H36 Group B: H29	1 day	Image Analysis Technology (ΔE)
Polydorou et al., 2013 [92]	Parallel	60	n.r.	27.64±5	Group A: O23 Group B: O23 Group C: O23	3 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Reis et al., 2013 [42]	Parallel	60	33♀ 27♂	Group A: 25.0±6.8 Group B: 29±9.9	Group A: O6 Group B: O20	1 week	Vita Shade Guide (ΔSGU)
Zhao et al., 2013 [109]	Split-Mouth	36	38♀ 22♂	24.1±n.r.	Group A: M16 Group B: M17	6 months	Spectrophotometer (ΔE)
De la Peña and Ratón, 2014 [106]	Parallel	96	68♀ 28♂	25.9±5.6	Group A: H15 Group B: H22 Group C: H17 Group D: H17	Immediately after	Colorimeter (ΔE)
Farhat et al., 2014 [43]	Split-Mouth	16	n.r.	n.r.	Group A: O1 Group B: O1	6 months	Vita Shade Guide (ΔSGU)
Bernardon et al., 2015 [44]	Split-Mouth	30	20♀ 10♂	n.r.	Group A: O11 Group B: O11 Group C: H7 Group D: H8	Immediately after	Spectrophotometer (ΔE)

De Paula et al., 2015 [45]	Parallel	40	23♀ 17♂	Group A: 25.6±5.4 Group B: 23.9±6.6	Group A: O16 Group B: O6	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Martín et al., 2015 [93]	Split-Mouth	31	12♀ 19♂	24.5±6.33	Group A: O2 Group B: O17	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Al-Omiri et al., 2016 [108]	Parallel	26	13♀ 13♂	27 ±5	Group A: O4 Group B: O5	Immediately after	Colorimeter (ΔE)
Bernardon et al., 2016 [46]	Split-Mouth	50	n.r.	n.r.	Group A: H4 Group B: H4 Group C: H9 Group D: H9	6 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Bortolatto et al., 2016 [47]	Parallel	48	24♀ 24♂	Group A: 24.3±3.7 Group B: 24.0±4.2	Group A: O13 Group B: O1	Immediately after	Spectrophotometer (ΔE)
De Freitas et al., 2016 [48]	Split-Mouth	22	12♀ 10♂	20.5±n.r.	Group A: O3 Group B: O15	2 weeks	Vita Shade Guide (ΔSGU)
Kose et al., 2016 [49]	Parallel	53	34♀ 19♂	Group A: 23.2±3.3 Group B: 21.2±4.0 Group C: 25.6±2.4	Group A: O19 Group B: O1 Group C: O9	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Machado et al., 2016 [2]	Split-Mouth	21	15♀ 6♂	23±n.r.	Group A: M6 Group B: H27	2 weeks	Spectrophotometer (ΔE)
Mena-Serrano et al., 2016 [50]	Parallel	77	50♀ 27♂	Group A: 22.9±4.0 Group B: 22.0±4.4 Group C: 23.0±3.4 Group D: 22.0±3.6	Group A: O9 Group B: O9 Group C: O20 Group D: O20	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Montenegro-Arana et al., 2016 [51]	Parallel	40	17♀ 23♂	Group A: 24.4±4.4 Group B: 24.2±3.9	Group A: H31 Group B: H31	Immediately after	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)

Rezende et al., 2016 [13]	Parallel	30	15♀ 15♂	Group A: 25.9±8.1 Group B: 24.0±6.6	Group A: M11 Group B: M12	12 months	Vita Shade Guide (ΔSGU)
Carlos et al., 2017 [52]	Parallel	75	n.r.	n.r.	Group A: H16 Group B: H16 Group C: H6	2 weeks	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Darriba et al., 2017 [107]	Parallel	80	40♀ 40♂	Group A: 30.75±10.52 Group B: 29.29±9.67 Group C: 31.09±11.17 Group D: 29.25±9.43	Group A: H15 Group B: H16 Group C: H17 Group D: H20	Immediately after	Spectrophotometer (ΔE)
Fernandez et al., 2017 [94]	Split-Mouth	27	10♀ 17♂	24.1±4.95	Group A: O2 Group B: O17	9 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Loguercio et al., 2017 [114]	Split-Mouth	45	21♀ 34♂	Group A: 25.2±5.0 Group B: 22.2±4.0	Group A: O1 Group B: O1	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Nie et al., 2017 [14]	Parallel	40	30♀ 10♂	27±n.r.	Group A: O3 Group B: H28	3 months	Spectrophotometer (ΔE)
Vildósola et al., 2017 [95]	Split-Mouth	30	14♀ 16♂	27.24±8.0	Group A: O25 Group B: O25	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Vildósola et al., 2017 (2) [96]	Split-Mouth	31	12♀ 19♂	24.1±5.0	Group A: O2 Group B: O17	12 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Angel et al., 2018 [97]	Split-Mouth	35	16♀ 17♂	27.11±n.r.	Group A: O6 Group B: O7	3 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Chemin et al., 2018 [53]	Parallel	78	50♀ 28♂	Group A: 23.6±5.9 Group B: 24.3±9.1	Group A: H3 Group B: H17	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Martins et al., 2018 [54]	Split-Mouth	44	n.r.	Group A: 27.5±6.2 Group B: 26.1±5.5	Group A: O6 Group B: O6	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Mondelli et al., 2018 [55]	Split-Mouth	34	n.r.	n.r.	Group A: O21 Group B: O21 Group C: O3	12 months	Spectrophotometer (ΔE)

					Group D: O3		
Peixoto et al., 2018 [56]	Parallel	40	23♀ 17♂	Group A: 23.5±4.5 Group B: 23.8±3.5	Group A: O3 Group B: O22	1 month	Spectrophotometer (ΔE)
Rodrigues et al., 2018 [57]	Parallel	40	28♀ 12♂	Group A: 24.5±5.3 Group B: 23.7±4.7	Group A: O9 Group B: M13	6 months	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)
Cordeiro et al., 2019 [58]	Parallel	60	n.r.	Group A: 17.8±1.4 Group B: 17.7±1.6 Group C: 17.9±1.4	Group A: H16 Group B: H16 Group C: W3	1 month	Vita Shade Guide and Spectrophotometer (ΔSGU, ΔE)

n: number of patients; ♀: women; ♂: men; n.r.: not mentioned by the author

Table 3
Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for Randomized Controlled Trials Studies [22].

Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Q.11	Q.12	Q.13	% yes/ Risk
Cibirka et al., 1999 [60]	√	-	-	N/A	N/A	-	√	√	-	√	√	√	√	63.6
Kihn et al., 2000 [61]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Matis et al., 2000 [62]	√	-	√	N/A	N/A	√	√	√	-	√	√	√	√	81.8
Mokhlis et al., 2000 [59]	√	-	√	√	-	√	√	√	-	√	√	√	√	76.9
Nathoo et al., 2001 [63]	√	√	√	√	√	-	√	√	-	√	√	√	√	84.6
Gerlach and Zhou, 2002 [64]	√	-	√	N/A	N/A	√	√	√	-	√	√	√	√	81.8
Gerlach et al., 2002 [65]	√	√	√	N/A	√	-	√	√	-	√	√	√	√	83.3
Al Shethri et al., 2003 [66]	√	√	√	√	-	-	√	√	√	√	√	√	√	84.6
Karpinia et al., 2003 [67]	-	-	√	N/A	-	-	√	√	N/A	√	√	√	√	63.6
Nathoo et al., 2003 [68]	√	√	√	√	√	-	√	√	-	√	√	√	√	84.6
Tavares et al., 2003 [69]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	81.8
Zekonis et al., 2003 [70]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	81.8
Brunton et al., 2004 [98]	√	-	-	√	√	-	√	√	-	√	√	√	√	69.2
Ferrari et al., 2004 [104]	√	√	-	√	√	-	√	√	-	√	√	√	√	76.9
Gerlach and Zhou, 2004 [71]	-	√	√	N/A	N/A	√	√	-	-	√	√	√	√	72.7
Auschill et al., 2005 [83]	-	√	-	√	√	-	√	√	√	√	√	√	√	76.9
Cronin et al., 2005 [72]	√	-	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Matis et al., 2005 [73]	-	√	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Tsubura and Yamaguchi, 2005 [111]	-	-	√	N/A	N/A	√	√	√	-	√	√	√	√	72.7
Soares et al., 2006 [28]	-	-	√	N/A	-	√	√	√	-	√	√	√	√	66.7
Zantner et al., 2006 [84]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9

Braun et al., 2007 [85]	-	√	√	√	√	√	√	-	-	√	√	√	√	76.9
Delgado et al., 2007 [113]	√	-	√	√	N/A	√	√	√	-	√	√	√	√	83.3
Deliperi et al., 2007 [74]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Hannig et al., 2007 [86]	√	-	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Ziebolz et al., 2007 [87]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Krause et al., 2008 [88]	-	-	√	√	√	-	√	-	-	√	√	√	√	61.5
Marson et al., 2008 [29]	-	-	√	N/A	N/A	-	√	√	-	√	√	√	√	63.6
Meireles et al., 2008 [30]	√	√	√	N/A	-	√	√	√	-	√	√	√	√	83.3
Meireles et al., 2008 [31]	√	√	√	N/A	√	√	√	√	√	√	√	√	√	100
Bizhang et al., 2009 [89]	√	√	√	N/A	N/A	-	√	-	-	√	√	√	√	72.7
Kugel et al., 2009 [75]	-	-	√	N/A	N/A	√	√	√	-	√	√	√	√	72.7
Matis et al., 2009 [76]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	92.3
Meireles et al., 2009 [32]	√	√	√	N/A	√	√	√	√	-	√	√	√	√	91.7
Ontiveros and Paravina, 2009 [77]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9
Wetter et al., 2009 [33]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Alomari and El Daraa, 2009 [112]	√	-	-	√	N/A	√	√	√	√	√	√	√	√	83.3
Bernardon et al., 2010 [23]	√	√	-	N/A	N/A	-	√	-	-	√	√	√	√	63.6
Cardoso et al., 2010 [15]	√	√	√	√	-	√	√	√	-	√	√	√	√	84.6
Da Costa et al., 2010 [78]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	92.3
Giachetti et al., 2010 [105]	√	-	-	N/A	N/A	√	√	√	-	√	√	√	√	72.7
Gurgan et al., 2010 [101]	√	-	-	N/A	-	√	√	√	-	√	√	√	√	66.7
Meireles et al., 2010 [34]	√	√	√	N/A	√	√	√	√	-	√	√	√	√	91.7
Strobl et al., 2010 [90]	-	-	√	N/A	N/A	-	√	√	-	√	√	√	√	63.6
Turkun et al., 2010 [102]	√	-	√	N/A	N/A	√	√	√	N/A	√	√	√	√	90
Al-Quran et al., 2011 [107]	-	-	-	-	N/A	√	√	√	√	√	√	√	√	66.6

Dawson et al., 2011 [99]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Firat et al., 2011 [103]	√	-	-	N/A	N/A	√	√	√	-	√	√	√	√	72.7
Grobler et al., 2011 [110]	√	-	-	N/A	N/A	-	√	√	-	√	√	√	√	63.6
Kossatz et al., 2011 [35]	√	-	√	N/A	N/A	√	√	√	N/A	√	√	√	√	90
Reis et al., 2011 [36]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9
Almeida et al., 2012 [37]	√	-	-	-	-	√	√	√	√	√	√	√	√	69.2
Basting et al., 2012 [38]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Da Costa et al., 2012 [79]	√	-	√	N/A	N/A	√	√	√	-	√	√	√	√	81.8
De Almeida et al., 2012 [39]	√	-	-	N/A	N/A	-	√	√	-	√	√	√	√	63.6
Henry et al., 2012 [81]	√	-	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Mondelli et al., 2012 [40]	√	-	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Tay et al., 2012 [41]	√	√	√	N/A	N/A	√	√	√	√	√	√	√	√	100
Ward and Felix, 2012 [80]	√	-	√	N/A	-	-	√	√	-	√	√	√	√	66.7
Auschill et al., 2013 [91]	√	√	√	-	√	-	√	√	√	√	√	√	√	84.6
Nutter et al., 2013 [100]	√	-	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Oliveira et al., 2013 [82]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9
Polydorou et al., 2013 [92]	√	-	√	N/A	N/A	√	√	√	-	√	√	√	√	81.8
Reis et al., 2013 [42]	√	√	√	N/A	√	√	√	√	√	√	√	√	√	100
Zhao et al., 2013 [109]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	91.9
De la Peña and Ratón, 2014 [106]	√	-	-	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Farhat et al., 2014 [43]	√	√	√	N/A	√	√	√	√	-	√	√	√	√	91.7
Bernardon et al., 2015 [44]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9
De Paula et al., 2015 [45]	√	√	√	N/A	√	-	√	√	-	√	√	√	√	83.3
Martín et al., 2015 [93]	√	√	√	N/A	√	√	√	√	-	√	√	√	√	91.7
Al-Omiri et al., 2016 [108]	√	-	-	N/A	-	-	√	√	√	√	√	√	√	66.6
Bernardon et al., 2016 [46]	-	√	-	-	-	√	√	√	-	√	√	√	√	61.5
Bortolatto et al., 2016 [47]	√	√	√	√	√	√	√	√	-	√	√	√	√	92.3

De Freitas et al., 2016 [48]	-	-	√	N/A	N/A	√	√	√	-	√	√	√	√	72.7
Kose et al., 2016 [49]	√	√	√	N/A	N/A	√	√	√	√	√	√	√	√	100
Machado et al., 2016 [2]	√	-	√	N/A	N/A	√	√	√	N/A	√	√	√	√	90
Mena-Serrano et al., 2016 [50]	√	√	√	N/A	N/A	√	√	√	√	√	√	√	√	100
Montenegro-Arana et al., 2016 [51]	√	√	√	N/A	N/A	√	√	√	√	√	√	√	√	100
Rezende et al., 2016 [13]	√	√	√	N/A	-	√	√	√	√	√	√	√	√	91.7
Carlos et al., 2017 [52]	-	-	√	N/A	N/A	-	√	√	√	√	√	√	√	72.7
Darriba et al., 2017 [107]	√	√	√	N/A	√	√	√	√	-	√	√	√	√	91.7
Fernandez et al., 2017 [94]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9
Loguercio et al., 2017 [114]	√	√	√	N/A	√	√	√	√	√	√	√	√	√	100
Nie et al., 2017 [14]	√	-	√	N/A	N/A	-	√	√	-	√	√	√	√	72.7
Vildósola et al., 2017 [95]	√	-	√	N/A	-	√	√	√	-	√	√	√	√	75
Vildósola et al., 2017 [96]	√	√	√	N/A	√	√	√	√	√	√	√	√	√	100
Angel et al., 2018 [97]	√	√	√	N/A	-	√	√	√	√	√	√	√	√	91.7
Chemin et al., 2018 [53]	√	√	√	√	√	√	√	√	-	√	√	√	√	92.3
Martins et al., 2018 [54]	√	√	√	N/A	N/A	√	√	√	√	√	√	√	√	100
Mondelli et al., 2018 [55]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8
Peixoto et al., 2018 [56]	√	√	√	N/A	-	√	√	√	-	√	√	√	√	83.3
Rodrigues et al., 2018 [57]	√	√	√	N/A	N/A	√	√	√	-	√	√	√	√	90.9
Cordeiro et al., 2019 [58]	√	√	√	N/A	N/A	-	√	√	-	√	√	√	√	81.8

Q.1 - Was true randomization used for assignment of participants to treatment groups? Q.2 - Was allocation to treatment groups concealed? Q.3 - Were treatment groups similar at the baseline? Q.4 - Were participants blind to treatment assignment? Q.5 - Were those delivering treatment blind to treatment assignment? Q.6 - Were outcomes assessors blind to treatment assignment? Q.7 - Were treatment groups treated identically other than the intervention of interest? Q.8 - Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Q.9 - Were participants analyzed in the groups to which they were randomized? Q.10 - Were outcomes measured in the same way for treatment groups? Q.11 - Were outcomes measured in a reliable way? Q.12 -Was appropriate statistical analysis used? Q.13 - Was the trial design appropriate, and any deviations from the standard RCT design accounted for in the conduct and analysis on the trial? / √ - Yes; -- - No; U – Unclear; N/A – Not applicable.

Table 4
Summary of the main results of the studies included in the quantitative analysis.

Authors	Groups	ΔE Immediately After Mean ±SD [n]	ΔE 7 days Mean ±SD [n]	ΔE 30 days Mean ±SD [n]	ΔE 180 days Mean ±SD [n]
Gerlach and Zhou, 2002 [64]	W2	4.55±0.38 [10]	n.r.	n.r.	n.r.
	H25	2.55±0.38 [10]	n.r.	n.r.	n.r.
Karpinia et al., 2003 [67]	H15	1.6±0.38 [26]	n.r.	n.r.	n.r.
	W2	3.37±0.19 [29]	n.r.	n.r.	n.r.
Zekonis et al. (2003) [70]	H6	12.32±2.89 [10]	7.83±2.77* [10]	6.64±2.48* [10]	n.r.
	O2	5.32±1.93 [10]	4.33±1.95* [10]	3.63±1.12* [10]	n.r.
Matis et al., 2009 [76]	O3	5.10±0.44 [25]	2.29±0.37 [25]	n.r	n.r
	M7	9.23±0.52 [25]	6.13±0.54 [25]	n.r	n.r
	O18	6.26±0.54 [12]	2.41±0.37 [12]	n.r	n.r
	M8	8.53±0.56 [12]	4.49±0.60 [12]	n.r	n.r
Bernardon et al. 2010 [23]	H6	8.4±3.59 [15]	n.r.	9.08±3.39 [15]	n.r.
	H6	9.3±3.56 [15]	n.r.	9.50±3.46 [15]	n.r.
	O10	7.41±3.33 [15]	n.r.	9.39±3.72 [15]	n.r.
	O10	6.17±2.62 [15]	n.r.	7.96±3.26 [15]	n.r.
	O10	6.64±3.08 [15]	n.r.	8.61±3.48 [15]	n.r.
	M1	10.07±3.52 [15]	n.r.	10.09±3.54 [15]	n.r.
Cardoso et al., 2010 [15]	H13	3.9±1.8 [15]	n.r.	n.r.	n.r.
	H14	4.4±1.8 [15]	n.r.	n.r.	n.r.
	H15	5.8±2.1 [15]	n.r.	n.r.	n.r.
	H6	8.5±3.3 [15]	n.r.	n.r.	n.r.
Gurgan et al., 2010 [101]	O15	n.r.	5.69±0.17 [10]	n.r.	n.r.
	O15	n.r.	5.54±0.15 [10]	n.r.	n.r.
	O3	n.r.	5.28±0.09 [10]	n.r.	n.r.
	O18	n.r.	5.43±0.20 [10]	n.r.	n.r.
Firat et al., 2011 [103]	H24	5.32±0.15 [10]	n.r.	n.r.	n.r.
	O15	5.42±0.08 [10]	n.r.	n.r.	n.r.
	O15	5.59±0.01 [10]	n.r.	n.r.	n.r.
Mondelli et al. 2012 [40]	O15	7.80±1.42 [10]	6.45±1.40 [10]	5.64±1.45 [10]	4.49±1.45 [10]
	O15	7.83±1.89 [9]	6.77±1.32 [9]	5.78±1.37 [9]	4.64±1.26 [9]
	O3	7.49±1.45 [10]	6.54±1.37 [10]	5.43±1.47 [10]	4.33±1.39 [10]
	O3	7.76±1.50 [10]	6.67±1.56 [10]	5.64±1.38 [10]	4.42±1.47 [10]
	H30	9.8±1.75 [9]	8.70±2.1.64 [9]	7.67±1.57 [9]	6.52±1.62 [9]
De la Peña and Ratón, 2014 [106]	H15	6.6±3.5 [24]	n.r.	n.r.	n.r.
	H22	6.5±4.0 [24]	n.r.	n.r.	n.r.
	H17	7.1±4.0 [24]	n.r.	n.r.	n.r.
	H17	7.4±2.6 [24]	n.r.	n.r.	n.r.
Martín et al., 2015 [93]	O2	5.73±2.42 [31]	5.3±2.29* [31]	5.03±2.30 [30]	n.r.
	O17	5.33±2.37 [31]	5.1±2.31* [31]	4.82±2.28 [30]	n.r.
Kose et al., 2016 [49]	O19	n.r.	n.r.	4.5±2.0 [18]	n.r.
	O1	n.r.	n.r.	7.9±2.1 [18]	n.r.
	O9	n.r.	n.r.	8.4±3.6 [17]	n.r.
Mena-Serrano et al., 2016 [50]	O9	n.r.	13.5±2.3* [20]	14.1±2.9 [20]	n.r.
	O9	n.r.	14.5±3.5* [19]	12.4±3.7 [19]	n.r.

	O20	n.r.	12.0±4.9* [19]	11.8±4.0 [19]	n.r.
	O20	n.r.	13.2±4.1* [19]	13.2±4.1 [19]	n.r.
Darriba et al., 2017 [107]	H15	8.05±3.86 [20]	n.r.	n.r.	n.r.
	H6	10.59±2.68 [20]	n.r.	n.r.	n.r.
	H17	7.08±1.99 [20]	n.r.	n.r.	n.r.
	H20	8.95±2.32 [20]	n.r.	n.r.	n.r.
Fernández et al., 2017 [94]	O2	n.r.	n.r.	5.86±3.69 [27]	n.r.
	O17	n.r.	n.r.	8.24±2.45 [27]	n.r.
Loguercio et al., 2017 [114]	O1	n.r.	n.r.	8.3±3.5 [54]	n.r.
	O1	n.r.	n.r.	7.7±3.6 [54]	n.r.
Vildósola et al., 2017 [96]	O2	n.r.	7.9±1.1* [31]	8.2±2.5 [29]	n.r.
	O17	n.r.	8.2±2.7* [31]	5.9±3.8 [29]	n.r.
Chemin et al., 2018 [53]	H3	6.8±3.0 [39]	n.r.	7.9±3.5 [39]	n.r.
	H17	9.0±3.2 [39]	n.r.	8.4±3.5 [39]	n.r.
Mondelli et al., 2018 [55]	O21	7.58±1.44 [17]	7.99±1.48 [17]	8.23±2.64 [17]	7.72±1.95 [17]
	O21	6.96±1.48 [17]	7.93±1.58 [17]	7.46±1.72 [17]	7.77±2.28 [17]
	O3	7.57±3.12 [17]	8.26±2.52 [17]	7.41±2.31 [17]	8.26±2.28 [17]
	O3	7.87±2.21 [17]	7.81±1.83 [17]	7.41±1.37 [17]	7.87±1.76 [17]

n: number of patients; n.r.: not mentioned by the author; *:results excluded in the meta-analysis because they didn't have any comparison group

Figure 1

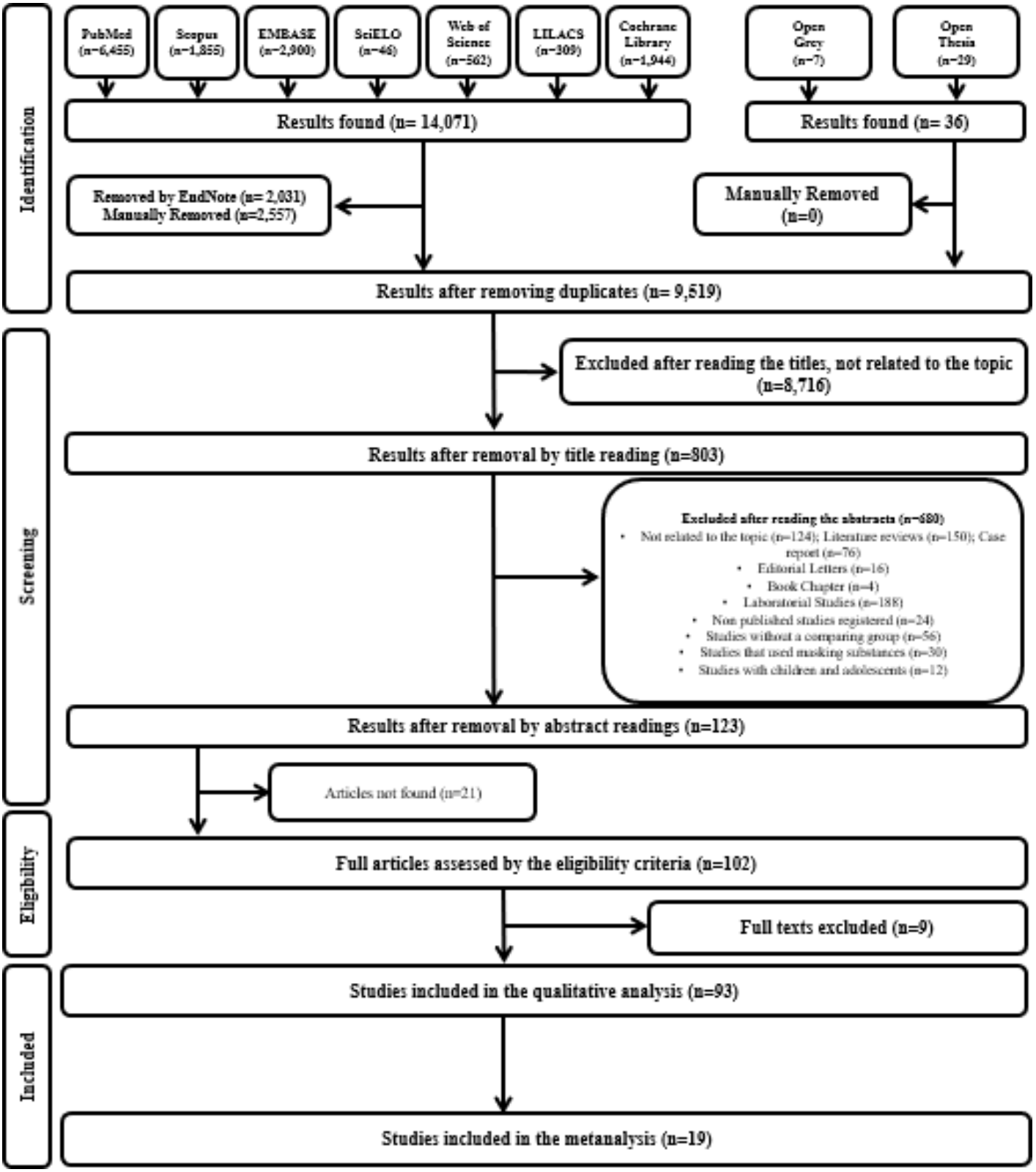

Identification
PubMed (n=6,455)
Scopus (n=1,855)
EMBASE (n=2,900)
SciELO (n=46)
Web of Science (n=562)
LILACS (n=309)
Cochrane Library (n=1,944)
Open Grey (n=7)
Open Thesis (n=29)
Results found (n= 14,071)
Results found (n= 36)
Removed by EndNote (n= 2,031)
Manually Removed (n=2,557)
Manually Removed (n=0)
Results after removing duplicates (n= 9,519)
Screening
Excluded after reading the titles, not related to the topic (n=8,716)
Results after removal by title reading (n=803)
Excluded after reading the abstracts (n=680)
Not related to the topic (n=124); Literature reviews (n=150); Case report (n=76)
Editorial Letters (n=16)
Book Chapter (n=4)
Laboratorial Studies (n=188)
Non published studies registered (n=24)
Studies without a comparing group (n=56)
Studies that used masking substances (n=30)
Studies with children and adolescents (n=12)
Results after removal by abstract readings (n=123)
Articles not found (n=21)
Eligibility
Full articles assessed by the eligibility criteria (n=102)
Full texts excluded (n=9)
Included
Studies included in the qualitative analysis (n=93)
Studies included in the metanalysis (n=19)

Figure 2

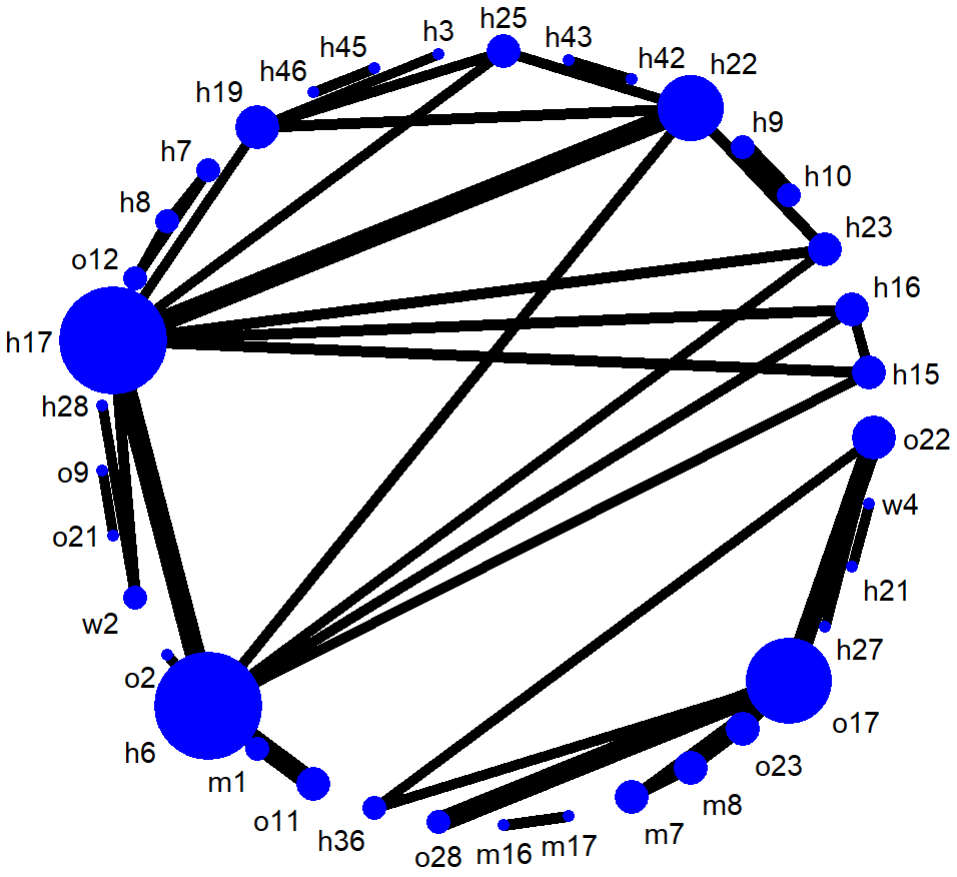


Figure 2a: Metanalysis map immediately after the bleaching treatment.

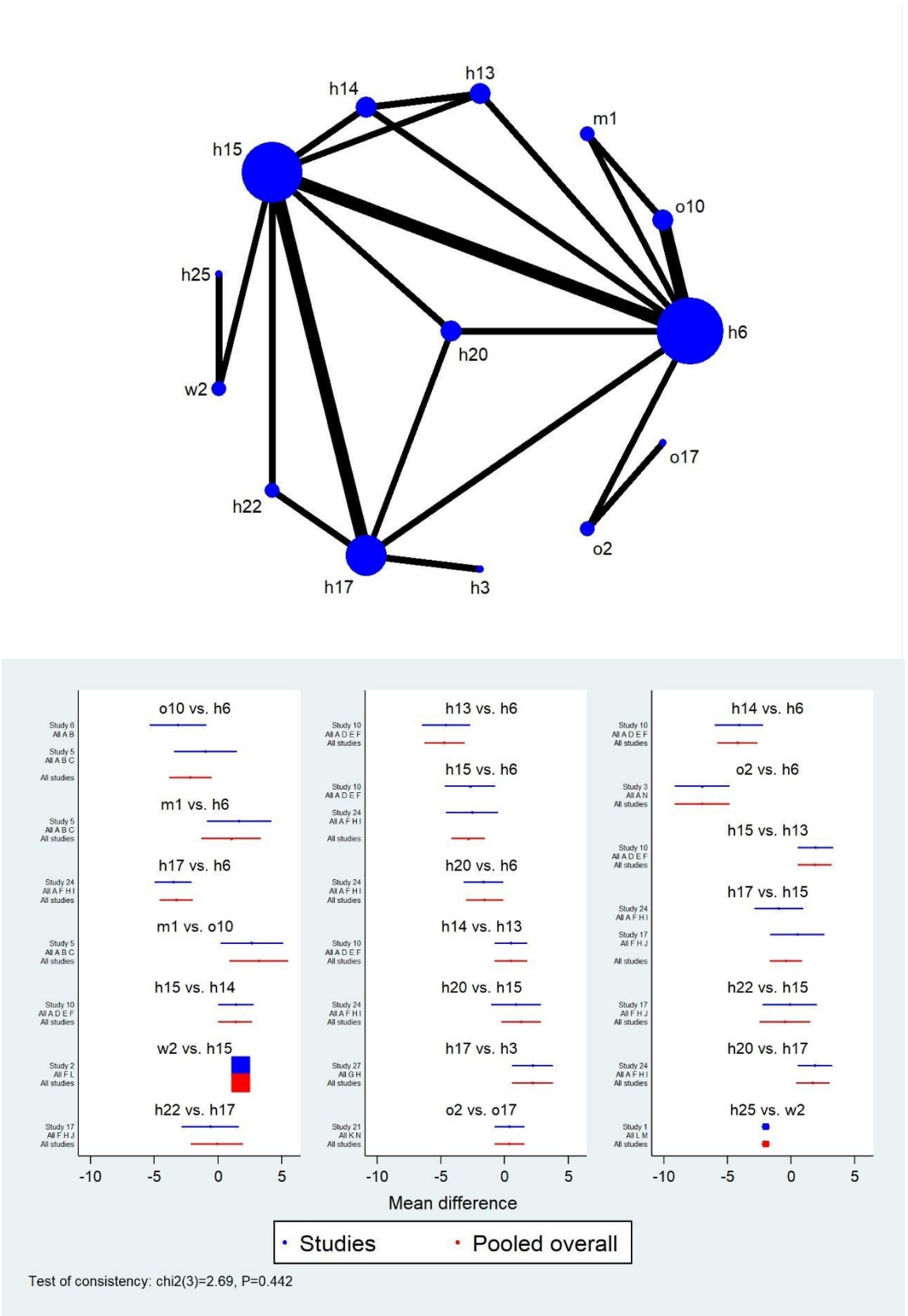


Figure 2b: Metanalysis map and forest plot immediately after the bleaching treatment (Part 1)

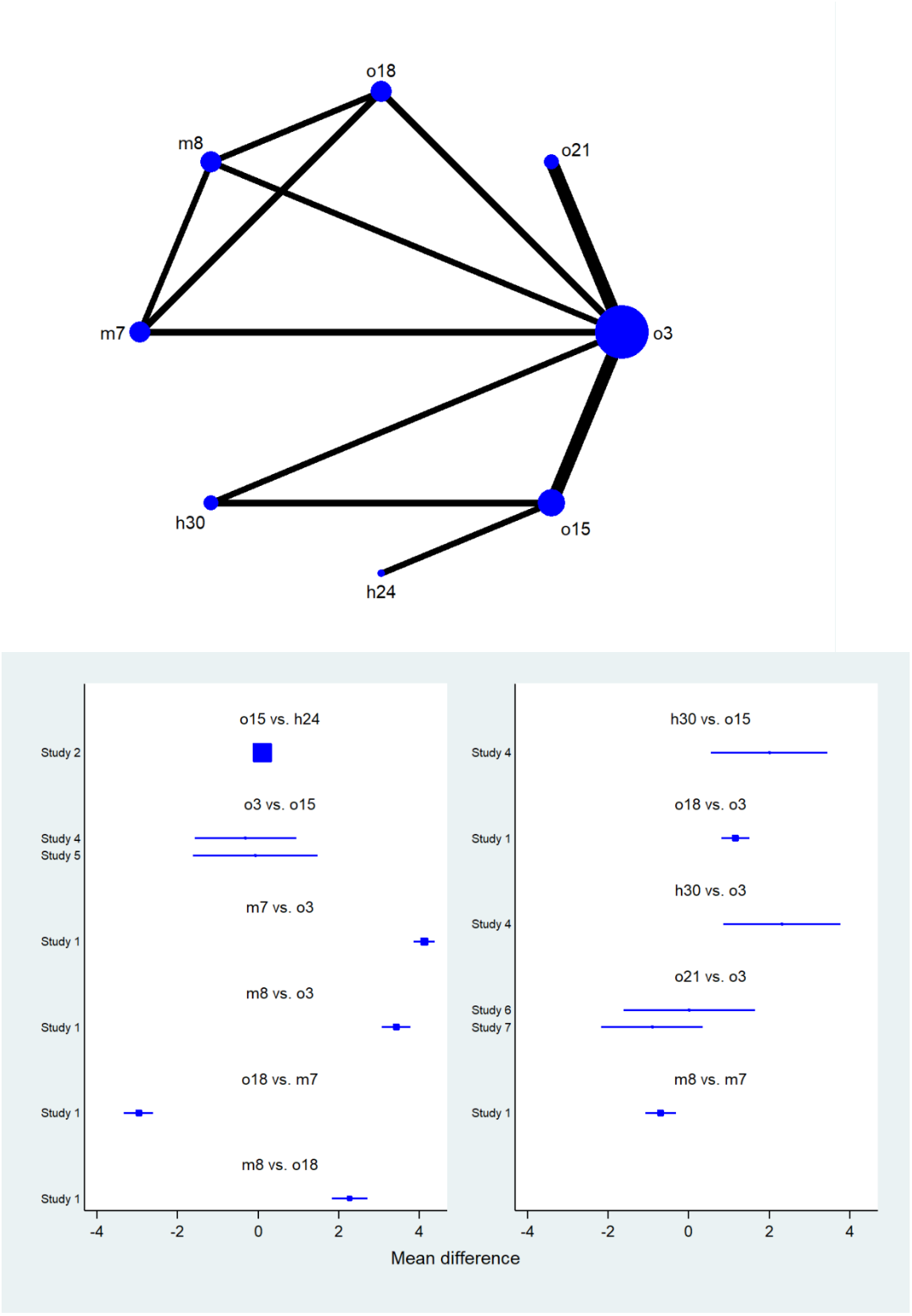


Figure 2c: Metanalysis map and forest plot immediately after the bleaching treatment (Part2)

Figure 3

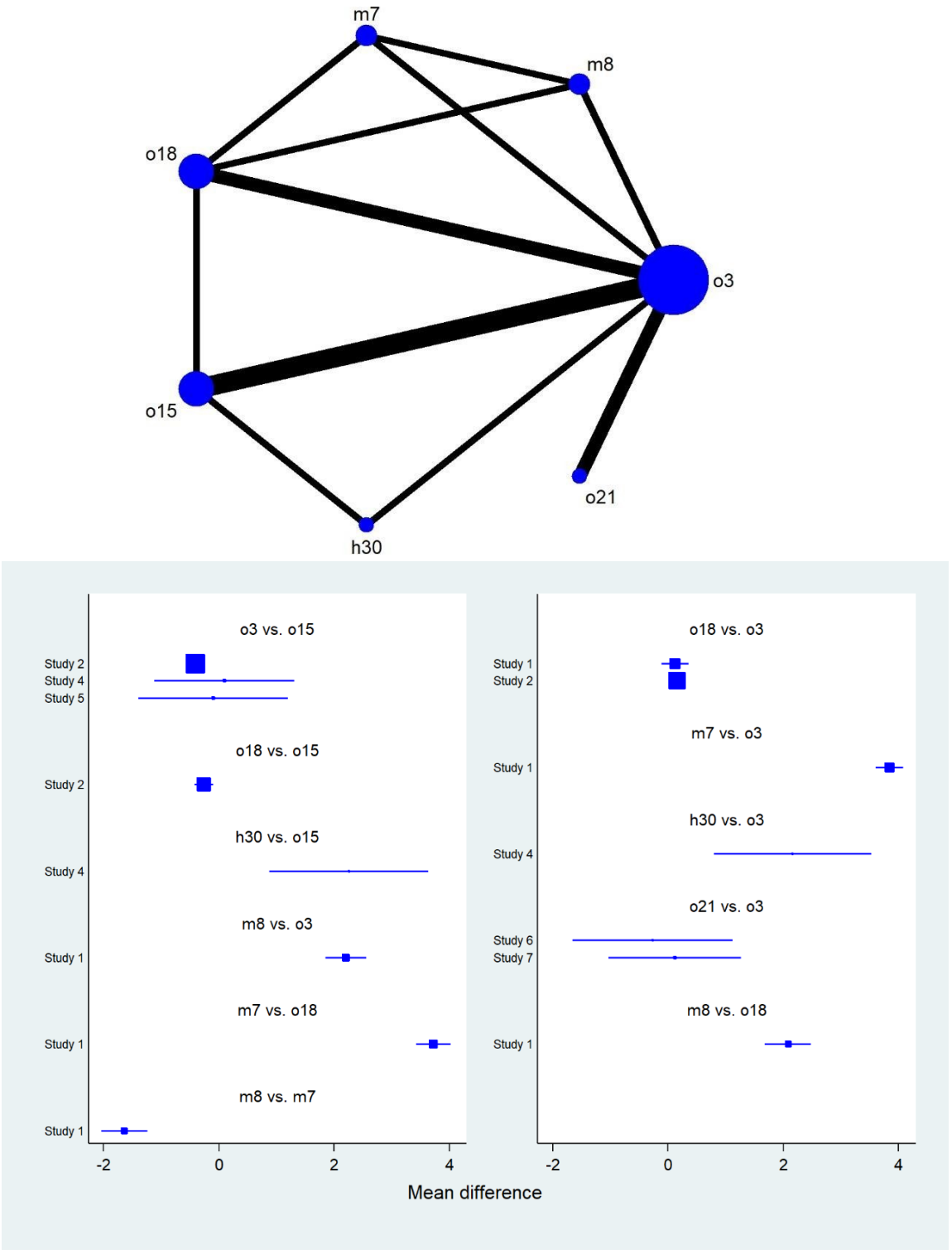


Figure 3: Metanalysis map and forest plot seven days after the bleaching treatment

Figure 4

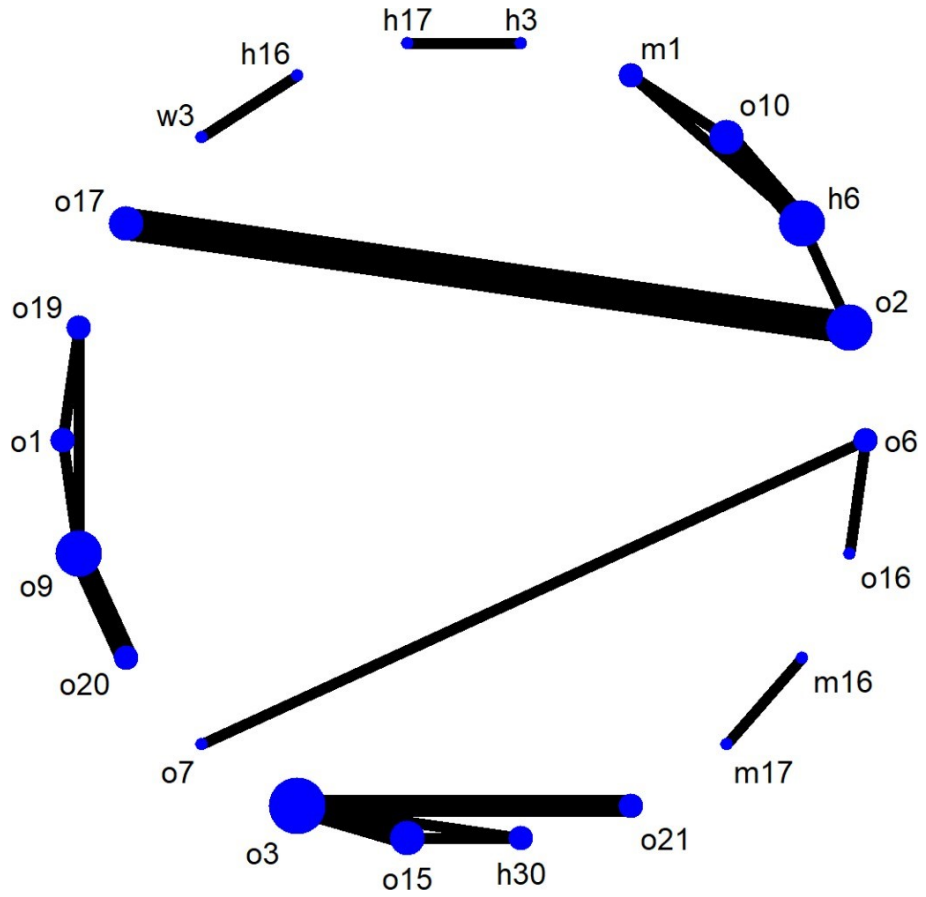


Figure 4a: Metanalysis map 30 days after the bleaching treatment

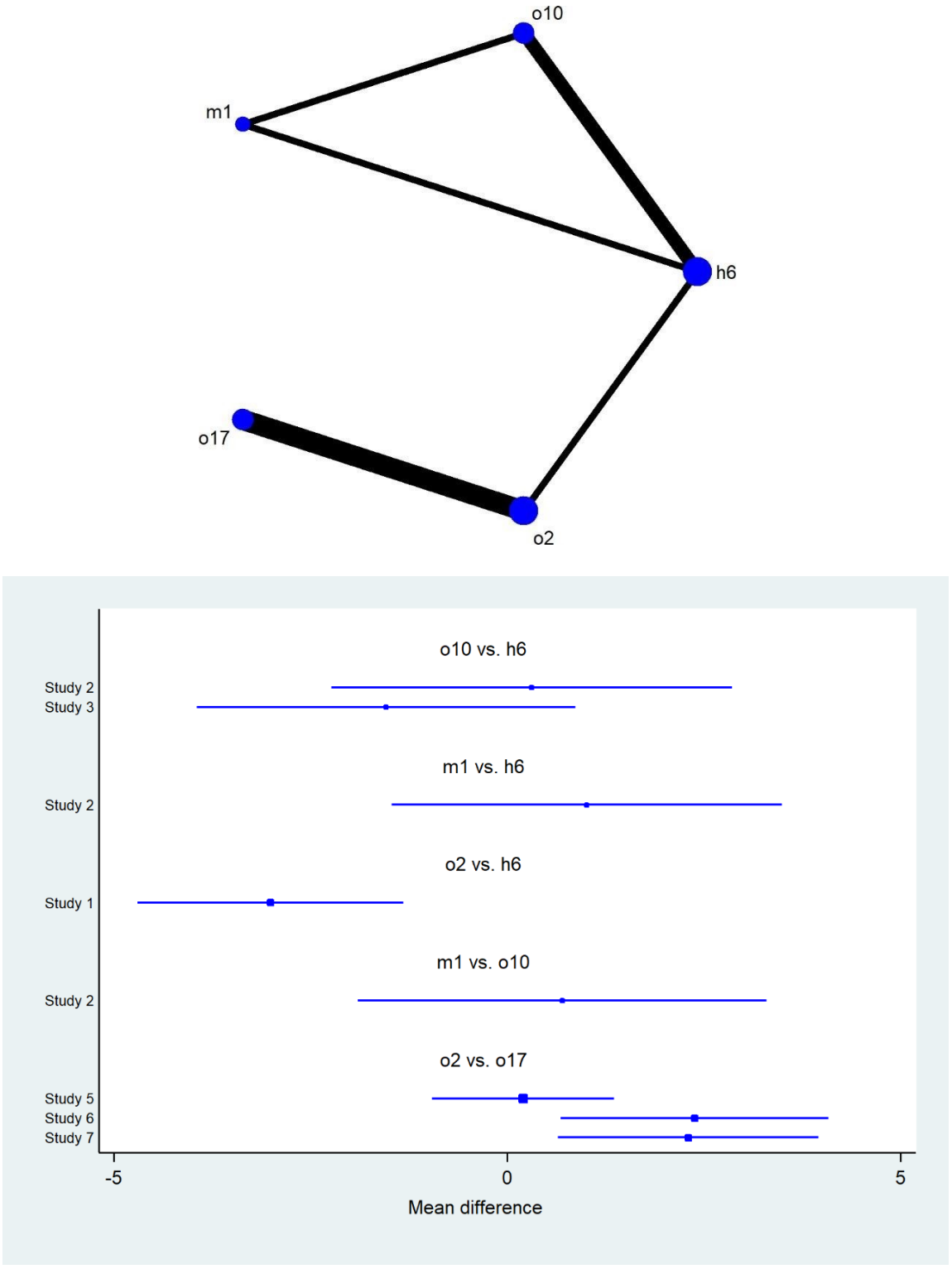


Figure 4b: Metanalysis map and forest plot immediately after the bleaching treatment (Part 1)

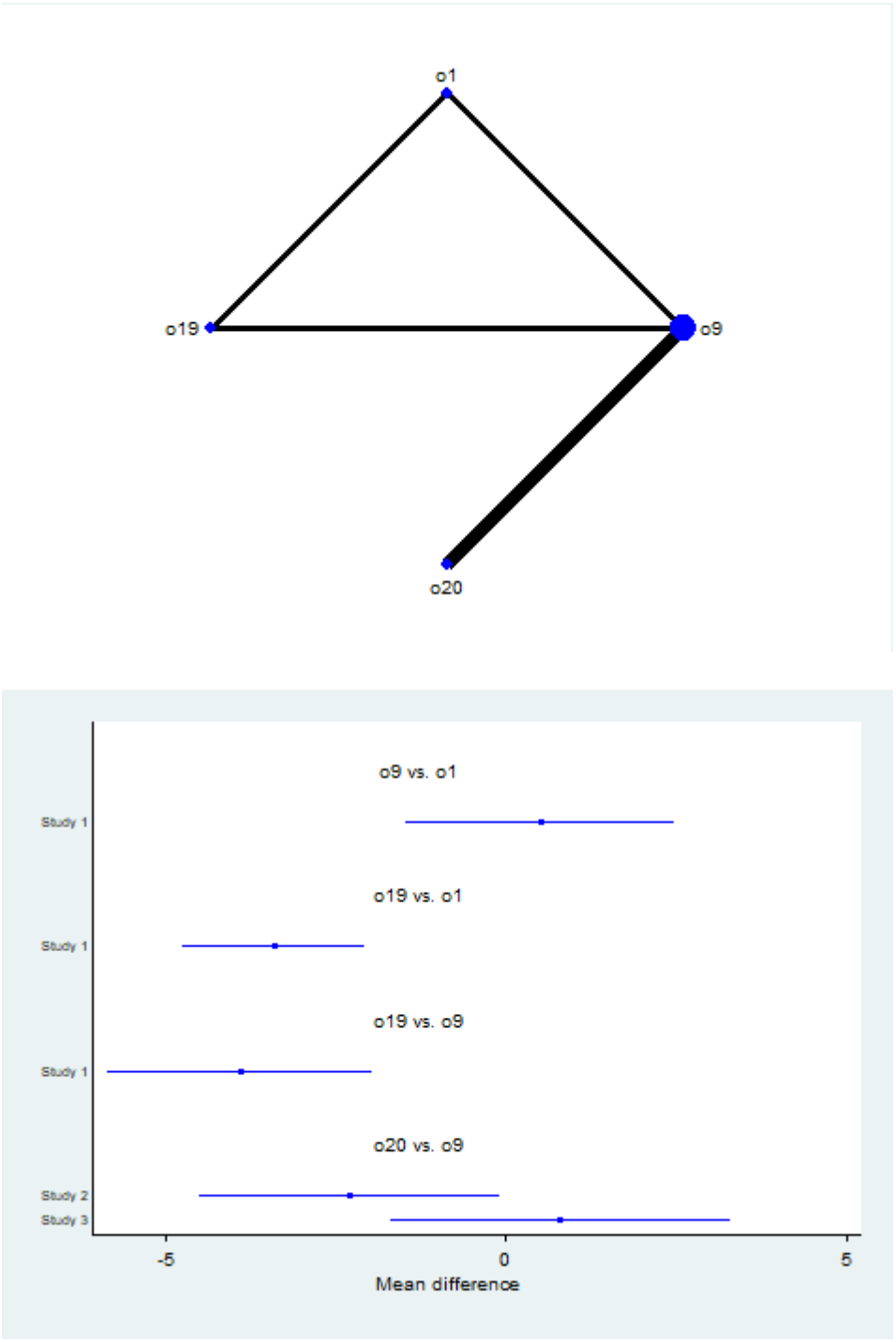
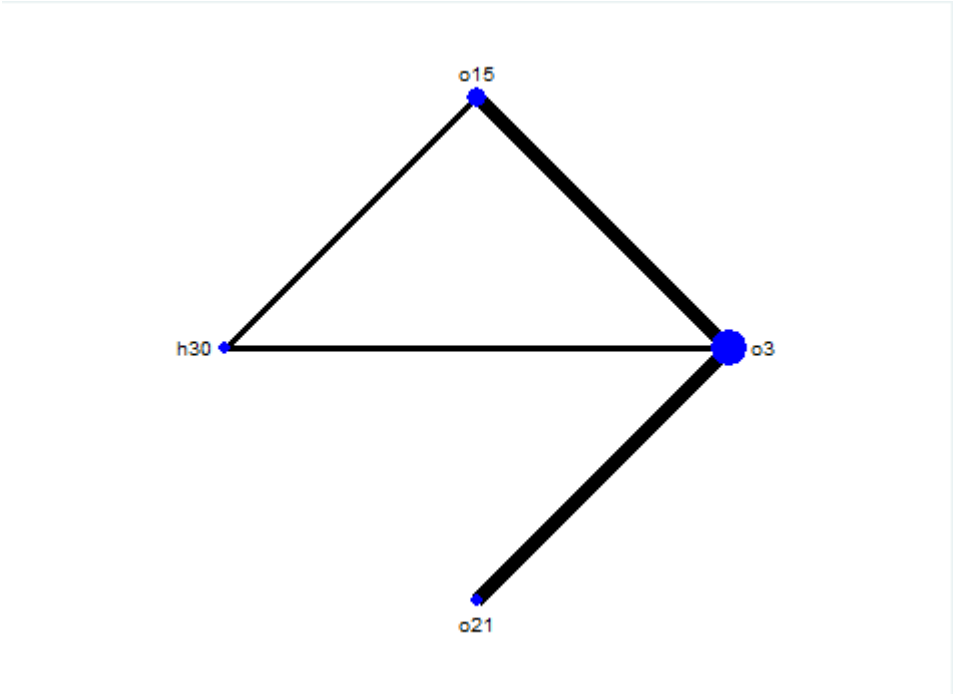


Figure 4c: Metanalysis map and forest plot 30 days after the bleaching treatment (Part 2)



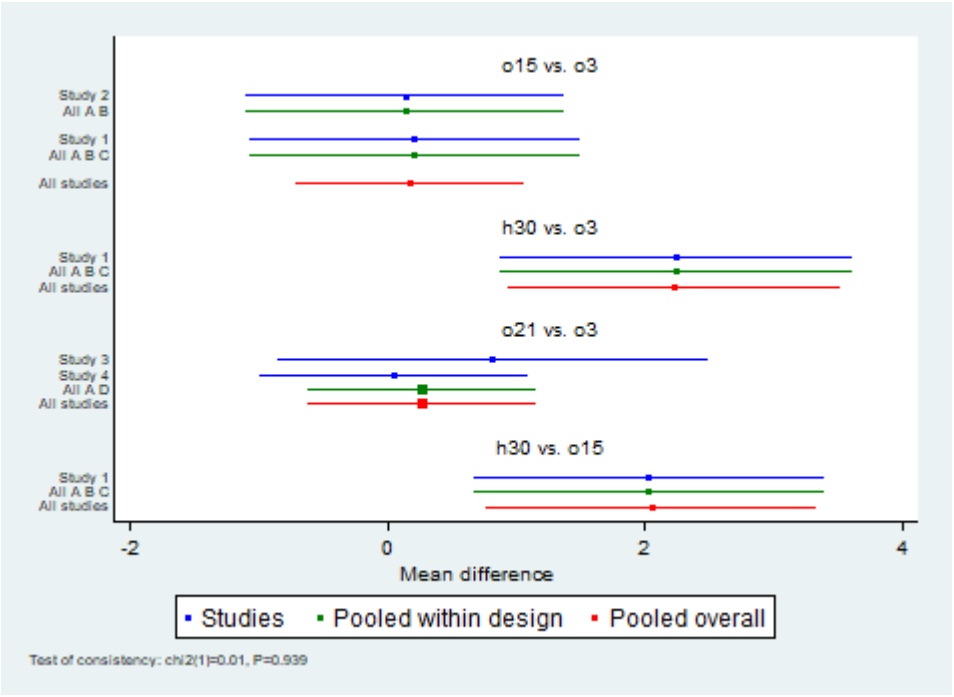
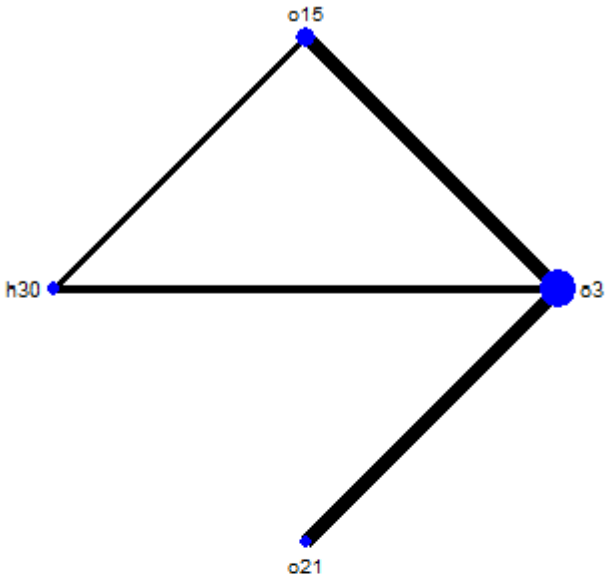


Figure 4d: Metanalysis map and forest plot 30 days after the bleaching treatment (Part3)

Figure 5



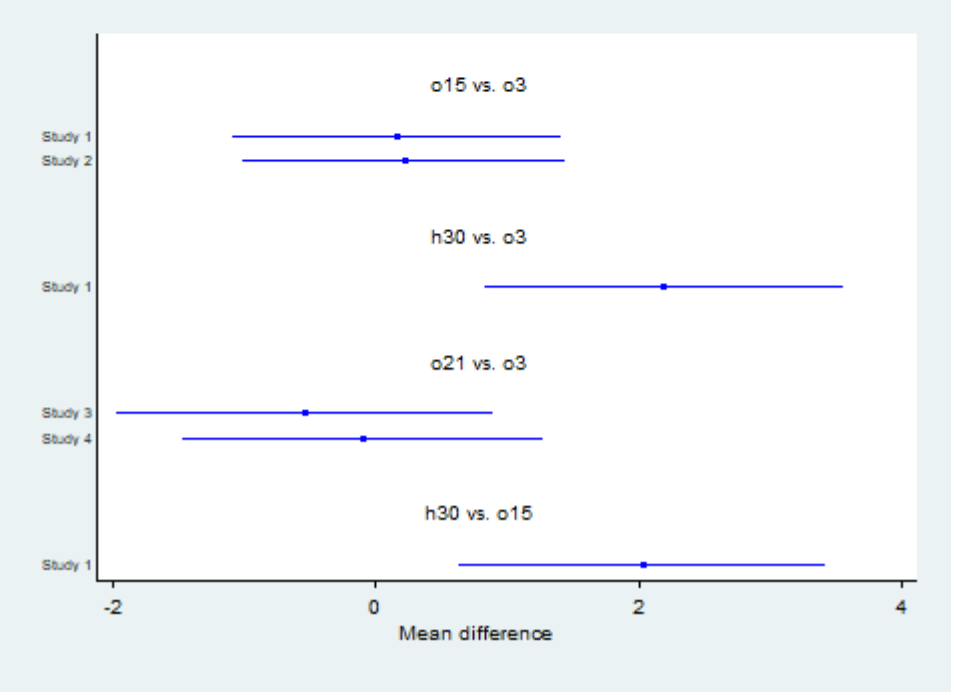


Figure 5: Metanalysis map and forest plot 180 days after the bleaching treatment

Appendix 1

Studies excluded in the reading of the full texts and the reasons for exclusion

Study excluded	Reason for exclusion
Haywood et al., 1993 [1]	Descriptive study
Matis et al., 1998 [2]	Prospective study without comparing group
Maggio et al., 2003 [3]	Prospective study without comparing group
Browning et al., 2004 [4]	Prospective study without comparing group
Gerlach and Sagel, 2004 [5]	Compares a whitening protocol to a placebo group
Swift Jr. et al., 2004 [6]	Compares a whitening protocol to a placebo group
Alonso de la Peña and Balboa Cabrita, 2006 [7]	Descriptive study
Meireles et al., 2014 [8]	Doesn't evaluate change of color
Nakonieczna-Rudnicka et al., 2015 [9]	Doesn't evaluate change of color

References

[1] Haywood VB, Leonard RH Jr, Nelson CF (1993) Efficacy of foam liner in 10% carbamide peroxide bleaching technique *Quintessence International* **24(9)** 663-666.

[2] Matis BA, Cochran MA, Eckert G, Carlson TJ (1998) The efficacy and safety of a 10% carbamide peroxide bleaching gel *Quintessence International* **29(9)** 555-563.

[3] Maggio B, Gallagher A, Bowman J, Barrett K, Borden L, Mason S, Felix H (2003) Evaluation of a whitening gel designed to accelerate whitening *Compendium of continuing education in dentistry* **24(7)** 519-520, 523-526, 528 passim; quiz 536.

[4] Browning WD, Chan DC, Frazier KB, Callan RS, Blalock JS (2004) Safety and efficacyof a nightguard bleaching agent containing sodium fluoride and potassium nitrate. *Quintessence International* **35(9)** 693-8.

[5] Gerlach RW & Sagel PA (2004) Vital bleaching with a thin peroxide gel: the safety and efficacy of a professional-strength hydrogen peroxide whitening strip *The Journal of the American Dental Association* **135(1)** 98-100.

[6] Swift EJ Jr, Miguez PA, Barker ML, Gerlach RW (2004) Three-week clinical trial of a 14% hydrogen-peroxide, strip-based bleaching system. *Compendium of continuing education in dentistry* **25(8 Suppl 2)** 27-32.

[7] Alonso de la Peña V & Balboa Cabrita O (2006) Comparison of the clinical efficacy and safety of carbamide peroxide and hydrogen peroxide in at-home bleaching gels *Quintessence International* **37(7)** 551-6.

[8] Meireles SS, Goettems ML, Dantas RV, Bona ÁD, Santos IS, Demarco FF (2014) Changes in oral health related quality of life after dental bleaching in a double-blind randomized clinical trial. *Journal of dentistry* **42(2)** 114-21.

[9] Nakonieczna-Rudnicka M, Bachanek T, Madejczyki M, Grajewskai I, Kobyłecka E (2015) Teeth whitening versus the influence of extrinsic factors on teeth stains *Przegląd lekarski* **72(3)** 126-30.

Appendix 2

Table I. Metanalysis results immediately after the bleaching treatment. Part 1 (Protocol H6 was used as reference)

Protocol	Coef.	SE	z	p	[95% Conf. Interval]	
O10	-2.16	0.84	-2.56	0.01	-3.82	-0.50
M1	1.03	1.19	0.87	0.38	-1.30	3.38
H13	-4.71	0.80	-5.83	0.00	-6.30	-3.13
H14	-4.21	0.80	-5.21	0.00	-5.80	-2.63
H15	-2.86	0.67	-4.25	0.00	-4.18	-1.54
H3	-5.47	1.05	-5.17	0.00	-7.55	-3.39
H17	-3.27	0.66	-4.95	0.00	-4.57	-1.97
H20	-1.55	0.74	-2.09	0.03	-3.02	-0.09
H22	-3.35	1.13	-2.95	0.00	-5.59	-1.12
O17	-7.39	1.25	-5.89	0.00	-9.85	-4.93
W2	-1.09	0.67	-1.62	0.10	-2.41	0.23
H25	-3.09	0.69	-4.44	0.00	-4.46	-1.72
O2	-6.99	1.09	-6.37	0.00	-9.15	-4.84

SE – Standard Error

Table II. Metanalysis results immediately after the bleaching treatment. Part 2 (Protocol H24 was used as reference)

SE –

O15 0.99 0.53 1.86 0.06 0.00 -0.20 **O3** -0.11 0.50 -0.23 0.81 -1.09 -

Standard Error

Table III. Metanalysis results seven days after the bleaching treatment (Protocol O15 was used as reference)

Protocol	Coef.	SE	z	p	[95% Conf. Interval]	
O3	-0.40	0.06	-6.69	0.00	-0.51	-0.28
O18	-0.26	0.77	-3.36	0.00	-0.41	-0.10
M7	3.44	0.13	26.13	0.00	3.18	3.70
M8	1.80	0.18	9.54	0.00	1.43	2.17
H30	1.99	0.62	3.18	0.00	0.76	3.23
O21	-0.43	0.45	-0.97	0.33	-1.33	0.45

Table IV. Metanalysis results 30 days after the bleaching treatment. Part 1 (Protocol H6 was used as reference)

Protocol	Coef.	SE	z	p	[95% Conf. Interval]	
O10	-0.64	1.14	-0.57	0.57	-2.88	1.59
M1	0.55	1.51	0.37	0.71	-2.41	3.53
O17	-4.51	1.51	-2.98	0.00	-7.47	-1.54
O2	-3.00	1.32	-2.27	0.02	-5.60	-0.41

Table V. Metanalysis results 30 days after the bleaching treatment. Part 2 (Protocol O1 was used as reference)

Protocol	Coef.	SE	z	p	[95% Conf. Interval]	
O9	0.49	2.09	0.24	0.81	-3.59	4.59
O19	-3.40	1.95	-1.74	0.08	-7.23	0.43
O20	-0.30	2.60	-0.12	0.90	-5.40	4.79

Table VI. Metanalysis results 30 days after the bleaching treatment. Part 3 (Protocol O3 was used as reference)

Protocol	Coef.	SE	z	p	[95% Conf. Interval]	
O15	0.17	0.45	0.38	0.70	-0.71	1.06
H30	2.22	0.65	3.37	0.00	0.93	3.51
O21	0.26	0.45	0.59	0.55	-0.61	1.15

Table VII. Metanalysis results 180 days after the bleaching treatment. (Protocol O3 was used as reference)

Protocol	Coef.	SE	z	p	[95% Conf. Interval]	
O15	0.19	0.44	0.43	0.66	-0.68	1.06
H30	2.20	0.66	3.33	0.00	0.90	3.50
O21	-0.31	0.50	-0.62	0.53	-1.29	0.67

REFERÊNCIAS

1. Höfel L, Lange M, Jacobsen T. Beauty and the teeth: perception of tooth color and its influence on the overall judgment of facial attractiveness. *Int J Periodontics Restorative Dent*. 2007;27(4):349-357
2. Al-Zarea B. Satisfaction with appearance and the desired treatment to improve aesthetics. *Int J Dent*. 2013; 2013:7. https://doi.org/10.1155/2013/912368
3. Kihn PW. Vital tooth whitening. *Dent Clin North Am.* 2007;51(2):319-331. https://doi.org/10.1016/j.cden.2006.12.001
4. Brunton PA, Ellwood R, Davies R. A six-month study of two self-applied tooth whitening products containing carbamide peroxide. *Operative dentistry. 2008;29(6): 623-626*
5. Junior MT, Rodrigues CA, Bernardes VL, Araujo TSB, Nicoli A, Derceli JR. Dental Bleaching and New Possibilities: Literature Review. *Health Science Journal.* 2018;12(6). https://doi.org/10.21767/1791-809X.1000600
6. Féliz-Matos L, Hernández LM, and Abreu N. Dental Bleaching Techniques; Hydrogen-carbamide Peroxides and Light Sources for Activation, an Update. Mini Review Article. *Open Dent J.* 2014;8:264-26. https://doi.org/10.2174/1874210601408010264
7. Peixoto AC, Vaez SC, Pereira NAR et al. High-concentration carbamide peroxide can reduce the sensitivity caused by in-office tooth bleaching: a single-blinded randomized controlled trial *Journal of Applied Oral Science* 2018;26:20170573. https://doi.org/10.1590/1678-7757-2017-0573
8. Serraglio CR, Zanella L, Dalla-Vecchia KB, Rodrigues-Junior AS. Efficacy and safety of over-the-counter whitening strips as compared to home-whitening with 10 % carbamide peroxide gel--systematic review of RCTs and metanalysis *Clinical oral investigations* 2016;20(1):1-14. https://doi.org/10.1007/s00784-015-1547-8
9. Machado L, Anchieta R, dos Santos P et al. Clinical Comparison of At-Home and In-Office Dental Bleaching Procedures: A Randomized Trial of a Split-Mouth Design *The International journal of periodontics & restorative dentistry* 2016;36(2):251-260. https://doi.org/10.11607/prd.2383
10. Silva FBD, Chisini LA, Demarco FF, Horta BL, Correa MB. Desire for tooth bleaching and treatment performed in Brazilian adults: findings from a birth cohort *Brazilian oral research* 2018;8(32):e12

11. Demarco FF, Meireles SS, Masotti AS. Over-the-counter whitening agents: a concise review *Brazilian oral research* 2009;23(Supplementary 1):64-70
12. Bruhn AM, Darby ML, McCombs GB, Lynch CM. Vital tooth whitening effects on oral health-related quality of life in older adults *Journal of dental hygiene* 2012;86(3):239-247
13. Luque-Martinez I, Reis A, Schroeder M, Muñoz MA, Loguercio AD, Masterson D, Maia LC. Comparison of efficacy of tray-delivered carbamide and hydrogen peroxide for at- home bleaching: a systematic review and meta-analysis *Clinical oral investigations* 2016;20(7):1419- 1433. https://doi.org/10.1007/s00784-016-1863-7
14. de Geus JL, Wambier LM, Boing TF, Loguercio AD, Reis A. At-home Bleaching With 10% vs More Concentrated Carbamide Peroxide Gels: A Systematic Review and Meta- analysis *Operative dentistry* 2018;43(4):e210-e222. https://doi.org/10.2341/17-222-L
15. Markowitz K. Pretty painful: why does tooth bleaching hurt? *Medical hypotheses* 2010;74(5):835-840. https://doi.org/10.1016/j.mehy.2009.11.044
16. Goldberg M, Grootveld M, Lynch E. Undesirable and adverse effects of tooth-whitening products: a review *Clinical oral investigation* 2009;14(1):1-10. https://doi.org/10.1007/s00784-009-0302-4
17. Cartagena AF, Parreiras SO, Loguercio AD, Reis A, Campanha NH. In-office bleaching effects on the pulp flow and tooth sensitivity - case series *Brazilian oral research* 2014;29(1):1-6. https://doi.org/10.1590/1807-3107BOR-2015.vol29.0026
18. Majeed A, Farooq I, Grobler SR, Rossouw RJ. Tooth-Bleaching: A Review of the Efficacy and Adverse Effects of Various Tooth Whitening Products. 2015; *Journal of the College of Physicians and Surgeons—Pakistan*
19. Pinto CF, Oliveira R, Cavalli V, Giannini M. Peroxide bleaching agent effects on enamel surface microhardness, roughness and morphology. *Brazilian Oral Research* 2004;18(4):306-311. https://doi.org/10.1590/S1806-83242004000400006
20. Soares CJ, Silva NR, Quagliatto OS, Campos RE. Avaliação clínica de clareamento caseiro com gel de peróxido de carbamida industrializado e manipulado em farmácia *Revista de Odontologia da UNESP* 2006;35(1):69-74
21. Darriba IL, Novoa L, de la Peña VA. Efficacy of different protocols for at-home bleaching: A randomized clinical trial *American journal of dentistry*

2017;30(6):329-334. https://doi.org/10.2341/12-335-C

22. Moncada G, Sepúlveda D, Elphick K, Contente M, Estay J, Bahamondes V, Fernandez E, Oliveira OB, Martin J. Effects of light activation, agent concentration, and tooth thickness on dental sensitivity after bleaching *Operative dentistry* 2013;38(5):467-476. https://doi.org/10.2341/12-335-C
23. Rezende M, Ferri L, Kossatz S, Loguercio AD, Reis A. Combined Bleaching Technique Using Low and High Hydrogen Peroxide In-Office Bleaching Gel *Operative dentistry* 2016;41(4) :88-39. https://doi.org/10.2341/15-266-C
24. Cardoso PC, Reis A, Loguercio A, Vieira LC, Baratieri LN. Clinical effectiveness and tooth sensitivity associated with different bleaching times for a 10 percent carbamide peroxide gel *The Journal of the American Dental Association* 2010;141(10):1213-1220. https://doi.org/10.14219/jada.archive.2010.0048
25. Nie J, Tian FC, Wang ZH, Yap AU, Wang XY. Comparison of efficacy and outcome satisfaction between in-office and home teeth bleaching in Chinese patients *Journal of oral science* 2017;59(4):527-532. https://doi.org/10.2334/josnusd.16-0636
26. Chu JS. Use of a Reflectance Spectrophotometer in Evaluating Shade Change Resulting from Tooth-Whitening Products *Journal of Esthetic and Restorative Dentistry* 2003;**15(Supplementary 1)**:S42-S48. https://doi.org/10.1111/j.1708-8240.2003.tb00317.x
27. Cho BH, Lim YK, Lee YK. Comparison of the color of natural teeth measured by a colorimeter and Shade Vision System *Dental materials 2007;23(10):1307-1312.* https://doi.org/10.1016/j.dental.2006.11.008
28. Pérez MM, Ghinea R, Rivas MJ, Yebra A, Ionescu AM, Paravina RD, Herrera LJ. Development of a customized whiteness index for dentistry based on CIELAB color space *Dental materials* 2015;32(3):461-467. https://doi.org/10.1016/j.dental.2015.12.008
29. Paul S, Peter A, Pietrobon N, Hämmerle CH. Visual and spectrophotometric shade analysis of human teeth *Journal of dental research* 2002;81(8):578-582. https://doi.org/10.1177/154405910208100815
30. Loguercio AD, Servat F, Stanislawczuk R, Mena-Serrano A, Rezende M, Prieto MV, Cereño V, Rojas MF, Ortega K, Fernandez E, Reis A. Effect of acidity of in-office bleaching gels on tooth sensitivity and whitening: a two-center double-blind randomized clinical trial *Clinical oral investigations* 2017;21(9):2811-2818. https://doi.org/10.1007/s00784-017-2083-5
31. Maran BM, Ziegelmann PK, Burey A, de Paris Matos T, Loguercio AD, Reis A . Different light-activation systems associated with dental bleaching: a systematic

review and a network meta-analysis *Clinical oral investigations* 2019;23(4):1499-1512. https://doi.org/10.1007/s00784-019-02835-x

32. Mokhlis GR1, Matis BA, Cochran MA, Eckert GJ. A clinical evaluation of carbamide peroxide and hydrogen peroxide whitening agents during daytime use *The Journal of the American Dental Association* 2000;**131(9):**1269-1277. https://doi.org/10.14219/jada.archive.2000.0380
33. Lu G & Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons *Statistics in medicine* 2004;23(20):3105-3124. https://doi.org/10.1002/sim.1875
34. Hutton B, Salanti G, Caldwell DM et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations *Annals of internal medicine* 2015;162(11):777-784. https://doi.org/10.7326/M14-2385