



**Universidade Federal de Uberlândia
Faculdade de Odontologia
Programa de Pós-Graduação em Odontologia**

AVALIAÇÃO DA ALTERAÇÃO DE PROPRIEDADES ÓPTICAS, MECÂNICAS E EFEITOS ADVERSOS DE CLAREADORES *OVER-THE-COUNTER*

Murilo Navarro de Oliveira

Tese apresentada à faculdade de Odontologia da
Universidade Federal de Uberlândia, para obtenção
do título de Doutor em Odontologia na Área de
Concentração de Clínica Odontológica Integrada.

Orientador: Prof. Dr. Luiz Renato Paranhos

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Avaliação da alteração de propriedades ópticas, mecânicas e efeitos adversos de clareadores *over-the-counter*

Assessment of changes in optical and mechanical properties and adverse effects of over-the-counter bleaching agents

Tese apresentada à faculdade de Odontologia da Universidade Federal de Uberlândia, para obtenção do título de Doutor em Odontologia na Área de Concentração de Clínica Odontológica Integrada.

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“A sorrir eu pretendo levar a vida... pois chorando eu vi a mocidade perdida.”

Cartola

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RESUMO

Produtos over-the-counter (OTC) surgiram no início dos anos 2000 nos Estados Unidos como alternativa para pacientes que não possuíam condições financeiras de procurar um cirurgião-dentista, mas que buscavam tratamentos clareadores, esses produtos possuem baixas concentrações de peróxido de hidrogênio e, dependendo a legislação de cada país, podem ser comercializados sem a prescrição de um profissional da odontologia. A literatura contém uma variedade de estudos clínicos e laboratoriais que utiliza produtos OTC, e mostra que eles proporcionam efetiva alteração de cor dos elementos dentais, porém, carece de uma revisão que possa incluir todos os tipos de produtos descritos de forma a se comparar a alteração de cor proporcionada por cada um deles, e se eles conseguem atingir uma alteração de cor semelhante a clareamentos convencionais. Essa tese tem como objetivo geral, avaliar a eficácia de clareadores over-the-counter na alteração de propriedades ópticas e mecânicas de dentes, e levantar seus possíveis efeitos adversos. Objetivo específico 1: Realizar uma revisão sistemática de ensaios clínicos randomizados para avaliar a alteração de cor e efeitos adversos de clareadores over-the-counter. Objetivo específico 2: Avaliar in-vitro, o impacto de produtos over-the-counter nas propriedades ópticas (alteração de cor e brilho) de dentes bovinos submetidos a tratamento ortodôntico simulado. Objetivo específico 3: Avaliar in-vitro, o impacto de produtos over-the-counter nas propriedades mecânicas (rugosidade superficial e cisalhamento) de dentes bovinos submetidos a tratamento ortodôntico simulado. Após a análise dos dados, foi possível concluir que: 1) Produtos over-the-counter atingiram resultados satisfatórios na alteração de cor, com pouco ou nenhum impacto na sensibilidade dental, mas os estudos apresentaram baixa certeza de evidência. 2) Com exceção dos dentifrícios com peróxido, os clareadores over-the-counter testados apresentaram resultados de alteração de cor semelhante ao clareamento de consultório. Nenhum dos grupos apresentou diferença na alteração de brilho. 3) Os produtos over-the-counter testados não influenciaram nos resultados de propriedades mecânicas dos dentes submetidos a tratamento ortodôntico simulado.

Palavras-chave: Alteração de cor. Clareamento dental. Produtos over-the-counter.

ABSTRACT

Over-the-counter (OTC) products appeared in the early 2000s in the United States as an alternative for patients who could not afford a dentist but sought bleaching treatments. These products have a low hydrogen peroxide concentration and may be sold without a prescription from a dental professional, depending on the legislation of each country. The literature includes several clinical and laboratory studies using OTC products, showing they effectively change the color of dental elements. However, it lacks a review that may use all described products to compare color changes and whether they promote color changes similar to conventional bleaching. The general objective of this thesis is to assess the efficacy of OTC bleaching agents in changing the optical and mechanical properties of teeth, identifying potential adverse effects. Specific objective 1: To perform a systematic review of randomized clinical trials to assess color changes and adverse effects of OTC bleaching agents. Specific objective 2: To assess in vitro the impact of OTC products on the optical properties (color and gloss changes) of bovine teeth subjected to a simulated orthodontic treatment. Specific objective 3: To assess in vitro the impact of OTC products on the mechanical properties (surface roughness and shear) of bovine teeth subjected to a simulated orthodontic treatment. The analyzed data concluded that: 1) OTC products achieved satisfactory color change outcomes with little or no impact on tooth sensitivity, but the studies presented a low certainty of evidence. 2) Except for dentifrices with peroxide, the tested OTC bleaching agents presented color change outcomes similar to in-office bleaching. Gloss did not change in any group. 3) The tested OTC products did not influence the mechanical property outcomes of teeth subjected to a simulated orthodontic treatment.

Keywords: Tooth bleaching. Over-the-counter products. Color change.

1. INTRODUÇÃO E JUSTIFICATIVA

O escurecimento dos elementos dentais é uma condição que pode ser causada por fatores intrínsecos; como genética ou idade, ou fatores extrínsecos; relacionados a condições ambientais, alimentação, ou hábitos como tabagismo ou ingestão de bebidas pigmentadas (Hattab et al., 1999; Sulieman, 2005), essa condição tem influência direta em fatores psicológicos e na autopercepção estética, afetando diretamente a qualidade de vida de pacientes (Hofel et al., 2007; Carey, 2014). Essa busca por estética vem levando a um crescente aumento na procura por procedimentos de clareamento dental em clínicas odontológicas nas últimas décadas, influenciada também pelo fato desses procedimentos serem minimamente invasivos, e apresentarem resultados satisfatórios em um curto intervalo de tempo (Kihn, 2007; Brunton et al., 2012).

O agente clareador mais utilizado durante o clareamento de consultório é o peróxido de hidrogênio (H_2O_2), uma molécula altamente instável que se quebra liberando radicais hidroxila, responsáveis pela quebra dos cromógenos, resultando em alteração de cor do elemento dental (Féliz-Matos et al., 2014; Epple et al., 2019). O peróxido de carbamida é uma alternativa para o clareamento dental, e é uma molécula maior que se divide em peróxido de hidrogênio e ureia, necessitando um maior tempo de uso para que resulte em uma ação de clareamento eficaz (Peixoto et al., 2018).

O clareamento dental idealmente deve ser realizado sob supervisão do cirurgião-dentista, que pode utilizar a técnica de consultório (in-office), na qual o agente clareador com alta concentração de peróxido é aplicado sobre a superfície vestibular dos elementos dentais que o profissional deseja alterar a cor (Altinsik et al., 2023), ou a técnica de clareamento caseiro (at-home), na qual, uma moldeira personalizada é confeccionada para o paciente a partir de um modelo obtido do mesmo, para que o paciente aplique o agente clareador com uma menor concentração de peróxido de hidrogênio na superfície interna da moldeira e utilize em sua rotina diária (de Geus et al., 2016).

Porém, no início dos anos 2000 vários produtos com baixas concentrações de peróxido de hidrogênio passaram a ser comumente disponibilizados em farmácias, supermercados e lojas em geral, e podiam ser vendidos sem a prescrição de um profissional da odontologia, - são os produtos over-the-counter (OTC) (Ghalili et al., 2014). A comercialização destes agentes foi incentivada e popularizada nos Estados Unidos como uma forma de facilitar o acesso a procedimentos clareadores a população que não possuía condições financeiras para buscar um cirurgião-dentista (Demarco et al., 2009).

Esses produtos são comercializados principalmente na forma de fitas, dentifrícios, bochechos, goma de mascar e vernizes (Hasson et al., 2006, Caldas et al., 2014) e, a legislação a respeito de sua comercialização pode variar de acordo com a agência de vigilância de cada país (Demarco et al., 2009). Apesar da facilidade dos pacientes em se obter esses produtos, deve-se ressaltar que a automedicação pode causar efeitos adversos quando são usados de forma inadequada, podendo causar alterações na morfologia do esmalte dentário, e nas propriedades dos materiais restauradores, sendo indicado sempre buscar a orientação de um profissional antes de se utilizar qualquer agente clareador (Tostes et al., 2009, Lima et al., 2010).

O forte investimento de propaganda sobre esses produtos, associado a busca desenfreada por estética, faz com que pacientes se sintam atraídos pela fácil oferta de alteração de cor dos elementos dentais, mesmo sem a comprovação científica de sua efetividade, especialmente em situações em que a autoestima dos pacientes já pode estar afetada, como por exemplo, durante tratamentos ortodônticos com aparelhos fixos convencionais (Consolaro et al., 2013; DeFreitas et al., 2021).

Sabe-se que o momento ideal para se realizar o tratamento clareador seria após o término do tratamento ortodôntico, já que durante o mesmo, os dentes podem estar sobreposicionados ou intruídos de maneira desarmônica, o que levaria a uma alteração de cor maior em alguns elementos do que em outros, além disso, a utilização de aparelhos fixos convencionais favorece o acúmulo de placa, o que prejudicaria a eficácia do tratamento clareador (Consolaro et al., 2013). Porém, desde que seja realizado sob supervisão de um profissional, é possível indicar e obter bons resultados de clareamento em pacientes sob tratamento ortodôntico (Jadad et al., 2011). Além disso, devemos levar em consideração a facilidade de acesso a esses produtos através de plataformas de vendas online, na qual são comercializados indiscriminadamente, atraindo os pacientes (Naidu et al., 2020).

A literatura contém uma variedade de estudos clínicos e laboratoriais que utiliza produtos OTC, e mostra que eles proporcionam efetiva alteração de cor dos elementos dentais (Bizhang et al., 2009, Jiang et al., 2018, Kim et al., 2018), porém, carece de uma revisão que possa incluir todos os tipos de produtos descritos de forma a se comparar a alteração de cor proporcionada por cada um deles, e se eles conseguem atingir uma alteração de cor semelhante a clareamentos convencionais. Logo, um dos nossos objetivos foi realizar uma revisão sistemática de forma a se mapear os tratamentos OTC disponíveis para se responder as perguntas, ‘Os métodos clareadores over-the-counter

podem atingir resultados de alteração de cor tão satisfatórios quanto os métodos convencionais? Quais métodos de clareamento over-the-counter apresentam os melhores resultados de alteração de cor?’. A hipótese do nosso estudo é que não existiria diferença estatística de alteração de cor entre os tratamentos OTC, e que eles apresentem resultado de alteração de cor menor do que clareamentos convencionais.

Sabe-se que o agente clareador, a base de peróxido de hidrogênio, atua por difusão nas estruturas dentais (Féliz-Matos et al., 2014), porém a literatura ainda é incerta sobre a efetividade de clareadores over-the-counter sob a região de instalação dos bráquetes ortodônticos. Assim, nosso segundo estudo teve como objetivo, avaliar in-vitro a alteração de propriedades ópticas proporcionada por diferentes produtos OTC (colutório, dentifrício e paint-on) em dentes bovinos sob tratamento ortodôntico simulado. A hipótese do estudo é que não haveria diferença de alteração de cor entre os grupos e nem entre os pontos de avaliação. E por fim, sabendo do risco de agentes clareadores causarem alterações morfológicas em esmalte dentário, e nas propriedades dos materiais restauradores, nosso terceiro estudo teve como objetivo, avaliar in-vitro a alteração de propriedades mecânicas de produtos OTC em dentes bovinos sob tratamento ortodôntico simulado, partindo da hipótese de que não haveria diferença nas propriedades mecânicas entre os grupos de tratamento e os grupos controle.

2. Objetivos

Objetivo Geral

Avaliar a eficácia de clareadores over-the-counter na alteração de propriedades ópticas, mecânicas e avaliar os seus possíveis efeitos adversos

Objetivos específicos

Objetivo específico 1

Capítulo 1 - Assessment of color changes and adverse effects of over-the-counter bleaching protocols: a systematic review and network meta-analysis

Realizar uma revisão sistemática de ensaios clínicos randomizados para avaliar a alteração de cor e efeitos adversos de clareadores over-the-counter

Objetivo específico 2

Capítulo 2 - Impact of over-the-counter bleaching products on teeth with orthodontic brackets: an in vitro assessment of optical properties - part I

Avaliar in-vitro, o impacto de produtos over-the-counter nas propriedades ópticas (alteração de cor e brilho) de dentes bovinos submetidos a tratamento ortodôntico simulado.

Objetivo específico 3

Capítulo 3 - Impact of over-the-counter bleaching products on teeth with orthodontic brackets: an in vitro assessment of mechanical properties - part II

Avaliar in-vitro, o impacto de produtos over-the-counter nas propriedades mecânicas (rugosidade superficial e cisalhamento) de dentes bovinos submetidos a tratamento ortodôntico simulado.



Assessment of color changes and adverse effects of over-the-counter bleaching protocols: a systematic review and network meta-analysis

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Abstract

Objectives To assess color change efficacy and the adverse effects of varied over-the-counter (OTC) bleaching protocols.

Methodology The study included randomized clinical trials evaluating color changes from OTC bleaching agents. Nine databases were searched, including the partial capture of the grey literature. The RoB2 tool analyzed the individual risk of bias in the studies. Frequentist network meta-analyses compared treatments through common comparators (ΔEab^* and ΔSGU color changes, and tooth sensitivity), integrating direct and indirect estimates and using the mean and risk differences as effect measures with respective 95% confidence intervals. The GRADE approach assessed the certainty of the evidence.

Results Overall, 37 remaining studies constituted the qualitative analysis, and ten composed the meta-analyses. The total sample included 1,932 individuals. ΔEab^* was significantly higher in groups 6% hydrogen peroxide (HP) strips (≥ 14 h). ΔSGU was significantly higher in groups at-home 10% carbamide peroxide (CP) (≥ 14 h), followed by 6% HP strips (≥ 14 h) and 3% HP strips (≥ 14 h). At-home 10% CP (7–13 h) and placebo showed lower risks of tooth sensitivity without significant differences between these treatments.

Conclusion Considering the low level of evidence, OTC products presented satisfactory short-term effects on tooth bleaching compared to the placebo, with little to no impact on dentin hypersensitivity and gingival irritation.

Clinical Relevance.

OTC products are proving to be practical alternatives for tooth whitening. However, patients should be advised about the possible risks of carrying out such procedures without professional supervision.

Keyword Dentin sensitivity · Tooth bleaching · Tooth bleaching agents · Over-the-counter

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Introduction

Over-the-counter (OTC) products appeared in the early 2000s and represent bleaching agents that are available in drugstores, supermarkets, and general stores [1, 2]. These products, encompassing strips, dentifrices, paint-on gels, mouthwashes, chewing gum, and varnishes, are self-appliable and commonly marketed without the need for dentist supervision [3]. They contain hydrogen or carbamide peroxide in their composition, although the concentration may vary according to the regulatory agency of each country [4]. While some regions, such as Europe, prohibit the commercialization of whitening products with hydrogen peroxide concentrations exceeding 0.1% without dentist supervision [5], OTC products are classified as “cosmetics” in other locations. This categorization facilitates their worldwide purchase through online sales without necessitating a prescription [4, 5].

Although several clinical studies have used methodologies with OTC products demonstrating significant color changes, the delivery methods present various application protocols [6–10]. Such a scenario opens comparison possibilities that are unfeasible for conventional randomized clinical trials because of the need for numerous groups and samples [11, 12].

Network meta-analyses (NMA) create simultaneous direct and indirect estimates and are applied to these cases to integrate several groups [13]. Moreover, systematic reviews promote the data survey of possible adverse effects in tooth bleaching procedures with OTC products. Considering that these products are not individualized, the occurrence and intensity of dentin hypersensitivity and gingival irritation are concerning [14, 15].

Considering the variety of OTC products available and their easy purchase and use, the primary objective of this systematic review was to map the global scientific literature to assess the color change efficacy from different OTC bleaching protocols. The secondary goal was to evaluate the adverse effects of the various techniques.

Methodology

Protocol registration

The protocol of this systematic review was reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [16] and registered in the PROSPERO database (<http://www.crd.york.ac.uk/PROSPERO>) under CRD42021276125. The systematic review was produced

according to the JBI Manual for Evidence Synthesis [17] and reported following the PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [18]. There were no deviations from the registered original protocol.

Research question and eligibility criteria

This systematic review aimed to answer the following guiding question based on the PICOS acronym (Population, Intervention, Comparator, Outcome, and Study design): “In adult patients undergoing vital tooth whitening, does the application of over-the-counter whitening protocols result in a superior effect on color change when compared to placebo or dentist-supervised protocols?”. To compare their effectiveness, we included comparisons between dentist-supervised treatment to evaluate if OTC treatment can reach the same results in color change as the gold standard treatments. Additionally, we also included comparisons between OTC products and placebo treatments to analyze if these products would provide real effects for color change, and comparisons between different OTC bleaching protocols.

Inclusion criteria

- Population: Adult individuals subjected to tooth bleaching in vital teeth;
- Intervention: At least one group treated with OTC products composed of hydrogen peroxide (HP) or carbamide peroxide (CP), regardless of the concentration or application method;
- Comparator: OTC products based on HP or CP, placebo (negative control), or conventional at-home and/or in-office tooth bleaching methods, regardless of the bleaching agent (positive control);
- Outcomes: Color changes after tooth bleaching (ΔE_{ab}^* / ΔSGU) as the primary outcome, and adverse effects, such as dentin sensitivity or gingival irritation, as a secondary outcomes;
- Study design: Parallel or split-mouth randomized clinical trials without restricting publication year or language.

Exclusion criteria

- Studies with participants subjected to tetracycline staining;
- Studies with participants undergoing orthodontic treatment;
- Studies that did not clearly describe the used bleaching technique.

Information sources and search

The electronic searches were performed until December 2021 in the Cochrane Library, Embase, LILACS, MedLine (via PubMed), SciELO, Scopus, and Web of Science databases. Google Scholar and ProQuest partially captured the "grey literature" to reduce selection bias. An update was performed up to January 2023 in the MedLine (via PubMed) database. The search strategies in each database agreed to their respective syntax rules (Table 1).

Study selection

The results obtained in the primary databases were initially exported to the EndNote Web™ software (Thomson Reuters, Toronto, Canada) for cataloging and deduplicating. The "grey literature" results were exported to Microsoft Word (Microsoft™, Ltd, Washington, USA) for manually extracting duplicates.

The results were exported to Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar) [19] for study selection. Two reviewers performed all phases independently, and in case of disagreements, a third reviewer (LRP) was consulted for a final decision. Examiners were considered eligible for the subsequent phase only after reaching an agreement of $\text{Kappa} \geq 0.81$, and this procedure was applied for all steps of the systematic review. In the first phase, the titles were read and those unrelated to the topic were excluded. In the second phase, the abstracts were evaluated with the initial application of the eligibility criteria. The titles that met the study objectives but did not have abstracts available were fully analyzed in the next phase. In the third phase, the full texts of eligible articles so far were read to verify whether they met the eligibility criteria. If the full texts were not found, a bibliographic request was made to a library database, and e-mails were sent to the corresponding author up to three times within 15 days to obtain the texts. Full texts published in languages other than English or Portuguese were translated for applying the eligibility criteria.

Data collection process

A calibration exercise was performed before data extraction, in which the reviewer's extracted information from three eligible studies jointly to ensure consistency. Next, the full texts of the selected articles were reviewed, and the following data were systematically extracted: (a) study identification (author, year, location, and funding sources); (b) sample characteristics (the number of participants, distribution by sex, and mean age); (c) bleaching protocol (OTC product and application method); (d) contact time between the bleaching agent and the tooth surface; (e) assessment methods for color changes (spectrophotometry / Vita scale) and

sensitivity; (f) outcomes of color changes (ΔEab^* / ΔSGU), tooth sensitivity, and gingival irritation; (g) follow-up time for post-bleaching color assessment. The corresponding author was contacted via e-mail in the case of incomplete or insufficient information.

The color change estimate could be extracted using two metrics. The first is the Commission Internationale de l'Eclairage (CIE) LAB coordinates system, an objective method to evaluate color change using a spectrophotometer. This system is based on the luminosity (L^* coordinate) and the a^* (red-green axis) and b^* (yellow-blue axis) chromaticity coordinates. The result is calculated using the following formula: $\Delta\text{Eab}^* = \sqrt{(L1 - L2)^2 + (a1 - a2)^2 + (b1 - b2)^2}$ [20]. The second is a subjective method based on the Vita Shade Guide (Vita Zahnfabrik, Sackingen, Germany). Initially, the shade units are ranked by their value, according to the manufacturer, and the operator can use a spectrophotometer or visually evaluates the initial and final color using the Shade Guide. The difference is showed as the ΔSGU [21].

Only studies that reported mean values and respective standard deviations of ΔEab^* or ΔSGU were included in this NMA.

Risk of bias within individual studies

Two reviewers (MNO and MTCV) independently assessed the individual risk of bias in the eligible studies with the Risk of Bias Tool of the Cochrane Collaboration (version 2.0) (RoB2) for randomized clinical trials. This tool consists of five domains: bias from the randomization process, bias due to deviations from the intended interventions, bias from missing outcome data, bias from outcome measurements, and bias from the selection of the reported result. Each domain was assessed according to the algorithms proposed in the RoB2 manual and included signaling questions with "yes," "probably yes," "probably not," "no," or "no information" as potential answers. These answers showed the occurrence and provided the base to judge the risk of bias at the domain level, which could be "high risk," "some concerns," or "low risk." The article had a "low risk" of bias if all domains had a low risk, "some concerns" if at least one domain showed some concerns, and a "high risk" of bias if at least one domain presented a high risk, or several domains showed some concerns. Reviewer disagreements were solved by discussing and consulting with a third reviewer (LRP).

Data synthesis

Three review outcomes were quantitatively analyzed: ΔEab^* , ΔSGU , and tooth sensitivity. Firstly, we performed pairwise comparisons with available head-to-head data. Treatments were grouped into common nodes based on

Table 1 Strategies for database search

Database	Search Strategy (until December, 2021) and Update (until January, 2023)
Main databases	
PubMed http://www.ncbi.nlm.nih.gov/pubmed	#1 "Tooth Bleaching"[Mesh] OR "Teeth Whiten*" [tw] OR "Tooth Whiten*" [tw] OR "Teeth Bleaching" [tw] OR "Esthetics, Dental"[Mesh] OR "Dental Esthetic*" [tw] OR "Cosmetic Dentist*" [tw] #2 "Tooth Bleaching Agents"[Mesh] OR "Teeth Whitening Agent*" [tw] OR "Bleaching Agents"[Mesh] OR "Bleaching Product*" [tw] OR "Whitening Agent*" [tw] OR "Over the Counter" [tw] OR "OTC" [tw] OR "At Home" [tw] OR "Non-prescription" [tw] OR "Dentifrices"[Mesh] OR "Toothpastes"[Mesh] OR "Mouthwashes"[Mesh] OR "Whitestrip*" [tw] OR "Strip*" [tw] OR "Paint On" [tw] #1 AND #2
Embase http://www.embase.com	#1 'tooth whitening'/exp OR 'tooth whitening' OR 'dental procedure'/exp OR 'dental procedure' #2 'tooth bleaching agent'/exp OR 'tooth bleaching agent' OR 'bleaching agent'/exp OR 'bleaching agent' OR 'non prescription drug'/exp OR 'non prescription drug' OR 'toothpaste'/exp OR 'toothpaste' OR 'mouthwash'/exp OR 'mouthwash' #1 AND #2
Scopus http://www.scopus.com/	#1 TITLE-ABS-KEY "tooth bleaching" OR "teeth whiten*" OR "tooth whiten*" OR "teeth bleaching" OR "esthetics, dental" OR "dental esthetic*" OR "cosmetic dentist" #2 TITLE-ABS-KEY "tooth bleaching agents" OR "teeth whitening agent*" OR "bleaching agents" OR "bleaching product*" OR "whitening agent*" OR "over the counter" OR "otc" OR "at home" OR "non-prescription" OR "dentifrices" OR "toothpastes" OR "mouthwashes" OR "whitestrip*" OR "strip*" OR "paint on" #1 AND #2
SciELO https://scielo.org/	("Tooth Bleaching Agents" OR "Teeth Whitening Agents" OR "Bleaching Agents" OR "Bleaching Products" OR "Whitening Agent" OR "Over the counter" OR "OTC" OR "At Home" OR "Non-prescription" OR "Dentifrices" OR "Toothpastes" OR "Mouthwashes" OR "Whitestrips" OR "Strips" OR "Paint On")
LILACS https://lilacs.bvsalud.org/	#1 mh:(tooth bleaching) OR (teeth whiten*) OR (tooth whiten*) OR (teeth bleaching) OR mh:(esthetics, dental) OR (dental esthetic*) OR (cosmetic dentist*) #2 mh:(tooth bleaching agents) OR (teeth whitening agent*) OR mh:(bleaching agent*) OR (bleaching product*) OR (whitening agent*) OR (over the counter) OR (OTC) OR (at home) OR (non-prescription) OR mh:(dentifrices) OR mh:(toothpastes) OR mh:(mouthwashes) OR (whitestrip*) OR (strip*) OR (paint on) #1 AND #2
Web of Science http://apps.webofknowledge.com/	#1 TS = ("tooth bleaching" OR "teeth whitening" OR "tooth whitening" OR "teeth bleaching" OR "esthetics, dental" OR "dental esthetics" OR "cosmetic dentistry") #2 TS = ("tooth bleaching agents" OR "teeth whitening agent*" OR "bleaching agents" OR "bleaching products" OR "whitening agents" OR "over the counter" OR "otc" OR "at home" OR "non-prescription" OR "dentifrices" OR "toothpastes" OR "mouthwashes" OR "whitestrips" OR "strips" OR "paint on") #1 AND #2
Cochrane Library https://www.cochranelibrary.com/	#1 "tooth bleaching" OR "teeth whiten*" OR "tooth whiten*" OR "teeth bleaching" OR "esthetics, dental" OR "dental esthetic*" OR "cosmetic dentist" #2 "tooth bleaching agents" OR "teeth whitening agent*" OR "bleaching agents" OR "bleaching product*" OR "whitening agent*" OR "over the counter" OR "otc" OR "at home" OR "non-prescription" OR "dentifrices" OR "toothpastes" OR "mouthwashes" OR "whitestrip*" OR "strip*" OR "paint on" #1 AND #2 in trials
Grey Literature	
Google Scholar https://scholar.google.com.br/	allintitle: whitening over-the-counter OR dentifrice OR whitestrips OR mouthwashes "bleaching"
ProQuest https://www.proquest.com/	((("Tooth bleaching" OR "Dental Esthetic") AND ("OTC" OR "Non-prescription") AND ("Clinical Trial")))

The MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Embase Subject Headings) resources provided the descriptors. Moreover, synonyms and free words composed the search. The Boolean operators "AND" and "OR" improved the strategy with several combinations

each OTC bleaching product and respective use protocol. The treatments were grouped according to the delivery method (i.e., strips, gel), bleaching agent (HP or CP) and its respective concentrations, and the duration of the contact between the bleaching agent and the tooth structure. For example, in Kim et al., 2018 [10], the treatments were performed twice daily for 30 min each, for four weeks, totaling 28 h of contact between the bleaching agent and the teeth. Although classification decisions were arbitrary and may compromise the outcomes, the lack of grouping would merge several OTC products and contribute to network incoherence. Subsequently, a random-effects frequentist NMA compared multiple OTC bleaching protocols through common comparators by integrating direct and indirect estimates [13]. Transitivity was evaluated by comparing the distribution of important covariates across comparisons [22]: sex, age, and follow-up assessment time point for ΔE_{ab}^* ; age and follow-up assessment time point for ΔSGU ; and only follow-up assessment time point for tooth sensitivity [23]. We must anticipate that all analyses were conducted using data from the second week of follow-up; the low number of comparisons precluded analyses using other time points. Random-effects models with the Der-Simonian and Laird variance estimator [24] were preferred over fixed-effects models based on the deviance information criterion (DIC). Gingival irritation was narratively described due to the very low density in the network.

The effect estimate was the mean difference (MD) instead of standardized MD (SMD), as studies used comparable scales for the assessed outcomes and to prevent the standard deviation (SD) effect on SMD estimates. For the tooth sensitivity outcome, we used the risk difference (RD). The 95% confidence intervals (CI) were calculated for all estimates. Direct, indirect, and network estimate (0.05 significance level) comparisons evaluated local incoherence.

League tables presented the outcomes, and each treatment was ordered from best to worst according to the ranking probabilities of treatment effects. The MetaInsight, version 5.1.2, hosted all analyses.

Geometry of the network

The geometry of the networks was explored using conventional measurements of number of nodes and edges as well as additional metrics of density (the ratio between real and possible edges) and number of strong edges (edges with more than one trial) [25]. Edges proportional to the number of arms in the corresponding pairwise meta-analysis represented direct comparisons among the various OTC bleaching protocols.

Assessment of inconsistency

The presence of inconsistency in NMAs was assessed by examining the agreement between direct and indirect effect estimates. When applicable, the difference between head-to-head and indirect estimates was calculated, along with the respective 95% confidence interval.

Certainty of evidence

The GRADE tool classified the certainty of evidence of treatment effect estimates for the network meta-analysis [26, 27]. First, the certainty of evidence evaluation of each direct comparison verified the risk of bias, inconsistency, indirectness, and publication bias. Indirect comparisons considered the first-order loop with the lowest certainty and evaluated intransitivity. Finally, concerns of imprecision or incoherence in the network meta-analysis caused certainty of evidence downgrading. The certainty of evidence could be high, moderate, low, or very low [26].

Results

Study selection

The first study selection phase yielded 18,564 results distributed in nine electronic databases, including the "grey literature." After removing duplicates, 12,614 results remained for analysis. A careful reading of titles and abstracts excluded 12,535 articles. Five of the 79 remaining studies were not found, and 74 were fully read, of which 37 were excluded. Appendix S1 describes the reasons for exclusions. The 37 remaining articles constituted the qualitative analysis, and ten composed the meta-analyses (Fig. 1).

Characteristics of eligible studies

The articles were published between 2001 and 2022 and performed in 12 countries, with 20 studies in America [28–47], 12 in Europe [1, 6, 7, 9, 48–55], and five in Asia [10, 56–59]. Two studies [9, 41] had a split-mouth design, and the others were parallel. 27 articles declared funding sources [10, 28, 30, 31, 33–43, 48–57].

The total sample included 1,932 participants, with 548 men and 1,177 women in studies reporting the sex of participants. The age group ranged between 15 and 79 years. Among the products used, 25 studies tested the whitestrips (HP concentration ranging from 5.3% to 14%) [1, 10, 28–30, 33–47, 51, 52, 54, 56, 57], 13 studies evaluated paint-on products (HP concentration ranging from 3 to 9%) [7, 9, 10, 31, 32, 37, 38, 49, 50, 53, 56–58], three studies tested OTC

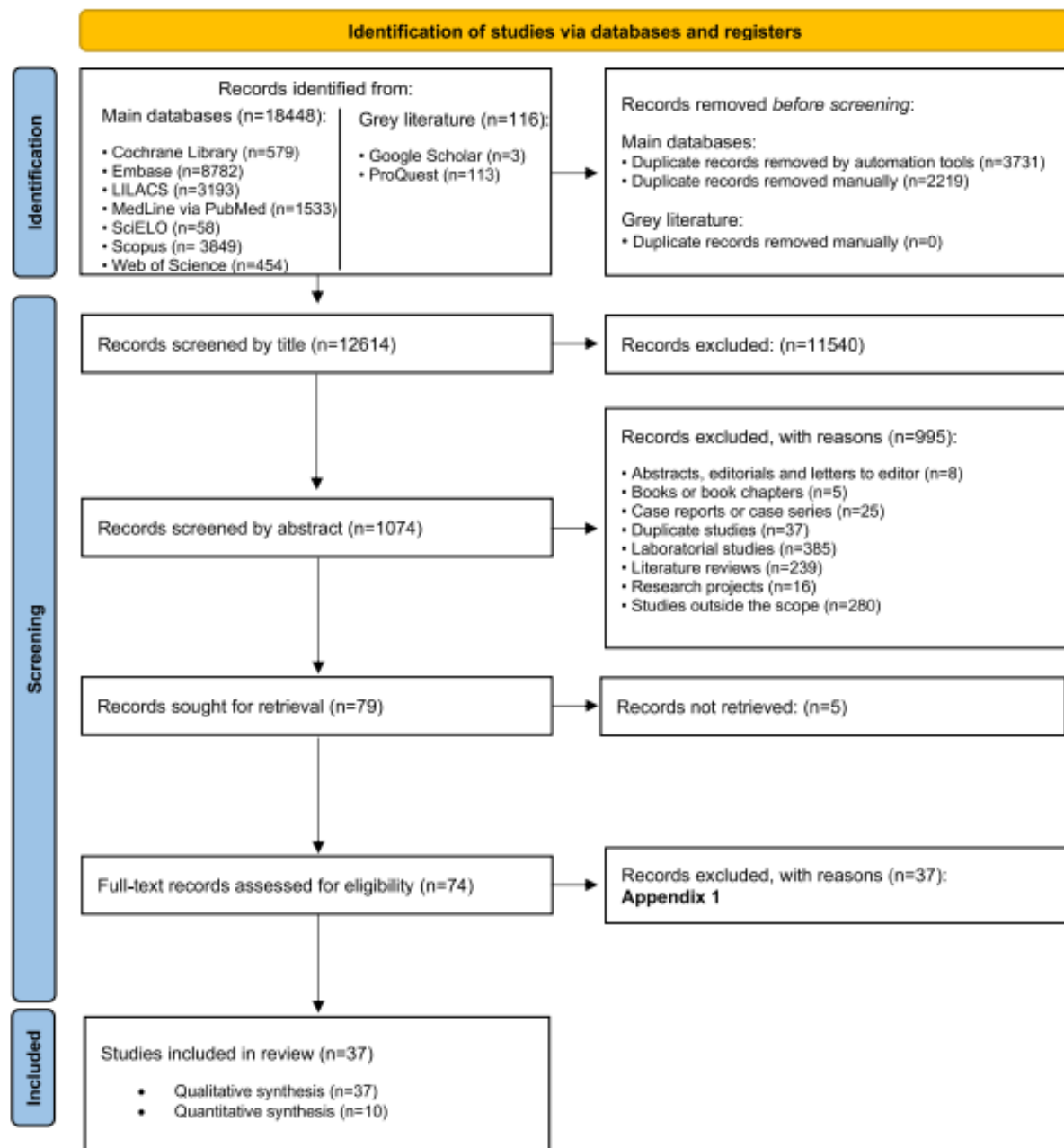


Fig. 1 Flowchart of the selection process according to PRISMA

bleaching gels (HP concentration ranging from 6 to 10%) [45–47] and dentifrices (HP concentration ranging from 0.75% to 2.8%) [6, 55, 59]. In 14 studies, a placebo group (negative control) was present [10, 32, 33, 36, 38–40, 44, 45, 49, 55–58] and 12 studies [1, 9, 10, 28, 30, 35, 41, 43, 46, 47, 51, 54] had a positive control group using a dentist supervised bleaching protocol – 10 of them, with an at-home

treatment [1, 10, 28, 30, 35, 41, 43, 46, 47, 54] and three with an in-office bleaching group [1, 9, 43]. More details about the bleaching protocols and the duration of the treatments are shown in (Table 2). Spectrophotometry (ΔE_{ab}^*) and the Vita scale (ΔSGU) analyzed tooth bleaching. The occurrence of tooth sensitivity and gingival irritation was assessed by self-perception with a categorical evaluation

Table 2 Summary of the main characteristics of the eligible studies with information about the bleaching agents and color assessment

Author [ref]	Location	Study Design	Sample (n)	Participants	Average age $\pm$ SD (years)	Bleaching Protocols (Contact Time)	Evaluation time	Color Assessment (outcome)	Financial Support
Gerlach et al. [28]	USA	Parallel	17	14 ♀ / 6 ♂	36.9 $\pm$ 8.2 (A); 38.2 $\pm$ 9.0 (B)	Whitestrips 6%HP (7 h) / At-Home 10% CP (7 h)	15 days	Spectrophotometer (ΔE)	The Procter & Gamble Company
Gerlach et al. [29]	USA	Parallel	36	31 ♀ / 5 ♂	33.3 $\pm$ 5.23 (A); 36.5 $\pm$ 8.57 (B); 39.1 $\pm$ 9.22 (C)	Whitestrips 5.3% HP (14 h) / Whitestrips 6.5% HP (14 h) / Whitestrips (6.5% HP 14 h)	14 days	Spectrophotometer (ΔE)	n.r
Karpinia et al. [30]	USA	Parallel	57	45 ♀ / 12 ♂	29.0 $\pm$ 9.15 (A); 33.5 $\pm$ 13.09 (B)	Whitestrips 6%HP (14 h) / At-Home 10% CP (14 h)	14 days	Spectrophotometer (ΔE)	The Procter & Gamble Company
Nathoo et al. [31]	USA	Parallel	59	30 ♀ / 29 ♂	41.1 (A); 36.5 (B)	Paint-on 25%CP (Overnight – 14 days) / Paint-on 8.7%HP (Overnight – 14 days)	21 days	Vita Shade Guide (Δ SGU)	Colgate Palmolive Company
Brunton et al. [48]	UK	Parallel	93	n.r	n.r	Paint-on 18%CP (7 h) / Paint-on 16.4% CP (7 h)	180 days	Vita Shade Guide (Δ SGU)	Colgate Palmolive Company
Collins et al. [32]	USA	Parallel	117	74 ♀ / 23 ♂	39.3 $\pm$ n.r (A); 39.6 $\pm$ n.r. (B)	Paint-on 6%HP (7 h) / Placebo	14 days	Vita Shade Guide (Δ SGU)	n.r
Gambarini et al. [49]	Italy	Parallel	30	n.r	n.r	Paint-on 5.9%HP (3.5 h) / Placebo	14 days	Vita Shade Guide (Δ SGU)	Colgate Palmolive Company
García-Godoy et al. [33]	USA	Parallel	39	24 ♀ / 15 ♂	32.1 $\pm$ 11.25	Whitestrips 14%HP (21 h) / Placebo	42 days	Spectrophotometer (ΔL^* , Δa^* , Δb^*)	The Procter & Gamble Company
Gerlach and Sagel [34]	USA	Parallel	38	23 ♀ / 15 ♂	33.8 $\pm$ n.r	Whitestrips 14%HP (14 h) / Whitestrips 6%HP (14 h)	14 days	Spectrophotometer (ΔE)	The Procter & Gamble Company
Gerlach and Zhou [35]	USA	Parallel	31	19 ♀ / 12 ♂	40.0 $\pm$ 12.7	Whitestrips 14%HP (21 h) / At-Home 9.5%HP (9 h)	22 days	Spectrophotometer (ΔL^* , Δa^* , Δb^*)	The Procter & Gamble Company
Swift et al. [36]	USA	Parallel	28	24 ♀ / 5 ♂	49.9 $\pm$ 11.71 (A); 50.9 $\pm$ 14.73 (B)	Whitestrips 14%HP (21 h) / Placebo	21 days	Vita Shade Guide (Δ SGU)	The Procter & Gamble Company
Auschill et al. [11]	Germany	Parallel	39	n.r	29.82 $\pm$ n.r	Whitestrips 5.3%HP / At-Home 10% CP / In-Office 38%HP	Immediately after	Vita Shade Guide (Δ SGU)	n.r
Cronin et al. [37]	USA	Parallel	59	49 ♀ / 10 ♂	42.3 $\pm$ 9.2	Whitestrips 6%HP / Paint-on 18%CP	Immediately after	Vita Shade Guide and Spectroscopy (Δ SGU, ΔE)	Pfizer, Inc

Table 2 (continued)

Author [ref]	Location	Study Design	Sample (n)	Participants	Average age $\pm$ SD (years)	Bleaching Protocols (Contact Time)	Evaluation time	Color Assessment (outcome)	Financial Support
Zantner et al. [7]	Germany	Parallel	53	39 ♀ / 21 ♂	25.1 $\pm$ 2.8	Paint-on 5.9%HP (7 h) / Sodium chloride-based whitening gel* Paint-on 8%CP (4.6 h) / Paint-on 8%CP (9.3 h)	180 days	Vita Shade Guide using Spectroscopy (Δ SGU)	n.r
Zantner et al. [50]	Germany	Parallel	46	35 ♀ / 11 ♂	29.1 $\pm$ 8.5	Whitestrips 6.5%HP (10.5 h) / Placebo	270 days	Vita Shade Guide (Δ SGU)	Ivoclar Vivadent
Guerrero et al. [38]	Mexico	Parallel	30	25 ♀ / 5 ♂	23.4 $\pm$ 2.53	Whitestrips 6%HP (14 h) / At-Home 10% CP (14 h)	21 days	Spectrophotometer (Δ L*, Δ a*, Δ b*)	The Procter & Gamble Company
Hamig et al. [51]	Germany	Parallel	47	22 ♀ / 25 ♂	29.8 $\pm$ 10.24 (A); 28.9 $\pm$ 7.69 (B)	Whitestrips 6%HP (14 h) / At-Home 10% CP (14 h)	14 days	Spectrophotometer and Vita Shade Guide (Δ SGU)	The Procter & Gamble Company
Lo et al. [57]	China	Parallel	63	43 ♀ / 20 ♂	20.8 $\pm$ 1.56	Whitestrips 6.5%HP (14 h) / Paint-on 18%CP (7 h) / Placebo	14 days	Spectrophotometer (Δ L*, Δ a*, Δ b*)	The Procter & Gamble Company
Xu et al. [56]	China	Parallel	49	48 ♀ / 4 ♂	21.85 $\pm$ 5.01	Whitestrips 6%HP (7 h) / Paint-on 5.9% HP (14 h) / Placebo	14 days	Spectrophotometer (Δ L*, Δ a*, Δ b*)	The Procter & Gamble Company
Yudhira et al. [52]	Belgium	Parallel	46	29 ♀ / 17 ♂	22.5 $\pm$ 2.74	Whitestrips 6%HP (14 h) / Sodium fluoride (NaF) whitening dentifrice*/ sodium mono-phosphate fluorophosphate (MFP) whitening dentifrice*	90 days	Spectrophotometer (Δ L*, Δ a*, Δ b*)	The Procter & Gamble Company
Ziebolz et al. [53]	Germany	Parallel	67	27 ♀ / 52 ♂	24.88 $\pm$ 3.56 (A); 27.66 $\pm$ 4.97 (B)	Paint-on 6%HP (2.3 h) – with desensitizer / Paint-on 6%HP (2.3 h) – without desensitizer	7 days	Vita Shade Guide (Δ SGU)	Ivoclar Vivadent
Calatayud et al. [9]	Spain	Split Mouth	16	10 ♀ / 6 ♂	23.8 $\pm$ 2.8	Paint-on 6%HP (1.6 h) / In-Office 6%HP (1.6 h)	n.r	Vita Shade Guide (Δ SGU)	n.r
Ferrari et al. [54]	Italy	Parallel	43	29 ♀ / 14 ♂	32.8 $\pm$ 11.4	Whitestrips 6%HP (14 h) / At-Home 10%CP (14 h)	42 days	Spectrophotometer (Δ L*, Δ a*, Δ b*)	The Procter & Gamble Company

Table 2 (continued)

Author [ref]	Location	Study Design	Sample (n)	Participants	Average age $\pm$ SD (years)	Bleaching Protocols (Contact Time)	Evaluation time	Color Assessment (outcome)	Financial Support
Papas et al. [39]	USA	Parallel	42	26 ♀ / 16 ♂	50 $\pm$ 17	Whitestrips 10% HP (14 h) / Placebo	15 days	Spectrophotometer (ΔL^* , Δa^* , Δb^*)	The Procter & Gamble Company
Swift et al. [40]	USA	Parallel	40	27 ♀ / 13 ♂	43.0 $\pm$ 9.04 (A); 41.2 $\pm$ 11.07 (B)	Whitestrips 6% HP (42 h) / Placebo	42 days	Spectrophotometer (ΔE)	The Procter & Gamble Company
Costa et al. [41]	USA	Split Mouth	24	12 ♀ / 12 ♂	n.r	At-Home 35%CP (14 h) / Whitestrips 14%HP (14 h)	30 days	Vita Shade Guide and Spectroscopy (Δ SGU, ΔE)	Ultradent Products Inc
Oliveira et al. [42]	USA	Parallel	29	12 ♀ / 17 ♂	41.6 $\pm$ 14.3 (A); 42.7 $\pm$ 12.7 (B)	Whitestrips 9.5% HP (16 h) / Whitestrips 10% HP (4 h)	9 days	Spectrophotometer (ΔE)	The Procter & Gamble Company
Perry et al. [43]	USA	Parallel	44	28 ♀ / 17 ♂	37.6 $\pm$ 10.4	Whitestrips 9.5%HP (10 h) / In-Office 25%HP (0.75 h)	21 days	Spectrophotometer (ΔL^* , Δa^*)	The Procter & Gamble Company
Simon et al. [44]	USA	Parallel	54	34 ♀ / 20 ♂	36.6 $\pm$ 11.16	Whitestrips 9.5% HP (10.5 h) / Placebo	21 days	Spectrophotometer (ΔL^* , Δa^*)	The Procter & Gamble Company
Llena et al. [55]	Spain	Parallel	45	34 ♀ / 11 ♂	29 $\pm$ 4	Denifrice 3%CP (Brushing for 12 weeks) / Placebo	90 days	Spectrophotometer (ΔL^* , Δa^* , Δb^*)	Laboratorios Kin
Pinto et al. [45]	Brazil	Parallel	42	18 ♀ / 24 ♂	14–25 (A); 13–19 (B); 14–27 (C); 13–27 (D)	OTC Bleaching Gel 6%HP (7 h) / OTC Bleaching Gel 7.5% HP (7 h) / Whitestrips 10%HP (7 h) / Placebo	15 days	Vita Shade Guide (Δ SGU)	n.r
Cordeiro et al. [46]	Brazil	Parallel	60	n.r	17.8 $\pm$ 1.4 (A); 17.7 $\pm$ 1.6 (B); 17.9 $\pm$ 1.4 (C)	At-Home 10%HP (7 h) / OTC Bleaching gel 10% HP (7 h) / Whitestrips 10%HP (7 h)	30 days	Vita Shade Guide and Spectroscopy (Δ SGU, ΔE)	n.r
Jung et al. [58]	South Korea	Parallel	122	122 ♀ / 0 ♂	n.r	Paint-on 3%HP (4.6 h) / Paint-on 3%HP (7 h) / Placebo	14 days	Spectrophotometer (ΔE)	n.r
Kim et al. [10]	South Korea	Parallel	75	64 ♀ / 11 ♂	49.3 $\pm$ 5.95	Whitestrips 2.9%HP (28 h) / Paint-on 2.9%HP (28 h) / At-Home 10%CP (28 h) / Placebo	30 days	Vita Shade Guide and Spectroscopy (Δ SGU, ΔE)	Ministry of Food and Drug Safety

Table 2 (continued)

Author [ref]	Location	Study Design	Sample (n)	Participants	Average age $\pm$ SD (years)	Bleaching Protocols (Contact Time)	Evaluation time	Color Assessment (outcome)	Financial Support
Monteiro et al. [47]	Brazil	Parallel	60	36 ♀ / 24 ♂	17.8 $\pm$ 1.4 (A); 17.7 $\pm$ 1.6 (B); 17.9 $\pm$ 1.4 (C)	At-Home 10%HP (7 h) / OTC Bleaching gel 10%HP (7 h) / Whitestrips 10% HP (7 h)	30 days	Vita Shade Guide (Δ SGU)	n.r
Kim et al. [59]	South Korea	Parallel	49	n.r	n.r	Dentifrice Containing HP (12.6 h) / Dentifrice 0.75%HP (12.6 h) / Dentifrice 2.8% HP (12.6 h)	90 days	Spectrophotometer (Δ E)	n.r
Vladislavic et al., [6]	Croatia	Parallel	161	96 ♀ / 65 ♂	29.70 $\pm$ 6.19 (A); 27.4 $\pm$ 9.2 (B)	Placebo / Dentifrice containing HP (3 h)	90 days	Spectrophotometer (Δ E)	n.r

n: number of patients; ♀: women; ♂: men; n.r.: not reported by the author; HP: Hydrogen Peroxide; CP: Carbamide Peroxide; *: products without hydrogen peroxide

(yes or no), and intensities were examined with visual analog scales (VAS) (Table 3). Moreover, color change assessments had different intervals, from immediately after, one day, seven days, and several others up to 360 days. The most common evaluation interval was 14 days, reported in nine studies [29, 30, 32, 34, 49, 51, 56–58].

Risk of individual bias in the studies

Only four studies had an overall low risk of bias [6, 46, 47, 55] (Fig. 2). Three studies showed an overall high risk of bias due to missing outcome data [49], deviations from the intended interventions [37], and outcome measurements [36, 49].

Syntheses of results and meta-analyses

Color changes (Δ Eab*)

Among the 13 studies that provided the Δ Eab* values, three [27, 33, 57] were excluded because they did not present the values of standard deviation, one [35] because used a different method of color assessment (colorimeter), one [8] did not provide the concentration of HP in the intervention group, four [28, 41, 42, 46] due to the lack of a common comparator group, and one [58] due to violating the transitivity assumption (the study sample exclusively comprised female individuals.). Hence, three studies [10, 30, 40] with five treatments and eight pairwise comparisons were included, totaling 169 participants. Density was 0.8 and each edge was composed by only one trial; that is, there was no strong edge. Figure 3 demonstrates the network and Appendix S2 presents direct evidence findings.

Figure 4 shows estimates from NMA. Δ Eab* was significantly higher for 6% HP strips (≥ 14 h) (MD: 3.07; 95% CI: 0.63–5.50) compared to placebo two weeks after treatment. No other significant differences were observed. The differences among direct, indirect, and NMA evidence suggested no inconsistency (Appendix S3).

Color changes (Δ SGU)

Among the 17 studies that presented Δ SGU evaluation, two [1, 37] were excluded due to not providing the exact contact time between the bleaching agent and tooth surface, and one [45] showed the results as visual graphs, without specifying the mean and standard deviation values. Moreover, this NMA excluded ten studies [7, 9, 31, 41, 46–50, 53] due to the lack of a common comparator group and one [36] due to violating the transitivity assumption (the study only provided the color assessment at the third week). Hence, three studies [10, 32, 51] with six treatments and eight pairwise comparisons

Table 3 Summary of the main characteristics about adverse effects related on the eligible studies

Author [ref]	Assessment form	Adverse effects	Occurrence of tooth sensitivity (%)	Intensity of tooth sensitivity	Occurrence of gingival irritation (%)	Intensity of gingival irritation
Gerlach et al. [28]	Application of own tolerance questionnaire	Tooth Sensitivity and Oral Irritation	Whitestrips 6% HP (7 h): 4 (40%) At-Home 10% CP (7 h): 1 (10%)	Not evaluated using VAS	Whitestrips 6%HP (7 h): 0 (0%) At-Home 10% CP (7 h): 7 (70%)	Not evaluated using VAS
Gerlach et al. [29]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Oral Irritation	Whitestrips 5.3% HP (14 h): 2 (16.7%) Whitestrips 6.5% HP (14 h): 3 (25%) Whitestrips 6.5% HP (14 h): 2 (16.7%)	n.r	Whitestrips 5.3% HP (14 h): 2 (16.7%) Whitestrips 6.5% HP (14 h): 6 (50%) Whitestrips (6.5% HP 14 h): 5 (41.7%)	n.r
Karpinia et al. [30]	Application of own tolerance questionnaire	Tooth Sensitivity and Oral Irritation	Whitestrips 6%HP: 5 (17%) At-Home 10% CP: 3 (11%)	Not evaluated using VAS	Whitestrips 6%HP: 9 (31%) At-Home 10% CP: 14 (50%)	Not evaluated using VAS
Brunton et al. [48]	Tooth Sensitivity: VAS (0–4) Gingival Sensitivity: VAS (0–3)	Tooth and Gingival Sensitivity	Paint-on 18%CP (7 h): 14 (30%) Paint-on 16.4% CP (7 h): 13 (28%) Paint-on 5.9% HP (3.5 h): 2 (13.3%)	Paint-on 18%CP (7 h): 0.47±n.r Paint-on 16.4% CP (7 h): 0.55±n.r n.r	Paint-on 18%CP (7 h): 14 (30%) Paint-on 16.4% CP (7 h): 16 (34%) n.r	Paint-on 18%CP (7 h): 0.43±n.r Paint-on 16.4% CP (7 h): 0.57±n.r n.r
Gamberini et al. [49]	Dentin Hypersensitivity: Number of teeth that responded to the thermal cold test	Tooth Sensitivity	Whitestrips 14% HP (21 h): 12 (63%) Whitestrips 14% HP (14 h): 8 (42%) Whitestrips 6% HP (14 h): 5 (26%)	Not evaluated using VAS	Does not report de exact number Whitestrips 14%HP (14 h): 2 (11%) Whitestrips 6%HP (14 h): 2 (11%)	Not evaluated using VAS
García-Godoy et al. [33]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Oral Irritation	Whitestrips 14% HP (21 h): 2 (14%) At-Home 9.5% HP (9 h): 4 (25%)	Not evaluated using VAS	Whitestrips 14%HP (21 h): 0 (0%) At-Home 9.5%HP: 8 (50%)	Not evaluated using VAS
Gerlach and Sagel [34]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Oral Irritation	Whitestrips 14% HP (21 h): 2 (15%) n.r	Not evaluated using VAS	Whitestrips 14%HP (21 h): 3 (23%) n.r	Not evaluated using VAS
Swift et al. [36]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Oral Irritation	Whitestrips 14% HP (21 h): 2 (14%) At-Home 9.5% HP (9 h): 4 (25%)	Not evaluated using VAS	Whitestrips 14%HP (21 h): 3 (23%) n.r	Not evaluated using VAS
Auschill et al. [11]	Occurrence of sensitivity and gingival irritation Tooth Sensitivity: VAS (0–10) Gingival Sensitivity: VAS (0–10)	Tooth Sensitivity and Oral Irritation Gingival Irritation	Whitestrips 14% HP (21 h): 2 (15%) n.r	Whitestrips 5.3%HP: 2.62±1.46 At-Home 10% CP: 3.38±1.66 Office 38%HP: 2.85±1.41	Whitestrips 5.3%HP: 0.85±1.82 At-Home 10% CP: 0.38±0.87 Office 38%HP: 0.23±0.44	Whitestrips 5.3%HP: 0.85±1.82 At-Home 10% CP: 0.38±0.87 Office 38%HP: 0.23±0.44

Table 3 (continued)

Author [ref]	Assessment form	Adverse effects	Occurrence of tooth sensitivity (%)	Intensity of tooth sensitivity	Occurrence of gingival irritation (%)	Intensity of gingival irritation
Zantner et al. [7]	Tooth Sensitivity: VAS (0–5) Gingival Sensitivity: VAS (0–5)	Tooth Sensitivity and Gingival Irritation	Paint-on 5.9% HP (7 h): 0 (0%) Paint-on 8% CP (9.3 h): 1 (4%) (First visit)	Paint-on 5.9%HP (7 h): 0.33±n.r	Paint-on 5.9%HP (7 h): 5 (24%)	Paint-on 5.9%HP (7 h): 0.43±n.r
Zantner et al. [50]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Paint-on 8% CP (4.6 h): 1 (4%) Paint-on 8% CP (9.3 h): 1 (4%) (First visit)	Not evaluated using VAS	Total sample: 10 (23.2%)	Not evaluated using VAS
Guerrero et al. [38]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 6.5% HP (10.5 h): 4 (26.7%)	Not evaluated using VAS	Whitestrips 6.5% HP (10.5 h): 1 (6.7%)	Not evaluated using VAS
Hamig et al. [51]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 6% HP (14 h): 2 (8.3%) At-Home 10% CP (14 h): 2 (8.6%)	n.r	Whitestrips 6%HP (14 h): 3 (13%) At-Home 10% CP (14 h): 3 (12.5%)	n.r
Xu et al. [56]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 6% HP (7 h): 2 (11%) Paint-on 5.9% HP (14 h): 0 (0%)	n.r	Whitestrips 6%HP (7 h): 0 (0%) Paint-on 5.9% HP (14 h): 0 (0%)	n.r
Yudhira et al. [52]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 6% HP (14 h): 6 (40%)	n.r	Whitestrips 6%HP (14 h): 1 (6.7%)	n.r
Ziebolz et al. [53]	Tooth Sensitivity (0–10) Gingival Sensitivity: VAS (0–10)	Tooth Sensitivity	Paint-on 6% HP (2.3 h) – with desensitizer: 13 (39.4%) Paint-on 6% HP (2.3 h) – without desensitizer: 10 (29.4%)	Paint-on 6%HP (2.3 h) – with desensitizer: 1.6±1.9 Paint-on 6%HP (2.3 h) – without desensitizer: 1.3±1.8	n.r	n.r
Ferrari et al. [54]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Total sample: 5 (12%)	n.r	Group A: 5 (23%) Group B: 5 (23%)	n.r
Papas et al. [39]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 10% HP (14 h): 6 (21.4%)	n.r	Whitestrips 10%HP (14 h): 8 (28.6%)	n.r
Swift et al. [40]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 6% HP (42 h): 7 (35%)	n.r	Whitestrips 6%HP (42 h): 5 (25%)	n.r
Oliveira et al. [42]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 9.5% HP (16 h): 4 (28.6%) Whitestrips 10% HP (4 h): 2 (13.3%)	n.r	Whitestrips 9.5% HP (16 h): 3 (21.4%) Whitestrips 10% HP (4 h): 6 (30%)	n.r
Costa et al. [41]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	At-Home 35% CP (14 h): 5 (21%) Whitestrips 14% HP (14 h): 0 (0%)	n.r	At-Home 35%CP (14 h): 6 (25%) Whitestrips 14%HP (14 h): 4 (16%)	n.r

Table 3 (continued)

Author [ref]	Assessment form	Adverse effects	Occurrence of tooth sensitivity (%)	Intensity of tooth sensitivity	Occurrence of gingival irritation (%)	Intensity of gingival irritation
Perry et al. [43]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Whitestrips 9.5% HP (10 h): 1 (3%) In-Office 25% HP (0.75 h): 7 (20%)	n.r	Whitestrips 9.5%HP (10 h): 3 (10%) In-Office 25%HP (0.75 h): 0 (0%)	n.r
Simon et al. [45]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	n.r	n.r	Test Group: 0 (0%)	n.r
Llena et al. [55]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Test Group: 0 (0%)	n.r	Test Group: 0 (0%)	n.r
Pinto et al. [45]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity, Gingival Irritation, Itching, Mouth ulcers, burning on lips, burning on gums	OTC Bleaching Gel 6%HP (7 h): 1 (10%) OTC Bleaching Gel 7.5% HP (7 h): 1 (10%) Whitestrips 10%HP (7 h): 0 (0%)	n.r	OTC Bleaching Gel 6%HP (7 h): 2 (20%) OTC Bleaching Gel 7.5% HP (7 h): 4 (40%) Whitestrips 10%HP (7 h): 2 (20%)	n.r
Cordeiro et al. [46]	Tooth Sensitivity: VAS (0–4) Gingival Sensitivity: VAS (0–4)	Tooth Sensitivity	At-Home 10%HP (7 h): 19 (95%) OTC Bleaching gel 10%HP (7 h): 15 (75%) Whitestrips 10%HP (7 h): 14 (70%)	At-Home 10%HP (7 h): 3.2 ± 3.2 OTC Bleaching gel 10%HP (7 h): 1.4 ± 1.7 Whitestrips 10%HP (7 h): 1.6 ± 2.3	n.r	n.r
Kim et al. [10]	Tooth Sensitivity: VAS (0–10)	Tooth Sensitivity, Gingival Index (GI), Plaque Index (PI)	n.r	Whitestrips 2.9% HP (28 h): 1.03 ± 13.89 Paint-on 2.9%HP (28 h): 4.09 ± 9.04 At-Home 10%CP (28 h): 3.34 ± 8.04	n.r	n.r
Monteiro et al. [47]	Occurrence of sensitivity and gingival irritation	Tooth Sensitivity and Gingival Irritation	Total sample: 48 (80%)	n.r	Total sample: 28 (46%)	n.r
Kim et al. [59]	Occurrence of sensitivity	Tooth Sensitivity	Dentifrice Containing HP: 3 (20%) Dentifrice 0.75%HP (12.6 h): 1 (7.14%) Dentifrice 2.8%HP: 4 (23.52%)	n.r	n.r	n.r

HP: Hydrogen Peroxide; CP: Carbamide Peroxide, n.r.: not reported by the author



Fig. 2 Individual risk of bias of studies

were included, totaling 239 participants. Figure 5 demonstrates the network, and Appendix S4 presents direct evidence findings. This geometry had a density of 0.53 and no strong edge.

Figure 6 shows estimates from NMA. The ranking probability showed that the most effective treatment was at-home 10% CP (≥ 14 h), followed by 6% HP strips (≥ 14 h) and 3% HP strips (≥ 14 h). The at home 10% CP (≥ 14 h) protocol had significantly higher Δ SGU than all other treatments, except for 6% HP strips (≥ 14 h) (MD: 0.41; 95% CI: -1.01 – 1.83). Moreover, Δ SGU was significantly higher for 6% HP strips (≥ 14 h) compared to 6% HP paint-on gel (7–13 h) (MD: 1.93; 95% CI: 0.27 – 3.59) and placebo (MD: 2.60; 95% CI: 1.01 – 4.19). The assessment of inconsistency was not possible due to the absence of mixed (both direct and indirect) evidence (Appendix S5).

Adverse effects

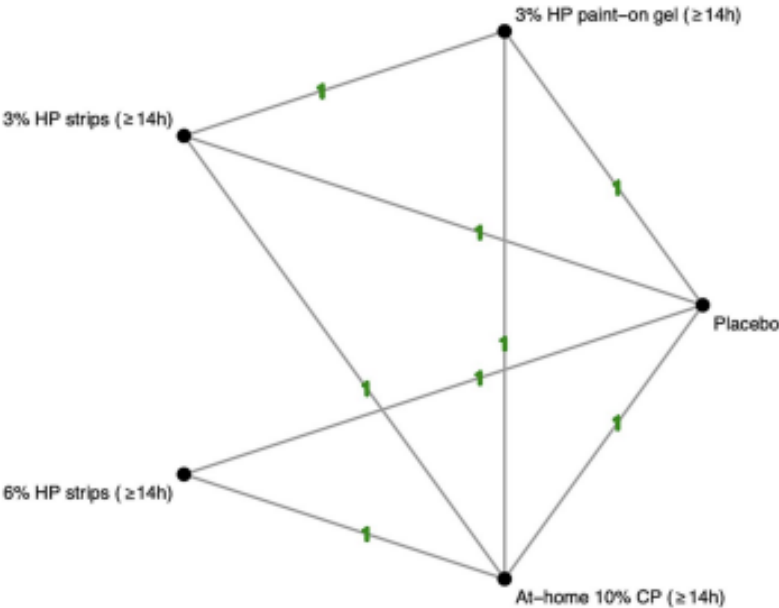
Among the 30 studies that evaluated tooth sensitivity, four [28, 30, 50, 51] employed desensitizing agents in at least one group (which could introduce bias in pooled estimates), three [42, 45, 52] were excluded due to providing only total sample estimates of tooth sensitivity occurrence (without specifying it according to comparison group), one [1] due to not providing the exact contact time between the bleaching agent and tooth surface, other [53] did not reported the assessment method for tooth sensitivity, and another [45] showed the results as visual graphs, without specifying the occurrence of tooth sensitivity according to each group. Furthermore, this NMA excluded ten studies [7, 9, 34, 35, 38, 41, 47, 48, 51, 57] due to the lack of a common comparator group and five [33, 35, 40, 42, 43] due to violating the transitivity assumption. The tooth sensitivity NMA included five studies [28, 39, 45, 46, 56] with 9 treatments and 11 pairwise comparisons, totaling 216 participants. Figure 7 demonstrates the network and Appendix S6 presents direct evidence findings. The geometry had very low density (0.31) and no strong edge.

Figure 8 shows estimates from NMA. The ranking probability showed that at-home 10% CP (7–13 h) exhibited lower risk of tooth sensitivity, followed by placebo, and 6% HP paint-on gel (≥ 14 h). Placebo (RD: -0.21; 95% CI: -0.39 – -0.04) and 6% HP paint-on gel (≥ 14 h) (RD: -0.21; 95% CI: -0.42 – -0.01) had significantly lower risk of tooth sensitivity than 10% HP strips (≥ 14 h). The assessment of inconsistency was not possible due to the absence of mixed (both direct and indirect) evidence (Appendix S7).

Certainty of evidence

Overall, this study analyzed 61 direct and indirect comparisons considering three outcomes (color changes (ΔE^*),

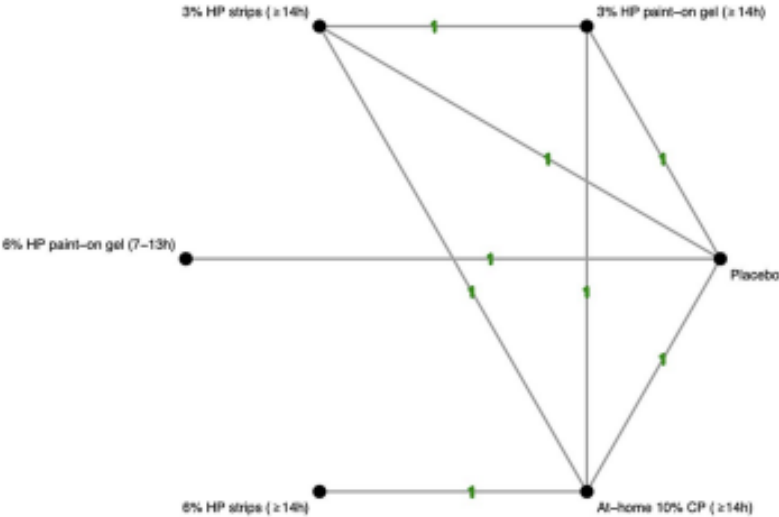
Fig. 3 Network plot geometry for ΔEab^* . HP: hydrogen peroxide; CP: carbamide peroxide



6% HP strips (≥14h)		At-home 10% CP (≥14h)		3% HP strips (≥14h)		3% HP paint-on gel (≥14h)		Placebo	
0.90 [-1.53; 3.34]		0.90 [-2.04; 3.83]		1.18 [-1.81; 4.17]		0.09 [-2.75; 2.92]			
1.80 [-1.56; 5.16]		2.08 [-0.83; 4.99]		1.27 [-1.59; 4.12]					
2.98 [-0.36; 6.32]		2.16 [-0.31; 4.63]							
3.07 [0.63; 5.50]									

Fig. 4 League table with ΔEab^* results from NMA. Treatments were ordered from best to worst according to the ranking probabilities of treatment effects. Results with statistical significance are in bold. HP: hydrogen peroxide; CP: carbamide peroxide

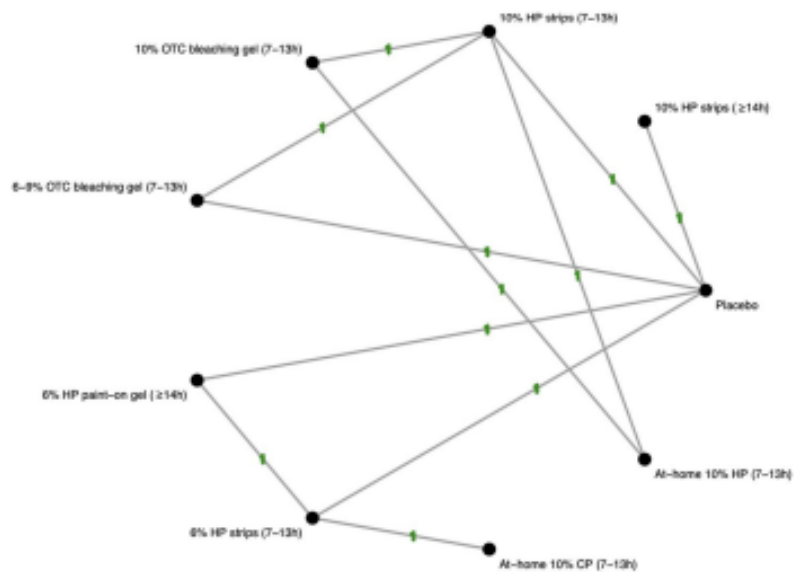
Fig. 5 Network plot geometry for ΔSGU . HP: hydrogen peroxide; CP: carbamide peroxide



At-home 10% CP (≥ 14 h)		6% HP strips (≥ 14 h)		3% HP strips (≥ 14 h)		3% HP paint-on gel (≥ 14 h)		6% HP paint-on gel (7–13h)		Placebo	
0.41 [-1.01; 1.83]		1.03 [-0.63; 2.69]		0.54 [-0.13; 1.21]		0.36 [-0.32; 1.04]		0.67 [0.20; 1.14]			
1.44 [0.59; 2.29]		1.57 [-0.07; 3.21]		0.90 [0.17; 1.63]							
1.98 [1.17; 2.79]		1.57 [-0.07; 3.21]		0.54 [-0.13; 1.21]		0.36 [-0.32; 1.04]		0.67 [0.20; 1.14]			
2.34 [1.48; 3.20]		1.93 [0.27; 3.59]		0.90 [0.17; 1.63]		0.36 [-0.32; 1.04]		0.67 [0.20; 1.14]			
3.01 [2.30; 3.72]		2.60 [1.01; 4.19]		1.57 [1.02; 2.12]		1.03 [0.54; 1.52]		0.67 [0.20; 1.14]			

Fig. 6 League table with Δ SGU results from NMA. Treatments were ordered from best to worst according to the ranking probabilities of treatment effects. Results with statistical significance are in bold. HP: hydrogen peroxide; CP: carbamide peroxide

Fig. 7 Network plot geometry for tooth sensitivity. HP: hydrogen peroxide; CP: carbamide peroxide; OTC: over-the-counter



At-home 10% CP (7–13h)		Placebo		6% HP paint-on gel (≥ 14 h)		10% HP strips (7–13h)		10% OTC bleaching gel (7–13h)		6% HP strips (7–13h)		6–8% OTC bleaching gel (7–13h)		10% HP strips (≥ 14 h)		At-home 10% HP (7–13h)	
-0.18 [-0.58; 0.22]		0.00 [-0.11; 0.11]		-0.00 [-0.10; 0.10]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]	
-0.18 [-0.58; 0.22]		0.00 [-0.11; 0.11]		-0.00 [-0.10; 0.10]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]	
-0.18 [-0.58; 0.22]		0.00 [-0.11; 0.11]		-0.00 [-0.10; 0.10]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]	
-0.24 [-0.75; 0.27]		-0.08 [-0.37; 0.21]		-0.08 [-0.37; 0.21]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]	
-0.24 [-0.75; 0.27]		-0.08 [-0.37; 0.21]		-0.08 [-0.37; 0.21]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]	
-0.24 [-0.75; 0.27]		-0.08 [-0.37; 0.21]		-0.08 [-0.37; 0.21]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]		-0.11 [-0.35; 0.12]	
-0.38 [-0.89; 0.06]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]	
-0.48 [-0.94; 0.02]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]	
-0.41 [-0.92; 0.04]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]		-0.20 [-0.48; 0.08]	

Fig. 8 League table with tooth sensitivity results NMA. Treatments were ordered from best to worst according to the ranking probabilities of treatment effects. Results with statistical significance are in bold. HP: hydrogen peroxide; CP: carbamide peroxide; OTC: over-the-counter

color changes (Δ SGU), and tooth sensitivity). The certainty of evidence varied from very low to low. The main reasons for evidence downgrading were the risk of bias and imprecision (Appendix S8).

Discussion

The Δ Eab* analysis did not show statistical differences between OTC protocols and the positive control. Considering meta-analysis limitations, only one supervised protocol could be compared (at-home 10%CP ≥ 14 h), and

the similar time of bleaching agent application among all groups (≥ 14 h) and the close HP concentration justify the results. However, the positive control in the Δ SGU analysis presented more color changes than all four evaluated OTC protocols. One analyzed study [10] used paint-on gel (3% ≥ 14 h) and reported participants with difficulties using the bleaching agent. That may explain the difference in results because OTC protocols are not personalized, and the absence of professional support may cause complications in product use.

The Δ Eab* analysis showed that two OTC protocols did not differ from the placebo group: 3%HP strips ≥ 14 h

[10] and 3%HP paint-on gel ≥ 14 h [10]. That may be due to the low bleaching agent concentration, reinforced by the higher color change achieved with 6%HP strips ≥ 14 h in two studies [20, 30]. The ΔE_{ab}^* indices of one positive control also did not differ from the placebo treatment: at-home 10%CP > 14 h [30]. The low product concentration in these cases associated with short application times (30 min) potentially influenced the findings. Carbamide peroxide takes longer to react and release hydroxyl radicals [60]. Therefore, at-home bleaching with carbamide peroxide should use an impression tray as the bleaching agent for longer.

It is worth noting that although ΔE_{ab}^* and ΔSGU provide two different analyses, both methods generally evaluate and identify color changes [61]. Therefore, the findings should be complementary.

Gingival irritation is an adverse effect of bleaching procedures caused by the direct contact of hydrogen peroxide with the gingival mucosa. The bleaching agent is highly toxic when working on fibroblasts in the gingival tissue, reducing cell survival [14]. OTC products are not customized for everyone, potentially promoting contact between the bleaching agent and the gingival tissue and consequent irritation [4]. The data from our search did not allow a meta-analysis comparing gingival irritation between OTC products and positive controls. Further clinical studies should perform this comparison.

An important point to emphasize is that the application of products containing HP should always be supervised by a professional. Indiscriminate use of bleaching products can potentially cause oral lesions. Additionally, the lack of a personalized reservoir for at-home use of these products may result in the ingestion of HP [4], leading to irritation of the gastrointestinal tract, nausea, and vomiting [62].

Tooth sensitivity is the most common adverse effect of bleaching treatments. Although its biological mechanism has not been established, it might occur from the permeability of oxygen ions, which are cytotoxic in odontoblastic extensions close to pulp cells [63]. Considering that tooth permeability is higher in exposed dentin due to dentinal tubules, OTC products may promote the direct contact of bleaching agents with the exposed dentin in patients with gingival recessions, or non-carious cervical lesions may lead to severe inflammatory reactions in pulp cells [15, 63]. Different standardizations in visual analog scales limited the sensitivity intensity assessment.

Despite our extensive search, none of the direct comparisons (ΔE_{ab} , ΔSGU , or sensitivity) included more than one study comparing similar treatments, restricting the application of the findings to clinical conditions, considering the high number of indirect comparisons. Moreover, the study limitations excluded other delivery methods from the meta-analysis, such as dentifrices and mouthwashes. Thus, we suggest that further studies standardize the outcomes,

providing means and standard deviations of ΔE_{ab} and/or ΔSGU in each group and assessing more bleaching products.

Another factor worth noting is that 25 eligible articles declared funding sources by private companies related to dental material production and all presented satisfactory results for bleaching with OTC products. Bradley et al. [64] advocate that conflict reporting or interest statements should become more open, thus establishing reliability in study objectivity. More studies unattached to company funding should be conducted.

The body of evidence in this review presents noteworthy limitations. First, only four studies showed a low risk of bias [6, 46, 47, 55]. The primary source of bias referred to randomization, which is common in dental randomized clinical trials and significantly implicates the internal validity of studies. Second, the low number of studies in each comparison and the small sample sizes directly impacted estimate precision, contributing to the uncertainty of findings. Lastly, the low density (indicating low graph connectedness) and the lack of strong edges (meaning a low weight of evidence on each pair) impacted the certainty of NMA estimates. Nevertheless, these metrics indicate potential evidence gaps that should be addressed in further RCTs.

Conclusion

Over-the-counter products achieved satisfactory effects on tooth bleaching compared to the placebo, with little to no impact on dentin hypersensitivity and gingival irritation but with very uncertain evidence. Lower risks of bias and larger study samples are required to draw more conclusive directions.

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Authors' contribution MNO: Conception and design, analysis and interpretation of data, drafting the manuscript, final approval.

MTCV: Conception and design, analysis and interpretation of data, drafting the manuscript, final approval.

WAV: Analysis and interpretation of data, drafting the manuscript, final approval.

CLLC: Analysis and interpretation of data, drafting the manuscript, final approval.

LMO: Analysis and interpretation of data, drafting the manuscript, final approval.

GGN: Interpretation of data, drafting the manuscript (review), final approval.

GRS: Interpretation of data, drafting the manuscript (review), final approval.

LRP: Drafting the manuscript (review), final approval.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

Conflict of interest The authors declare no commercial or associative interest representing a conflict of interest regarding the manuscript. The authors do not have any financial interests or commercial associations to disclose. The authors declare that they have no conflict of interest.

References

- Auschill TM, Hellwig E, Schmidale S, Sculean A, Arweiler NB (2005) Efficacy, side-effects and patients' acceptance of different bleaching techniques (OTC, in-office, at-home). *Oper Dent* 30:156–163
- Ghalili KM, Khawaleh K, Rozen D, Afsahi V (2014) Clinical study of the safety and effectiveness of a novel over-the-counter bleaching tray system. *Clin Cosmet Investig Dent* 6:15–19
- Naidu AS, Bennani V, Brunton JMAP, Brunton P (2020) Over-the-counter tooth whitening agents: a review of literature. *Braz Dent J* 31:221–235
- Demarco FF, Meireles SS, Masotti AS (2009) Over-the-counter whitening agents: a concise review. *Braz Oral Res* 23:64–70
- European Commission on Consumer Products (2005) Scientific committee on consumer products. Preliminary opinion on hydrogen peroxide in tooth whitening products 0844(4):1–50
- Vladislavic NZ, Tadin A, Gavic L, Jerkovic D, Franic I, Verzak Z (2022) In vivo evaluation of whitening toothpaste efficiency and patient treatment satisfaction: a randomized controlled trial. *Clin Oral Investig* 26:739–750
- Zantner C, Derdlopoulou F, Martus P, Kielbassa AM (2006) Randomized clinical trial on the efficacy of 2 over-the-counter whitening systems. *Quintessence Int* 37:695–706
- Bizhang M, Chun YH, Damerau K, Singh P, Raab WH, Zimmer S (2009) Comparative clinical study of the effectiveness of three different bleaching methods. *Oper Dent* 34:635–641
- Calatayud J, Mateos de la Varga P, Oteo Calatayud C, Calvo Box MJ (2009) Comparative clinical study of two tooth bleaching protocols with 6% hydrogen peroxide. *Int J Dent* 2009:928306
- Kim YM, Ha AN, Kim JW, Kim SJ (2018) Double-blind Randomized Study to Evaluate the Safety and Efficacy of Over-the-counter Tooth-whitening Agents Containing 2.9% Hydrogen Peroxide. *Oper Dent* 43:272–281
- Sanson-Fisher RW, Bonevski B, Green LW, D'Este C (2007) Limitations of the randomized controlled trial in evaluating population-based health interventions. *Am J Prev Med* 33:155–161
- Wang X, Ji X (2020) Sample Size Estimation in Clinical Research: From Randomized Controlled Trials to Observational Studies. *Chest* 158:S12–S20
- Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ (2018) Network meta-analysis for comparative effectiveness research. Hoboken, New Jersey: John Wiley & Sons Ltd
- Furukawa M, K-Kaneyama JR, Yamada M, Senda A, Manabe A, Miyazaki A (2015) Cytotoxic Effects of Hydrogen Peroxide on Human Gingival Fibroblasts In Vitro. *Oper Dent* 40:430–9
- Silva-Costa RSGD, Ribeiro AEL, Assunção IV et al (2018) In-office tooth bleaching with 38% hydrogen peroxide promotes moderate/severe pulp inflammation and production of IL-1 β , TNF- β , GPX, FGF-2 and osteocalcin in rats. *J Appl Oral Sci* 26:e20170367
- Shamseer L, Moher D, Clarke M et al (2015) Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 350:g7647
- Aromataris E, Munn Z (2020) JBI Manual for Evidence Synthesis. JBI. <https://doi.org/10.46658/JBIMES-20-01>. Access in: 18 Oct 2023
- Hutton B, Salanti G, Caldwell DM et al (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 162(11):777–784
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. *Clin Exp Metastasis* 5:210
- CIE Publication 15: Colorimetry Technical Report (2004) Commission Internationale de l'Eclairage; 3:18
- Browning WD (2003) Use of shade guides for color measurement in tooth-bleaching studies. *J Esthet Restor Dent* 15(Suppl 1):S13–S20
- Chaimani A, Caldwell DM, Li T et al. (2023) Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Chapter 11, Cochrane
- Rezende M, Loguercio AD, Kossatz S, Reis A (2016) Predictive factors on the efficacy and risk/intensity of tooth sensitivity of dental bleaching: A multi regression and logistic analysis. *J Dent* 45:1–6
- DerSimonian R (2023) Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* 7:177–188. [https://doi.org/10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2). Access in: 18 Oct
- Tonin FS, Borba HH, Mendes AM et al (2019) Description of network meta-analysis geometry: A metrics design study. *PLoS ONE* 14(2):e0212650
- Puhan MA, Schünemann HJ, Murad MH et al (2014) A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 349:g5630
- Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerf B (2018) Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 93:36–44
- Gerlach RW, Barker ML, Sagel PA (2001) Comparative efficacy and tolerability of two direct-to-consumer tooth whitening systems. *Am J Dent* 14:267–272
- Gerlach RW, Sagel PA, Jeffers ME, Zhou X (2002) Effect of peroxide concentration and brushing on whitening clinical response. *Compend Contin Educ Dent* 23:16–49
- Karpinia K, Magnusson I, Barker ML, Gerlach RW (2003) Clinical comparison of two self-directed bleaching systems. *J Prosthodont* 12:242–248
- Nathoo S, Stewart B, Petrone ME et al (2003) Comparative clinical investigation of the tooth whitening efficacy of two tooth whitening gels. *J Clin Dent* 14:64–69
- Collins LZ, Maggio B, Liebman J et al (2004) Clinical evaluation of a novel whitening gel, containing 6% hydrogen peroxide and a standard fluoride toothpaste. *J Dent* 32:13–17

33. García-Godoy F, Villalta P, Barker ML, Gerlach RW (2004) Placebo-controlled, 6-week clinical trial on the safety and efficacy of a low-gel, 14% hydrogen-peroxide whitening strip. *Compend Contin Educ Dent* 25:21–26
34. Gerlach RW, Sagel PA (2004) Vital bleaching with a thin peroxide gel: the safety and efficacy of a professional-strength hydrogen peroxide whitening. *J Am Dent Assoc* 135:98–100
35. Gerlach RW, Zhou X (2004) Clinical trial comparing two daytime hydrogen-peroxide professional vital-bleaching systems. *Compend Contin Educ Dent* 25:33–40
36. Swift EJ Jr, Miguez PA, Barker ML, Gerlach RW (2004) Three-week clinical trial of a 14% hydrogen-peroxide, strip-based bleaching system. *Compend Contin Educ Dent* 25:27–32
37. Cronin MJ, Charles CA, Zhao Q, Dembling WZ (2005) Comparison of two over-the-counter tooth whitening products using a novel system. *Compend Contin Educ Dent* 26:140–148
38. Guerrero JC, Jiménez-Farfán MD, Lopez-Salgado A, Barker ML, Gerlach RW (2007) Professional whitening strips in a university population. *Am J Dent. 20 Spec No A:15A-18A*
39. Papas AS, Kugel G, Singh M, Barker ML, Gerlach RW (2009) Placebo-controlled clinical trial of use of 10% hydrogen peroxide whitening strips for medication-induced xerostomia. *Gerontology* 55:511–516
40. Swift EJ Jr, Heymann HO, Wilder AD Jr, Barker ML, Gerlach RW (2009) Effects of duration of whitening strip treatment on tooth color: a randomized, placebo-controlled clinical trial. *J Dent* 37:e51–e56
41. Costa JB, McPharlin R, Hilton T, Ferracane JL, Wang M (2012) Comparison of two at-home whitening products of similar peroxide concentration and different delivery methods. *Oper Dent* 37:333–339
42. Oliveira GM, Miguez PA, Oliveira GB et al (2013) Safety and efficacy of a high-adhesion whitening strip under extended wear regimen. *J Dent* 41:e46–e52
43. Perry R, Conde E, Farrell S, Gerlach RW, Towers J (2013) Comparative performance of two whitening systems in a dental practice. *Compend Contin Educ Dent. 34(8):15–18*
44. Simon JF, Powell L, Hollis S, Anastasia MK, Gerlach RW, Farrell S (2014) Placebo-controlled clinical trial evaluating 9.5% hydrogen peroxide high-adhesion whitening strips. *J Clin Dent* 25:49–52
45. Pinto MM, Gonçalves ML, Mota AC et al (2017) Controlled clinical trial addressing teeth whitening with hydrogen peroxide in adolescents: a 12-month follow-up. *Clinics (Sao Paulo)* 72:161–170
46. Cordeiro D, Toda C, Hanan S et al (2019) Clinical Evaluation of Different Delivery Methods of At-Home Bleaching Gels Composed of 10% Hydrogen Peroxide. *Oper Dent* 44:13–23
47. Monteiro MJF, Lindoso JBC, de Oliveira Conde NC, da Silva LM, Loguercio AD, Pereira JV (2019) Evaluation of the genotoxic potential of different delivery methods of at-home bleaching gels: a single-blind, randomized clinical trial. *Clin Oral Investig* 23:2199–2206
48. Brunton PA, Ellwood R, Davies R (2004) A six-month study of two self-applied tooth whitening products containing carbamide peroxide. *Oper Dent* 29:623–626
49. Gambarini G, Testarelli L, De Luca M, Dolci G (2004) Efficacy and safety assessment of a new liquid tooth whitening gel containing 5.9% hydrogen peroxide. *Am J Dent* 17:75–79
50. Zantner C, Derdlopoulou F, Martus P, Kielbassa AM (2006) Randomized clinical trial on the efficacy of a new bleaching lacquer for self-application. *Oper Dent* 31:308–316
51. Hannig C, Lindner D, Attin T (2007) Efficacy and tolerability of two home bleaching systems having different peroxide delivery. *Clin Oral Investig* 11:321–329
52. Yudhira R, Peumans M, Barker ML, Gerlach RW (2007) Clinical trial of tooth whitening with 6% hydrogen peroxide whitening strips and two whitening dentifrices. *Am J Dent. 20 Spec NoA:32A-36A*
53. Ziebolz D, Hannig C, Attin T (2008) Influence of a desensitizing agent on efficacy of a paint-on bleaching agent. *Am J Dent* 21:77–82
54. Ferrari M, Cagidiaco MC, Monticelli F, Kugel G, Barker ML, Gerlach RW (2007) Daytime use of a custom bleaching tray or whitening strips: initial and sustained color improvement. *Am J Dent. 20 Spec No A:19A-22A*
55. Llena C, Oteo C, Oteo J, Amengual J, Forner L (2016) Clinical efficacy of a bleaching enzyme-based toothpaste. A double-blind controlled clinical trial. *J Dent* 44:8–12
56. Xu X, Zhu L, Tang Y, et al. (2007) Randomized clinical trial comparing whitening strips, paint-on gel and negative control. *Am J Dent. 20 Spec No A:28A-31A*
57. Lo EC, Wong AH, McGrath C (2007) A randomized controlled trial of home tooth-whitening products. *Am J Dent* 20:315–318
58. Jung YS, Jo HY, Ahn JH et al (2019) In vivo and in vitro assessment of the bleaching effectiveness of a brush-off patch containing 3.0% hydrogen peroxide. *Clin Oral Investig* 23:2667–2673
59. Kim HJ, Jang JH, Choi D, Kim J, Shim JH, Kim DS (2020) Bleaching toothpaste with two different concentrations of hydrogen peroxide: A randomized double-blinded clinical trial. *Int J Dent* 103:103508
60. Peixoto AC, Vaez SC, Pereira NAR (2018) High-concentration carbamide peroxide can reduce the sensitivity caused by in-office tooth bleaching: a single-blinded randomized controlled trial. *J Appl Oral Sci* 26:e20170573
61. Guan YH, Lath DL, Lilley TH, Willmot DR, Marlow I, Brook AH (2005) The measurement of tooth whiteness by image analysis and spectrophotometry: a comparison. *J Oral Rehabil* 32(1):7–15
62. Ito A, Naito M, Naito Y et al (1982) Induction and characterization of gastro-duodenal lesions in mice given continuous oral administration of hydrogen peroxide. *Gan.* 73(2):315–22
63. Markowitz K (2010) Pretty painful: why does tooth bleaching hurt? *Med Hypotheses* 74:835–840
64. Bradley SH, DeVito NJ, Lloyd KE et al (2020) Reducing bias and improving transparency in medical research: a critical overview of the problems, progress and suggested next steps. *J R Soc Med* 113:433–443

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APPENDIX

Appendix S1. Studies excluded during full-text readings and the reasons for exclusion (n=42).

Excluded study	Reason for exclusion
Howard [1]	Does not use OTC bleaching products.
Rosentiel et al. [2]	Does not use OTC bleaching products.
Matis et al. [3]	Not reached.
Kihn et al. [4]	Does not use OTC bleaching products.
Nathoo et al. [5]	Not reached.
Sielsky et al. [6]	Evaluates only extrinsic stains removal.
Singh et al. [7]	Evaluates only extrinsic stains removal.
Barlow et al. [8]	Conference abstract.
Myers et al. [9]	Does not use OTC bleaching products.
Ferrari et al. [10]	Not reached.
Leonard et al. [11]	<i>In vitro</i> study.
Shahidi et al. [12]	Not reached.
Berga-Caballero et al. [13]	Does not use OTC bleaching products.
Bizhang et al. [14]	Not reached.
Wetter et al. [15]	Does not use OTC bleaching products.
Giachetti et al. [16]	Does not use OTC bleaching products.
Meireles et al. [17]	Does not use OTC bleaching products.
Turkun et al. [18]	Does not use OTC bleaching products.
Grobler et al. [19]	Does not use OTC bleaching products.
Mondelli et al. [20]	Does not use OTC bleaching products.
Silva et al. [21]	Does not use OTC bleaching products.
Bruzell et al. [22]	Does not use OTC bleaching products.
Santos et al. [23]	Does not use OTC bleaching products.
Zhao et al. [24]	Does not use OTC bleaching products.
Hyland et al. [25]	Does not use OTC bleaching products.
Vano et al. [26]	Does not use OTC bleaching products.
Machado et al. [27]	Does not use OTC bleaching products.
Pintado-Palomino et al. [28]	Does not use bleaching agents containing HP.
Aka and Celik [29]	Does not use OTC bleaching products.
de la Peña and Cabrita [30]	Does not use OTC bleaching products.
Darriba et al. [31]	Does not use OTC bleaching products.
Sever et al. [32]	Does not use OTC bleaching products.
Nie et al. [33]	Does not use OTC bleaching products.
Tao et al. [34]	Does not use bleaching agents containing HP.
Angel et al. [35]	Does not use OTC bleaching products.
Chemin et al. [36]	Does not use OTC bleaching products.
Chemin et al. [37]	Does not use OTC bleaching products.
Jiang et al. [38]	Does not evaluate isolated OTC products.
Bersezio et al. [39]	Does not use OTC bleaching products.
Ahrari et al. [40]	Does not use OTC bleaching products.
Meireles et al. [41]	Does not use bleaching agents containing HP.
Schlafer et al. [42]	Does not use bleaching agents containing HP.

OTC: Over-the-counter, HP: Hydrogen peroxide.

REFERENCES

1. Howard WR (1992). Patient-applied tooth whiteners. *J Am Dent Assoc.* 123:57-60. <https://doi.org/10.14219/jada.archive.1992.0055>
2. Rosenstiel SF, Gegauff AG, Johnston WM (1996). Randomized clinical trial of the efficacy and safety of a home bleaching procedure. *Quintessence Int.* 27:413-424.
3. Matis BA, Cochran MA, Eckert GJ, Matis JI (2007) In vivo study of two carbamide peroxide gels with different desensitizing agents. *Oper Dent.* 32:549-555. <https://doi.org/10.2341/07-10>
4. Kihn PW, Barnes DM, Romberg E, Peterson K (2000). A clinical evaluation of 10 percent vs. 15 percent carbamide peroxide tooth-whitening agents. *J Am Dent Assoc.* 131:1478-1484. <https://doi.org/10.14219/jada.archive.2000.0061>
5. Nathoo S, Stewart B, Zhang YP, et al. (2002) Efficacy of a novel, nontray, paint-on 18% carbamide peroxide whitening gel. *Compend Contin Educ Dent.* 23:26-31.
6. Sielski C, Berta RL, Petrone ME, et al. (2002) A study to assess the tooth whitening efficacy of a new dentifrice formulation variant containing a special grade of silica: a six-week study on adults. *J Clin Dent.* 13:77-81.
7. Singh S, Mankodi S, Chaknis P, et al. (2002) The clinical efficacy of a new tooth whitening dentifrice formulation: a six-month study in adults. *J Clin Dent.* 13:86-90.
8. Barlow AP, Brennan K, Desai AP, Harris R, Gerlach RW, Yudhira RT (2003). Comparison of the tooth-whitening effects of a direct application percarbonate bleaching film and two commercially available whitening dentifrices. Research presented at the 81ST General Session of the IADR, June 25-28.
9. Myers ML, Browning WD, Downey MC, Hackman ST (2003) Clinical evaluation of a 3% hydrogen peroxide tooth-whitening gel. *J Esthet Restor Dent.* 15:50-56. <https://doi.org/10.1111/j.1708-8240.2003.tb00282.x>
10. Ferrari M, Kugel G, Cagidiaco MC, Barker ML, Gerlach RW (2004) Clinical trial evaluating the peroxide concentration response of whitening strips over 28 days. *Am J Dent.* 17:291-294.
11. Leonard RH, Teixeira EC, Garland GE, Ritter AV (2005) Effect on enamel microhardness of two consumer-available bleaching solutions when compared with a dentist-prescribed, home-applied bleaching solution and a control. *J Esthet Restor Dent.* 17:343-351. <https://doi.org/10.1111/j.1708-8240.2005.tb00466.x>
12. Shahidi H, Barker ML, Sagel PA, Gerlach RW (2005) Randomized controlled trial of 10% hydrogen peroxide whitening strips. *J Clin Dent.* 16:91-95.

13. Berga-Caballero A, Forner-Navarro L, Amengual-Lorenzo J (2006) At-home vital bleaching: a comparison of hydrogen peroxide and carbamide peroxide treatments. *Med Oral Patol Oral Cir Bucal*. 11:E94-E99.
14. Bizhang M, Müller M, Phark JH, Barker ML, Gerlach RW (2007) Clinical trial of long-term color stability of hydrogen peroxide strips and sodium percarbonate film. *Am J Dent*. 20:23A-27A.
15. 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 Med Sci*. 24:941-947. <https://doi.org/10.1007/s10103-008-0575-x>
16. 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. *J Am Dent Assoc*. 141:1357-1364. <https://doi.org/10.14219/jada.archive.2010.0081>
17. Meireles SS, Santos IS, Bona AD, Demarco FF (2010) A double-blind randomized clinical trial of two carbamide peroxide tooth bleaching agents: 2-year follow-up. *J Dent*. 38:956-963. <https://doi.org/10.1016/j.jdent.2010.08.003>
18. Turkun M, Celik EU, Aladah A, Gokay N (2010) One-Year Clinical Evaluation of the Efficacy of a New Daytime At-Home Bleaching Technique. *J Esthet Restor Dent*. 22:139-148. <https://doi.org/10.1111/j.1708-8240.2010.00325.x>
19. 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. *Int J Dent*. 2011:167525. <https://doi.org/10.1155/2011/167525>
20. Mondelli RFL, Azevedo JFD, Francisconi CF, Almeida CM, Ishikiriama SK (2012) Comparative clinical study of the effectiveness of different dental bleaching methods - two year follow-up. *J Appl Oral Sci*. 20(4):435-443. <http://dx.doi.org/10.1590/S1678-77572012000400008>
21. Silva FMM, Nacano LG, Pizi ECG (2012) Clinical Evaluation of Two Tooth Whitening Systems. *Rev Odontol Bras Central* 21(56):473-479.
22. Bruzell EM, Pallesen U, Thoresen NR, Wallman C, Dahl JE (2013) Side effects of external tooth bleaching: a multi-centre practice-based prospective study. *Br Dent J*. 215(9):E17. <https://doi.org/10.1038/sj.bdj.2013.1047>

23. Santos ALE, Mendes NAR, Mello JAN, Borges AFS, Shinohara MS (2013) Evaluation of the effectiveness of external bleaching using 6% and 7.5% hydrogen peroxide. *Clin Int J Braz Dent.* 9(2):216-222.
24. Zhao K, Zong L, Zhang Q, Att W (2013) Clinical comparison between two bleaching techniques: a 180-day follow-up study. *Quintessence Int.* 44:601-607. <https://doi.org/10.3290/j.qi.a29702>
25. Hyland BW, McDonald A, Lewis N, et al. (2015) A new three-component formulation for the efficient whitening of teeth (Carbamide Plus). *Clin Oral Investig.* 19:1395-1404. <https://doi.org/10.1007/s00784-014-1352-9>
26. Vano M, Derchi G, Barone A, Genovesi A, Covani U (2015) Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: a 9-month follow-up randomized clinical trial. *Int J Dent Hyg.* 13:301-307. <https://doi.org/10.1111/idh.12123>
27. Machado LS, Anchieta RB, dos Santos PH, et al. (2016) Clinical comparison of at-home and in-office dental bleaching procedures: a randomized trial of a split-mouth design. *Int J Periodontics Restorative Dent.* 36:251-260. <https://doi.org/10.11607/prd.2383>
28. Pintado-Palomino K, Vasconcelos CV, Silva RJ, et al. (2016) Effect of whitening dentifrices: a double-blind randomized controlled trial. *Braz Oral Res.* 30:e82. <https://doi.org/10.1590/1807-3107bor-2016.vol30.0082>
29. Aka B, Celik EU (2017) Evaluation of the efficacy and color stability of two different at-home bleaching systems on teeth of different shades: a randomized controlled clinical trial. *J Esthet Restor Dent.* 29:325-338. <https://doi.org/10.1111/jerd.12296>
30. de la Peña VA, Cabrita OB (2006) Comparison of the clinical efficacy and safety of carbamide peroxide and hydrogen peroxide in at-home bleaching gels. *Quintessence Int.* 37:551-556.
31. Darriba IL, Novoa L, de la Peña VA (2017) Efficacy of different protocols for at-home bleaching: A randomized clinical trial. *Am J Dent.* 30:329-334.
32. Sever EK, Budimir Z, Cerovac M, et al. (2018) Clinical and patient reported outcomes of bleaching effectiveness. *Acta Odontol Scand.* 76:30-38. <https://doi.org/10.1080/00016357.2017.1376111>
33. 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. *J Oral Sci.* 59:527-532. <https://doi.org/10.2334/josnusd.16-0636>

34. Tao D, Smith RN, Zhang Q, et al. (2017) Tooth whitening evaluation of blue covarine containing toothpastes. *J Dent.* 67S:S20-S24. <https://doi.org/10.1016/j.jdent.2017.10.014>
35. Angel P, Bersezio C, Estay J, et al. (2018) Color stability, psychosocial impact, and effect on self-perception of esthetics of tooth whitening using low-concentration (6%) hydrogen peroxide. *Quintessence Int.* 49:557-566. <https://doi.org/10.3290/j.qi.a40468>
36. 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. *Oper Dent.* 43:232-240. <https://doi.org/10.2341/16-260-c>
37. Chemin K, Rezende M, Milan FM, Dantas TB, Gomes KDN, Kossatz S (2018) Clinical evaluation of 10% hydrogen peroxide on tooth sensitivity and effectiveness in at home dental bleaching. *J Contemp Dent Pract.* 19:1376-1380.
38. Jiang N, Zhang C, Agingu C, Attin T, Cheng H, Yu H (2019) Comparison of whitening dentifrices on the effectiveness of in-office tooth bleaching: a double-blind randomized Controlled Clin Trial *Oper Dent.* 44:138-145. <https://doi.org/10.2341/17-333-c>
39. Bersezio C, Martín J, Prieto MV, et al. (2019) One-year bleaching efficacy using two HP products with different pH: A double-blind randomized clinical trial. *J Esthet Restor Dent.* 31:493-499. <https://doi.org/10.1111/jerd.12505>
40. Ahrari F, Akbari M, Mohammadipour HS, Fallahrastegar A, Sekandari S (2020) The efficacy and complications of several bleaching techniques in patients after fixed orthodontic therapy. A randomized clinical trial. *Swiss Dent J.* 130:493-501.
41. Meireles SS, Sousa JP, Lins RBE, Sampaio FC (2020). Efficacy of whitening toothpaste containing blue covarine: A double-blind controlled randomized clinical trial. *J Est Rest Dent.* 33:1-10. <http://dx.doi.org/10.1111/jerd.12605>
42. Schlafer S, Poulsen PN, Johansen J, Trap L, Leite FRM (2021) The whitening effect of single brushing with blue-covarine containing toothpaste-A randomized controlled trial. *J Dent.* 105:103559. <https://doi.org/10.1016/j.jdent.2020.103559>

Appendix S2. Pairwise comparisons for ΔE_{ab}^* .

Study	Comparison	Treatment 1			Treatment 2			MD ^d	SE ^e	95% CI ^f
		N	Mean	SD ^c	N	Mean	SD			
Karpinia et al., 2003	At-home 10% CP ^a ($\geq 14h$):6% HP strips ($\geq 14h$)	26	1.60	1.05	29	3.37	1.05	-1.77	0.29	-2.33; -1.21
Kim et al., 2018	3% HP ^b strips ($\geq 14h$):3% HP paint-on gel ($\geq 14h$)	15	2.95	1.02	15	1.77	0.74	1.18	0.33	0.54; 1.82
Kim et al., 2018	3% HP paint-on gel ($\geq 14h$):At-home 10% CP ($\geq 14h$)	15	1.77	0.74	15	4.34	1.71	-2.57	0.48	-3.51; -1.63
Kim et al., 2018	3% HP paint-on gel ($\geq 14h$):Placebo	15	1.77	0.74	30	1.26	0.61	0.51	0.22	0.08; 0.94
Kim et al., 2018	3% HP strips ($\geq 14h$):At-home 10% CP ($\geq 14h$)	15	2.95	1.02	15	4.34	1.71	-1.39	0.51	-2.40; -0.38
Kim et al., 2018	3% HP strips ($\geq 14h$):Placebo	15	2.95	1.02	30	1.26	0.61	1.69	0.29	1.13; 2.25
Kim et al., 2018	At-home 10% CP ($\geq 14h$):Placebo	15	4.34	1.71	30	1.26	0.61	3.08	0.45	2.19; 3.97
Swift et al., 2009	6% HP strips ($\geq 14h$):Placebo	19	3.10	0.87	20	0.90	0.89	2.20	0.28	1.65; 2.75

^aCP, carbamide peroxide;

^bHP, hydrogen peroxide;

^cSD, standard deviation;

^dMD, mean difference;

^eSE, standard error;

^fCI, confidence interval;

Appendix S3. Assessment of inconsistency (ΔE_{ab}^*).

Comparison	No.Studies	NMA ^c	Direct	Indirect	Difference	Diff_95CI ^d		pValue
						lower	upper	
3% HP ^a paint-on gel ($\geq 14h$):3% HP strips ($\geq 14h$)	1	-1.18	-1.18	NA ^e	NA	NA	NA	NA
3% HP paint-on gel ($\geq 14h$):6% HP strips ($\geq 14h$)	0	-2.98	NA	-2.98	NA	NA	NA	NA
3% HP paint-on gel ($\geq 14h$):At-home 10% CP ^b ($\geq 14h$)	1	-2.08	-2.57	2.41	-4.98	-14.73	4.78	0.32
3% HP paint-on gel ($\geq 14h$):Placebo	1	0.09	0.51	-4.85	5.36	-5.14	15.85	0.32
3% HP strips ($\geq 14h$):6% HP strips ($\geq 14h$)	0	-1.80	NA	-1.80	NA	NA	NA	NA
3% HP strips ($\geq 14h$):At-home 10% CP ($\geq 14h$)	1	-0.90	-1.39	3.65	-5.04	-14.93	4.84	0.32
3% HP strips ($\geq 14h$):Placebo	1	1.27	1.69	-3.74	5.43	-5.22	16.08	0.32
6% HP strips ($\geq 14h$):At-home 10% CP ($\geq 14h$)	1	0.90	1.77	-0.88	2.65	-2.54	7.84	0.32
6% HP strips ($\geq 14h$):Placebo	1	3.07	2.2	4.85	-2.65	-7.84	2.54	0.32
At-home 10% CP ($\geq 14h$):Placebo	1	2.16	3.08	0.43	2.65	-2.54	7.84	0.32

^aHP, hydrogen peroxide;
^bCP, carbamide peroxide;
^cNMA, network meta-analysis;
^dCI, confidence interval;
^eNA, not applicable;

Appendix S4. Pairwise comparisons for Δ SGU.

Study	Comparison	Treatment 1			Treatment 2			MD ^d	SE ^e	95% CI ^f
		N	Mean	SD ^c	N	Mean	SD			
Collins et al., 2004	6% HP ^a paint-on gel (7-13h):Placebo	58	1.02	1.32	59	0.35	1.29	0.67	0.24	0.20; 1.14
Hanning et al., 2007	At-home 10% CP ^b (≥ 14 h):6% HP strips (≥ 14 h)	23	4.55	2.74	24	4.14	2.19	0.41	0.72	-1.01; 1.83
Kim et al., 2018	3% HP strips (≥ 14 h):3% HP paint-on gel (≥ 14 h)	15	1.84	1.01	15	1.30	0.87	0.54	0.34	-0.13; 1.21
Kim et al., 2018	3% HP paint-on gel (≥ 14 h):At-home 10% CP (≥ 14 h)	15	1.30	0.87	15	3.28	1.35	-1.98	0.41	-2.79; -1.17
Kim et al., 2018	3% HP paint-on gel (≥ 14 h):Placebo	15	1.30	0.87	30	0.27	0.57	1.03	0.25	0.54; 1.52
Kim et al., 2018	3% HP strips (≥ 14 h):At-home 10% CP (≥ 14 h)	15	1.84	1.01	15	3.28	1.35	-1.44	0.43	-2.29; -0.59
Kim et al., 2018	3% HP strips (≥ 14 h):Placebo	15	1.84	1.01	30	0.27	0.57	1.57	0.28	1.02; 2.12
Kim et al., 2018	At-home 10% CP (≥ 14 h):Placebo	15	3.28	1.35	30	0.27	0.57	3.01	0.36	2.30; 3.72

^aHP, hydrogen peroxide;

^bCP, carbamide peroxide;

^cSD, standard deviation;

^dMD, mean difference;

^eSE, standard error;

^fCI, confidence interval;

Appendix S5. Assessment of inconsistency (Δ SGU).

Comparison	No.Studies	NMA ^c	Direct	Indirect	Difference	Diff_95CI ^d		pValue
						lower	upper	
3% HP ^a paint-on gel (≥ 14 h):3% HP strips (≥ 14 h)	1	-0.54	-0.54	NA ^e	NA	NA	NA	NA
3% HP paint-on gel (≥ 14 h):6% HP paint-on gel (7-13h)	0	0.36	NA	0.36	NA	NA	NA	NA
3% HP paint-on gel (≥ 14 h):6% HP strips (≥ 14 h)	0	-1.57	NA	-1.57	NA	NA	NA	NA
3% HP paint-on gel (≥ 14 h):At-home 10% CP ^b (≥ 14 h)	1	-1.98	-1.98	NA	NA	NA	NA	NA
3% HP paint-on gel (≥ 14 h):Placebo	1	1.03	1.03	NA	NA	NA	NA	NA
3% HP strips (≥ 14 h):6% HP paint-on gel (7-13h)	0	0.90	NA	0.90	NA	NA	NA	NA
3% HP strips (≥ 14 h):6% HP strips (≥ 14 h)	0	-1.03	NA	-1.03	NA	NA	NA	NA
3% HP strips (≥ 14 h):At-home 10% CP (≥ 14 h)	1	-1.44	-1.44	NA	NA	NA	NA	NA
3% HP strips (≥ 14 h):Placebo	1	1.57	1.57	NA	NA	NA	NA	NA
6% HP paint-on gel (7-13h):6% HP strips (≥ 14 h)	0	-1.93	NA	-1.93	NA	NA	NA	NA
6% HP paint-on gel (7-13h):At-home 10% CP (≥ 14 h)	0	-2.34	NA	-2.34	NA	NA	NA	NA
6% HP paint-on gel (7-13h):Placebo	1	0.67	0.67	NA	NA	NA	NA	NA

6% HP strips (≥ 14 h):At-home 10% CP (≥ 14 h)	1	-0.41	-0.41	NA	NA	NA	NA	NA
6% HP strips (≥ 14 h):Placebo	0	2.60	NA	2.60	NA	NA	NA	NA
At-home 10% CP (≥ 14 h):Placebo	1	3.01	3.01	NA	NA	NA	NA	NA

^aHP, hydrogen peroxide;
^bCP, carbamide peroxide;
^cNMA, network meta-analysis;
^dCI, confidence interval;
^eNA, not applicable;

Appendix S6. Pairwise comparisons for tooth sensitivity.

Study	Comparison	Treatment 1		Treatment 2		RD ^d	SE ^e	95% CI ^f
		Events	N	Events	N			
Cordeiro et al., 2018	10% HP ^a strips (7-13h):10% OTC ^b bleaching gel (7-13h)	14	20	15	20	-0.05	0.14	-0.33; 0.23
Cordeiro et al., 2018	10% HP strips (7-13h):At-home 10% HP (7-13h)	14	20	19	20	-0.25	0.11	-0.47; -0.03
Cordeiro et al., 2018	10% OTC bleaching gel (7-13h):At-home 10% HP (7-13h)	15	20	19	20	-0.20	0.11	-0.41; 0.01
Gerlach et al., 2001	At-home 10% CP ^c (7-13h):6% HP strips (7-13h)	1	10	4	10	-0.30	0.18	-0.66; 0.06
Papas et al., 2009	Placebo:10% HP strips (≥14h)	0	14	6	28	-0.21	0.09	-0.39; -0.04
Pinto et al., 2017	Placebo:6-9% OTC bleaching gel (7-13h)	0	12	4	20	-0.20	0.10	-0.40; 0.00
Pinto et al., 2017	10% HP strips (7-13h):6-9% OTC bleaching gel (7-13h)	0	10	4	20	-0.20	0.11	-0.41; 0.01
Pinto et al., 2017	Placebo:10% HP strips (7-13h)	0	12	0	10	0.00	0.08	-0.16; 0.16
Xu et al., 2007	6% HP paint-on gel (≥14h):6% HP strips (7-13h)	0	17	2	18	-0.11	0.09	-0.28; 0.06
Xu et al., 2007	Placebo:6% HP paint-on gel (≥14h)	0	17	0	17	0.00	0.06	-0.11; 0.11
Xu et al., 2007	Placebo:6% HP strips (7-13h)	0	17	2	18	-0.11	0.09	-0.28; 0.06

^aHP, hydrogen peroxide;

^bOTC, over-the-counter;

^cCP, carbamide peroxide;

^dRD, risk difference;

^eSE, standard error;

^fCI, confidence interval;

Appendix S7. Assessment of inconsistency (tooth sensitivity).

Comparison	No.Studies	NMA ^d	Direct	Indirect	Difference	Diff_95CI ^e		pValue
						lower	upper	
10% HP ^a strips (≥14h):10% HP strips (7-13h)	0	0.21	NA ^f	0.21	NA	NA	NA	NA
10% HP strips (≥14h):10% OTC ^b bleaching gel (7-13h)	0	0.16	NA	0.16	NA	NA	NA	NA
10% HP strips (≥14h):6-9% OTC bleaching gel (7-13h)	0	0.01	NA	0.01	NA	NA	NA	NA
10% HP strips (≥14h):6% HP paint-on gel (≥14h)	0	0.21	NA	0.21	NA	NA	NA	NA
10% HP strips (≥14h):6% HP strips (7-13h)	0	0.10	NA	0.10	NA	NA	NA	NA
10% HP strips (≥14h):At-home 10% CP ^c (7-13h)	0	0.40	NA	0.40	NA	NA	NA	NA
10% HP strips (≥14h):At-home 10% HP (7-13h)	0	-0.04	NA	-0.04	NA	NA	NA	NA
10% HP strips (≥14h):Placebo	1	0.21	0.21	NA	NA	NA	NA	NA
10% HP strips (7-13h):10% OTC bleaching gel (7-13h)	1	-0.05	-0.05	NA	NA	NA	NA	NA
10% HP strips (7-13h):6-9% OTC bleaching gel (7-13h)	1	-0.20	-0.20	NA	NA	NA	NA	NA
10% HP strips (7-13h):6% HP paint-on gel (≥14h)	0	0.00	NA	0.00	NA	NA	NA	NA
10% HP strips (7-13h):6% HP strips (7-13h)	0	-0.11	NA	-0.11	NA	NA	NA	NA

10% HP strips (7-13h):At-home 10% CP (7-13h)	0	0.19	NA	0.19	NA	NA	NA	NA
10% HP strips (7-13h):At-home 10% HP (7-13h)	1	-0.25	-0.25	NA	NA	NA	NA	NA
10% HP strips (7-13h):Placebo	1	0	0	NA	NA	NA	NA	NA
10% OTC bleaching gel (7-13h):6-9% OTC bleaching gel (7-13h)	0	-0.15	NA	-0.15	NA	NA	NA	NA
10% OTC bleaching gel (7-13h):6% HP paint-on gel (≥14h)	0	0.05	NA	0.05	NA	NA	NA	NA
10% OTC bleaching gel (7-13h):6% HP strips (7-13h)	0	-0.06	NA	-0.06	NA	NA	NA	NA
10% OTC bleaching gel (7-13h):At-home 10% CP (7-13h)	0	0.24	NA	0.24	NA	NA	NA	NA
10% OTC bleaching gel (7-13h):At-home 10% HP (7-13h)	1	-0.2	-0.2	NA	NA	NA	NA	NA
10% OTC bleaching gel (7-13h):Placebo	0	0.05	NA	0.05	NA	NA	NA	NA
6-9% OTC bleaching gel (7-13h):6% HP paint-on gel (≥14h)	0	0.2	NA	0.2	NA	NA	NA	NA
6-9% OTC bleaching gel (7-13h):6% HP strips (7-13h)	0	0.09	NA	0.09	NA	NA	NA	NA
6-9% OTC bleaching gel (7-13h):At-home 10% CP (7-13h)	0	0.39	NA	0.39	NA	NA	NA	NA
6-9% OTC bleaching gel (7-13h):At-home 10% HP (7-13h)	0	-0.05	NA	-0.05	NA	NA	NA	NA
6-9% OTC bleaching gel (7-13h):Placebo	1	0.2	0.2	NA	NA	NA	NA	NA

6% HP paint-on gel (≥ 14 h):6% HP strips (7-13h)	1	-0.11	-0.11	NA	NA	NA	NA	NA
6% HP paint-on gel (≥ 14 h):At-home 10% CP (7-13h)	0	0.19	NA	0.19	NA	NA	NA	NA
6% HP paint-on gel (≥ 14 h):At-home 10% HP (7-13h)	0	-0.25	NA	-0.25	NA	NA	NA	NA
6% HP paint-on gel (≥ 14 h):Placebo	1	0	0	NA	NA	NA	NA	NA
6% HP strips (7-13h):At-home 10% CP (7-13h)	1	0.3	0.3	NA	NA	NA	NA	NA
6% HP strips (7-13h):At-home 10% HP (7-13h)	0	-0.14	NA	-0.14	NA	NA	NA	NA
6% HP strips (7-13h):Placebo	1	0.11	0.11	NA	NA	NA	NA	NA
At-home 10% CP (7-13h):At-home 10% HP (7-13h)	0	-0.44	NA	-0.44	NA	NA	NA	NA
At-home 10% CP (7-13h):Placebo	0	-0.19	NA	-0.19	NA	NA	NA	NA
At-home 10% HP (7-13h):Placebo	0	0.25	NA	0.25	NA	NA	NA	NA

^aHP, hydrogen peroxide;
^bOTC, over-the-counter;
^cCP, carbamide peroxide;
^dNMA, network meta-analysis;
^eCI, confidence interval;
^fNA, not applicable;

Appendix S8. Assessment of GRADE for direct and indirect comparisons evidence certainty

Outcome	Comparison	Direct evidence				Direct evidence certainty	Indirect evidence comparison from the closest loop	Indirect evidence comparison from the closest loop	Lowest between both	Intransitivity	Incoherence for NMA	Imprecision for NMA	Final certainty
		Risk of bias	Inconsistency	Indirectness	Publication Bias								
Color change (ΔE^*)	6% HP strip (> 14h) vs Placebo	Serious ^a	N/A	Not serious	Not serious	Mode rate	At home 10% CP (> 14h) vs 6% HP strip (> 14h)	At home 10% CP (> 14h) vs Placebo	Mode rate	Not serious	Not serious	Very serious ^b	Very low
	At home 10% CP (> 14h) vs Placebo	Not serious	N/A	Not serious	Not serious	High	At home 10% CP (> 14h) vs 6% HP strip (> 14h)	6% HP strip (> 14h) vs Placebo	Mode rate	Not serious	Not serious	Very serious ^b	Very low
	At home 10% CP (> 14h) vs 6% HP strip (> 14h)	Serious ^a	N/A	Not serious	Not serious	Mode rate	At home 10% CP (> 14h) vs Placebo	6% HP strip (> 14h) vs Placebo	Mode rate	Not serious	Not serious	Very serious ^b	Very low
	3% HP paint-on gel (> 14h) vs Placebo	Not serious	N/A	Not serious	Not serious	High	3% HP strip (> 14h) vs 3% HP paint-on gel (> 14h)	3% HP strip (> 14h) vs Placebo	High	Not serious	Not serious	Very serious ^b	Low
	3% HP paint-on gel (> 14h) vs at home 10% CP (>14h)	Not serious	N/A	Not serious	Not serious	High	3% HP strip (> 14h) vs at home 10% CP (>14h)	3% HP strip (> 14h) vs 3% HP paint-on gel (> 14h)	High	Not serious	Not serious	Very serious ^b	Low
	3% HP strip (> 14h) vs Placebo	Not serious	N/A	Not serious	Not serious	High	3% HP paint-on gel (> 14h) vs Placebo	3% HP strip (> 14h) vs 3% HP paint-on gel (> 14h)	High	Not serious	Not serious	Very serious ^b	Low
	3% HP strip (> 14h) vs at home 10% CP (>14h)	Not serious	N/A	Not serious	Not serious	High	3% HP strip (> 14h) vs 3% HP paint-on gel (> 14h)	3% HP paint-on gel (> 14h) vs at home 10% CP (>14h)	High	Not serious	Not serious	Very serious ^b	Low
	3% HP strip (> 14h) vs 3% HP paint-on gel (> 14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	3% HP paint-	-	-	-	-	-	3% HP paint-	6% HP strip (>	Mode rate	Not serious	N/A	Very serious ^b	Very Low

	on gel (> 14h) vs 6% HP strip (> 14h)						on gel (> 14h) vs Placebo	14h) vs Placebo					
	6% HP strip (> 14h) vs 3% HP strip (> 14h)	-	-	-	-	-	6% HP strip (> 14h) vs Placebo	3% HP strip (> 14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very Low
Color change (ΔSGU)	At home 10% CP (> 14h) vs Placebo	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	At home 10% CP (> 14h) vs 6% HP strip (14h)	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very Low
	6% HP painted on gel (7 – 14h) vs Placebo	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very Low
	3% HP painted on gel (> 14h) vs Placebo	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	3% HP painted on gel (> 14h) vs at home 10% CP (> 14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	3% HP strip (>14h) vs Placebo	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	3% HP strip (> 14h) vs at home 10% CP (> 14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	3% HP strip (> 14h) vs 3% HP painted on gel (> 14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	At home 10% CP (> 14h) vs 6% HP painted-on gel (7 – 14h)	-	-	-	-	-	At home 10% CP (> 14h) vs Placebo	6% HP painted on gel (7 – 14h) vs Placebo	Mode rate	Not serious	-	Very serious ^b	Very Low
	6% HP strip (> 14h) vs	-	-	-	-	-	At home 10%	3% HP strip (> 14h) vs	Mode rate	Not serious	-	Very serious ^b	Very Low

	3% HP strip (>14h)						CP (>14h) vs 6% HP strip (14h)	at home 10% CP (>14h)					
	6% HP strip (>14h) vs 3% HP paint-on gel (>14h)	-	-	-	-	-	At home 10% CP (>14h) vs 6% HP strip (14h)	3% HP painted on gel (>14h) vs at home 10% CP (>14h)	Mode rate	Not serious	-	Very serious ^b	Very Low
	6% HP strip (>14h) vs 6% HP paint-on gel (7-14h)	-	-	-	-	-	At home 10% CP (>14h) vs 6% HP strip (14h)	At home 10% CP (>14h) vs 6% HP painted-on gel (17-14h)	Very Low	Not serious	-	Very serious ^b	Very Low
	6% HP strip (>14h) vs placebo	-	-	-	-	-	At home 10% CP (>14h) vs 6% HP strip (14h)	At home 10% CP (>14h) vs Placebo	Mode rate	Not serious	-	Very serious ^b	Very Low
	3% HP paint-on gel (>14h) vs 6% HP paint-on gel (7-14h)	-	-	-	-	-	3% HP painted on gel (>14h) vs Placebo	6% HP paint-on gel (7-14h) vs Placebo	Mode rate	Not serious	-	Very serious ^b	Very Low
	3% HP strip (>14h) vs 6% HP paint-on gel (7-14h)	-	-	-	-	-	3% HP painted on gel (>14h) vs Placebo	6% HP painted on gel (7-14h) vs Placebo	Mode rate	Not serious	-	Very serious ^b	Very Low
Tooth sensitivity	6% HP strip (7-14h) vs Placebo	Serious ^a	Not serious	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very low
	6% HP strip (7-14h) vs at home 10% CP (7-14h)	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-		Very serious ^b	Very low
	6% HP strip (7-14h) vs at home 6% HP paint-on gel (>14h)	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very low
	6% HP strip (7-14h) vs 10% OTC bleaching gel (7-14h)	-	-	-	-	-	6% HP strip (7-14h) vs Placebo	10% OTC bleaching gel (7-14h) vs Placebo	Very low	Not serious	N/A	Very serious ^b	Very low

	6% HP strip (7-14h) vs 6-9% OTC bleaching gel (7-14h)	-	-	-	-	-	6% HP strip (7-14h) vs Placebo	6-9% OTC bleaching gel (7-14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6% HP strip (7-14h) vs at home 10% HP (7-14h)	-	-	-	-	-	6% HP strip (7-14h) vs Placebo	At home 10% HP (7-14h) vs placebo	Very low	Not serious	N/A	Very serious ^b	Very low
	6% HP strip (7-14h) vs 10% HP strip (>14h)	-	-	-	-	-	6% HP strip (7-14h) vs Placebo	10% HP strip (>14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6% HP strip (7-14h) vs 10% HP strip (7-14h)	-	-	-	-	-	6% HP strip (7-14h) vs Placebo	10% HP strip (7-14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	10% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	10% OTC bleaching gel (7-14h) vs at home 10% HP (7-14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	10% OTC bleaching gel (7-14h) vs 6-9% OTC bleaching gel (7-14h)	-	-	-	-	-	10% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	6-9% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	Mode rate	Not serious	N/A	Very serious ^b	Very low
	10% OTC bleaching gel (7-14h) vs 6% paint-on gel (14h)	-	-	-	-	-	6% HP strip (7-14h) vs 6-9% OTC bleaching gel (7-14h)	6% HP strip (7-14h) vs at home 6% HP paint-on gel (>14h)	Very low	Not serious	N/A	Very serious ^b	Very low
	10% OTC bleaching gel (7-14h) vs at home 10% CP (7-14h)	-	-	-	-	-	10% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	At home 10% CP (7-14h) vs 10% HP strip (7-14h)	Very low	Not serious	N/A	Very serious ^b	Very low
	10% OTC	-	-	-	-	-	10% OTC	At home	Mode rate	Not serious	N/A	Very serious ^b	Very low

	bleaching gel (7-14h) vs 10% HP strip (>14h)						bleaching gel (7-14h) vs at home 10% HP (7-14h)	10% HP (7-14h) vs 14% HP strip (>14h)					
	10% OTC bleaching gel (7-14h) vs Placebo	-	-	-	-	-	10% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	10% HP strip (7-14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6-9% OTC bleaching gel (7-14h) vs Placebo	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very low
	6-9% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very low
	6-9% OTC bleaching gel (7-14h) vs 6% HP paint-on gel (>14h)	-	-	-	-	-	6-9% OTC bleaching gel (7-14h) vs Placebo	6% HP paint-on gel (> 14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6-9% OTC bleaching gel (7-14h) vs at home 10% HP (7-14h)	-	-	-	-	-	6-9% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	At home 10% HP (7-14h) vs 10% HP strip (7-14h)	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6-9% OTC bleaching gel (7-14h) vs at home 10% CP (7-14h)	-	-	-	-	-	6-9% OTC bleaching gel (7-14h) vs Placebo	At home 10% CP (7-14h) vs placebo	Very low	Not serious	N/A	Very serious ^b	Very low
	6-9% OTC bleaching gel (7-14h) vs 10% HP strip (>14h)	-	-	-	-	-	6-9% OTC bleaching gel (7-14h) vs Placebo	10% HP strip (>14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6% HP paint-on gel (> 14h) vs Placebo	Serious ^a	N/A	Not serious	Not serious	Mode rate	-	-	-	-	-	Very serious ^b	Very low

	6% HP paint-on gel (> 14h) vs at home 10% HP (7-14h)	-	-	-	-	-	6% HP paint-on gel (> 14h) vs Placebo	At home 10% HP (7-14h) vs placebo	Very low	Not serious	N/A	Very serious ^b	Very low
	6% HP paint-on gel (> 14h) vs at home 10% CP (7-14h)	-	-	-	-	-	6% HP strip (7-14h) vs at home 10% CP (7-14h)	6% HP strip (7-14h) vs at home 6% HP paint-on gel (>14h)	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6% HP paint-on gel (> 14h) vs 10% HP strip (>14h)	-	-	-	-	-	6% HP paint-on gel (> 14h) vs Placebo	10% HP strip (>14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	6% HP paint-on gel (> 14h) vs 10% HP strip (7-14h)	-	-	-	-	-	6% HP paint-on gel (> 14h) vs Placebo	10% HP strip (7-14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	At home 10% HP (7-14h) vs at home 10% CP (7-14h)	-	-	-	-	-	At home 10% HP (7-14h) vs 14% HP strip (>14h)	At home 10% CP (7-14h) vs 14% HP strip (>14h)	Very low	Not serious	N/A	Very serious ^b	Very low
	At home 10% HP (7-14h) vs 10% HP strip (>14h)	-	-	-	-	-	At home 10% HP (7-14h) vs 14% HP strip (>14h)	14% HP strip (>14h) vs 10% HP strip (>14h)	Very low	Not serious	N/A	Very serious ^b	Very low
	At home 10% HP (7-14h) vs 10% HP strip (7-14h)	Not serious	N/A	Not serious	Not serious	High	-	-	-	-	-	Very serious ^b	Low
	At home 10% HP (7-14h) vs placebo	-	-	-	-	-	At home 10% HP (7-14h) vs 10% HP strip (7-14h)	10% HP strip (7-14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	At home 10% CP (7-14h) vs 10% HP strip (7-14h)	-	-	-	-	-	6% HP strip (7-14h) vs at home 10% CP (7-14h)	6% HP strip (7-14h) vs 10% HP strip (7-14h)	Very low	Not serious	N/A	Very serious ^b	Very low
	At home	-	-	-	-	-	6% HP strip	6% HP strip	Very low	Not serious	N/A	Very serious ^b	Very low

	10% CP (7-14h) vs 10% HP strip (>14h)						(7-14h) vs at home 10% CP (7 - 14h)	(7-14h) vs 10% HP strip (>14h)					
	At home 10% CP (7-14h) vs placebo	-	-	-	-	-	6% HP strip (7-14h) vs at home 10% CP (7 - 14h)	6% HP strip (7-14h) vs placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	10% HP strip (>14h) vs Placebo	Serious ^a	N/A	Not serious	Not serious	Mode rate	10% HP strip (>14h) vs 10% HP strip (< 7h)	10% HP strip (<7h) vs Placebo	Very low	Not serious	Not serious	Very serious ^b	Very low
	10% HP strip (>14h) vs 10% HP strip (7-14h)	-	-	-	-	-	10% HP strip (>14h) vs Placebo	10% HP strip (7 - 14h) vs Placebo	Mode rate	Not serious	N/A	Very serious ^b	Very low
	10% HP strip (7 - 14h) vs Placebo	Serious ^a	N/A	Not serious	Not serious	Mode rate	6-9% OTC bleaching gel (7-14h) vs 10% HP strip (7-14h)	6-9% OTC bleaching gel (7-14h) vs Placebo	Mode rate	Not serious	Not serious	Very serious ^b	Very low

N/A – not applicable. a - If there were important limitations in the trials (eg, problems in the randomization process and lack of blinding.) but the risk of bias was not high, we downgraded by 1 level. b - Certainty of evidence was downgraded by two levels because the total number of events was less than 300, and the 95%C.I. crosses the threshold of null effect and appreciable benefit or appreciable harm (SMD > 0.8 or < - 0.8). c - Downgraded by 2 levels if more than 50% of the participants were from trials with a high risk of bias. d – Absence of overlap of confidence intervals.

**Artigo 2 – Artigo a ser submetido na revista Dental Press Journal of Orthodontics
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**Impact of over-the-counter bleaching products on teeth with orthodontic brackets:
an *in vitro* assessment of optical properties - part I**

ABSTRACT

This *in vitro* study evaluated the impact of over-the-counter (OTC) products on the optical properties (color and gloss changes) of teeth subjected to a simulated orthodontic treatment. Thus, 80 bovine teeth were selected and subjected to a staining protocol and initial color and surface roughness assessments. Then, orthodontic brackets were bonded on the center of the clinical crown of each sample, and teeth underwent the bleaching protocols. The samples were allocated to five groups (n=16): Conventional in-office bleaching 35% Hydrogen peroxide (HP) - positive control; Dentifrice with 2% HP; Mouthwash with 2.5% HP; Paint-on with 6% HP; Conventional dentifrice without HP - negative control. After receiving the bleaching protocol, the samples underwent the shear bond strength test for orthodontic bracket removal. The remaining resin was then removed from the sample surfaces using multi-blade burs. The statistical assessment detected a significant difference between the groups for color change (ΔE_{ab} – $p = 0.0000532$; ΔE_{00} – $p = 0.000069$). Multiple comparison analyses showed significant differences ($p < 0.05$) in both metrics between groups DHP vs. MouHP, DSHP vs. MouHP, DHP vs. HP35, and DSHP vs. HP35. The statistical test did not detect a significant difference in post-bleaching gloss increase between the experimental groups ($p = 0.20$). Except for dentifrices, the color change outcomes of the evaluated OTC bleaching treatments were as satisfactory as in-office bleaching, without differences between groups for gloss change.

INTRODUCTION

Hydrogen peroxide (H_2O_2) is the main active ingredient of tooth-bleaching products ^{1,2}. Tooth bleaching is little invasive, well accepted by most patients, and presents satisfactory color change outcomes with few adverse effects when correctly

supervised by a dentist ^{3,4}. The success of these bleaching agents depends on their concentration and action time in contact with the tooth surface ⁵.

However, some products available in the market are sold without requiring the supervision of a dental professional, promising fast, effective, and inexpensive tooth bleaching ⁶. These products are known as over-the-counter (OTC), among which gels, dentifrices, mouthwashes, Whitestrips, and paint-on stand out. They are often marketed without the required research to assess efficacy and potential adverse effects ^{7,8}.

The high marketing investments in these products, associated with the unbridled search for esthetics, make patients attracted to the easy offer of changing the color of teeth, even without scientific proof of their effectiveness ^{7,9}. That occurs particularly when patients' self-esteem might be already affected, such as during orthodontic treatments with conventional fixed appliances ^{10,9}.

The optimal time to perform a bleaching treatment is after ending orthodontic therapy because, during the latter, teeth may be overlapped or disharmoniously intruded, which would cause more color change in some teeth than others. Moreover, the brackets reduce the contact area between the dental surface and the bleaching agent, and conventional fixed appliances favor plaque buildup, harming the efficacy of the bleaching treatment ¹¹. However, if supervised by a dentist, tooth bleaching may promote satisfactory outcomes in patients undergoing orthodontic treatment ¹². This study considers that patients using conventional orthodontic appliances seek OTC products because of their easy access.

Therefore, an *in vitro* assessment of the changes in optical properties (color and gloss) of different OTC products containing hydrogen peroxide were performed in bovine tooth samples with orthodontic brackets cemented on their buccal surface, simulating a conventional fixed appliance treatment. The study used the null hypothesis that the groups would not statistically differ.

METHODOLOGY

Study design and sample size:

The study design followed the CRIS (Checklist for Reporting *In vitro* Studies) tool guidelines ¹³, according to the recommendations for *in vitro* studies. The bovine tooth samples originated from slaughterhouse donations, exempting them from the ethical committee approval for animal testing. All tests followed the scientific requirements and research protocols established by the World Medical Association Declaration of Helsinki.

The sample size calculation was based on the experimental design and the primary study outcome (ΔE_{ab}), using the following parameters: 5% two-tailed significance level ($\alpha = 0.05$), 95% confidence interval, 90% statistical power ($\beta = 0.10$), 1:1 sample allocation ratio to experimental groups, and a large estimated effect size ($d = 0.80$), indicating the need for including at least 16 samples in each group, totaling 80 samples, based on Torres et al. (2013).

Sample selection and preparation:

After extraction, the bovine incisors were cleaned with periodontal curettes and stored in distilled water. Teeth selection followed the eligibility criteria: 1. Healthy permanent incisors; 2. Teeth without fractures in the coronal region; 3. The absence of macroscopically visible enamel cracks. The excluded teeth were discarded properly as biological materials. The initial color assessment had the samples cleaned, polished with pumice, and extrinsically stained by black coffee immersion for three days, replacing the solution every 24 hours and preparing it according to the manufacturer's instructions by diluting two teaspoons of powder (Nescafé®, Nestlé, São Paulo, SP, Brazil) in 100 ml of boiling water¹⁴. After finishing the staining protocol, the samples were cleaned in running water to remove the excess coffee and dried at room temperature for six hours. A diamond disc (American Burrs, Palhoça, SC, Brazil) helped remove the roots, and the samples were stabilized by the palatal surface in a colorless acrylic resin base (VIPI FLASH, Pirassununga, SP, Brazil) made with a polyvinyl chloride (PVC) tube (Conexões Tigre, Joinville, SC, Brazil) of 12 mm in diameter, completely exposing the buccal aspect of the crown. **Figure 1** shows the samples.

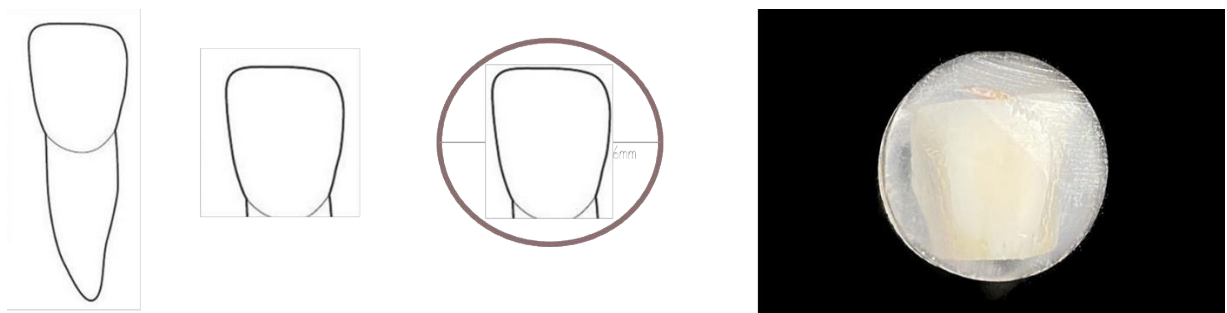


Figure 1: Samples prepared before bracket bonding.

Color assessment:

A reflectance spectrophotometer (Ci64UV, X-Rite, Grand Rapids, MI, USA) evaluated sample colors. This device has an opening diameter of 4 mm, and the readings

occurred at a 2° observation angle and illuminant D65. The LAB system coordinates of the *Commission Internationale de L'Eclairage* (CIE) were recorded. This system consists of luminosity (L* coordinate) and a* (red-green axis) and b* (yellow-blue axis) chromaticity coordinates. The color was measured at baseline (T0) and 72 hours after finishing the bleaching treatment (T1); the samples were stored in distilled water during that period. Color measurements occurred in triplicate on a white background (ColorChecker grayscale, X-Rite, Grand Rapids, MI, USA, L*white = 95.2, a*white = 21.2, b*white = 50.3), and the data analysis used the mean values of the three assessments. The CIEDE2000 color difference (ΔE_{00}) calculated the overall color changes between T0 and T1 as follows: $\Delta E_{00} = [(\Delta L / KLSL)^2 + (\Delta C / KCSC)^2 + (\Delta H / KHSH)^2 + RT (\Delta C / KCSC) (\Delta H / KHSH)]^{1/2}$, where ΔL , ΔC , and ΔH are luminosity, chroma, and hue differences between the measured colors; KL, KC, and KH are the parametric factors for visualization conditions and the influence of lighting conditions; RT is the interaction function of hue and chroma differences in the blue region; SL, SC, and SH are the weighing functions for color difference adjustments considering the variation of L*, a*, and b* coordinate locations (18). ΔE_{ab} was calculated with the formula $\Delta E_{ab} = [\Delta L^2 + \Delta a^2 + \Delta b^2]^{1/2}$.

Gloss assessment:

A gloss meter device (Microgloss, BYK, Geretsried, Germany) helped evaluate gloss, using a square area of 2 mm x 2 mm and 45° of incidence. Gloss measurements are expressed in gloss units (GU). A surface that does not reflect gloss has 0 GU and a glass surface with 1567 refraction has 100 GU. The mean of three measurements provided the result. The assessment occurred at baseline (T0) and 72 hours after finishing the treatment (T1).

Bracket bonding:

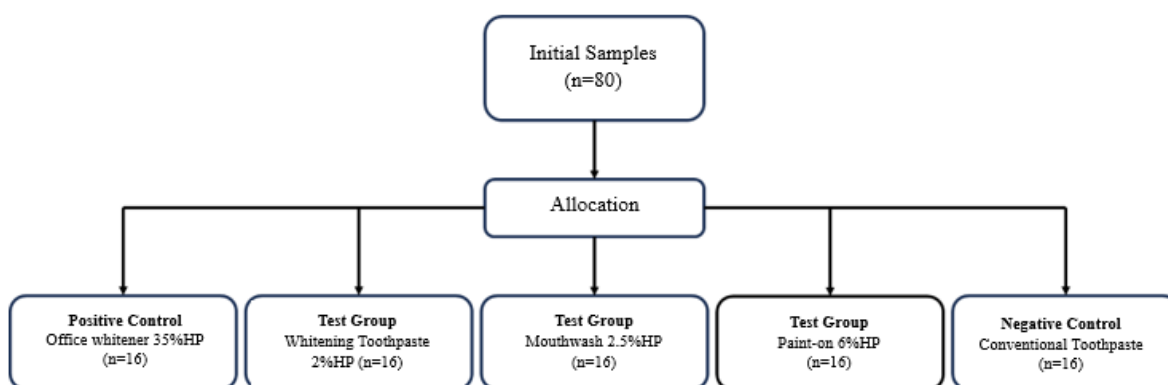
Eighty metal brackets with an area of 6 mm² (Kirium U1R Roth 022; Abzil 3M, São José do Rio Preto, SP, Brazil) were cemented on the center of the clinical crown of the samples. The region delimited by the mold was etched with 37% phosphoric acid (Alpha-Etch; Nova DFL, Rio de Janeiro, RJ, Brazil) for 30 seconds according to the manufacturer's specifications, then washed with water for 30 seconds and dried by air spray. Next, an adhesive layer (Scotchbond; 3M Unitek, Sumaré, SP, Brazil) was light-cured for 20 seconds according to the manufacturer's instructions (Valo – Ultradent,

Indaiatuba, SP, Brazil) and applied. A composite resin layer (Transbond™ XT, Sumaré, SP, Brazil) was then spread under the metal bracket base placed on the tooth surface aided by orthodontic tweezers. After a quick three-second light-curing, the excess resin was removed from the dental surface aided by a spatula (Golgran, São Caetano do Sul, SP, Brazil). Then, a final light-curing was performed for 20 seconds.

Bleaching treatment:

A blind evaluator allocated the samples to five groups using randomization software (www.random.org). Group HP35 underwent an in-office bleaching simulation using 35% hydrogen peroxide gel (Whiteness HP – FGM, Joinville, SC, Brazil) applied on the buccal surface of the samples with the help of a brush. Three 45-minute sessions (three 15-minute applications according to the product manufacturer's recommendations) occurred with a 48-hour interval between sessions, establishing the positive control group. Group DHP experienced bleaching with a dentifrice containing 2% hydrogen peroxide (Colgate Luminous White Advanced - Colgate - São Paulo, SP, Brazil). The samples were taken to the toothbrushing machine programmed to perform 60 reciprocating brushing movements per minute with a 200g load. This process accomplished 850 cycles, simulating approximately 180 toothbrushing days using soft-bristle toothbrushes (Colgate Classic – Colgate, São Paulo, SP, Brazil). Group MouHP underwent a simulated treatment with a mouthwash containing 2.5% hydrogen peroxide (Listerine Whitening Extreme – Johnson and Johnson, São José dos Campos, SP, Brazil). The samples were immersed in a recipient with mouthwash for 12 hours, simulating 12 months of use. The mouthwash was replaced every hour, and the samples were washed in running water at each exchange. Group PON underwent treatment using paint-on gel containing 6% hydrogen peroxide (Whitening Pen – Dazzling White, Guangzhou, China). The samples received the product in daily 10-minute applications for 14 days. Group DSHP underwent treatment using a conventional dentifrice (Colgate Total 12 - Colgate - São Paulo, SP, Brazil) without hydrogen peroxide. The samples were taken to a toothbrushing machine under the same settings of group DHP, simulating a 180-day treatment, establishing the negative control. The samples were stored in distilled water while not subjected to bleaching agents. Figure 2 exemplifies the allocation of samples.

Figure 2: Flowchart of sample allocations.



Initial samples (n=80) / Allocation / **Positive control** – 35% HP in-office bleaching (n=16) / **Test group** – 2% HP bleaching dentifrice (n=16) / **Test group** – 2.5% HP mouthwash (n=16) / **Test group** – 6% HP paint-on (n=16) / **Negative control** – Conventional dentifrice (n=16).

Bracket removal:

After ending the bleaching treatment, a shearing machine (EMIC DL-1000, Uberlândia, MG, Brazil) helped remove the brackets from the samples. This equipment used a 1kN cell and an active chiseled tip placed between enamel and resin, and the speed was 0.5 mm/min. After bracket removal, a multi-blade bur helped eliminate the excess surface resin to remove the orthodontic adhesive (Orthometric, Marília, SP, Brazil).

Data analysis:

A blinded participant performed the statistical analysis. The data were analyzed with R software, version 4.3.0, aided by the stats, rstatix, and ggplot2 packages. The Shapiro-Wilk and Bartlett tests evaluated the normality and homogeneity of data variance, respectively. The data from color change analyses (ΔE_{00}) presented a non-normal distribution ($p < 0.05$); hence, Kruskal-Wallis with Dunn post-hoc test and Bonferroni correction compared the groups. ANOVA compared the means of post-bleaching gloss increase in each experimental group. All analyses used a 5% significance level.

RESULTS

The analyses included the data from all specimens. The Kruskal-Wallis test detected a significant difference between the groups (ΔE_{00} – $p = 0.000069$). Multiple comparison analyses showed significant differences ($p < 0.05$) between groups DHP vs. MouHP, DSHP vs. MouHP, DHP vs. HP35, and DSHP vs. HP35 (Table 1, Figure 2). ANOVA did not detect a significant difference in the post-bleaching gloss increase between the experimental groups ($F(4.75) = 1.53$, $p = 0.20$) (Table 2, Figure 3).

Table 1. Comparison between groups for $\Delta E00$ and ΔEab values.

Groups	$\Delta E00$ (median, minimum-maximum value)	ΔEab (median, minimum-maximum value)
HP35	11.09 (6.17 – 12.60) ^A	16,38 (8,87 – 18,50)A
MouHP	10.47 (8.01 – 13.81) ^A	15,26 (11,41 - 19,46)A
DSHP	8.49 (4.15 – 12.47) ^B	11,45 (6,04 – 17,45)B
DHP	7.75 (2.06 – 10.83) ^B	11,17 (2,67 – 16,12)B
PON	10.24 (1.99 – 12.92) ^{AB}	14,40 (2,20 – 18,60)AB

Figure 3. Boxplots of the comparisons between groups for $\Delta E00$ values.

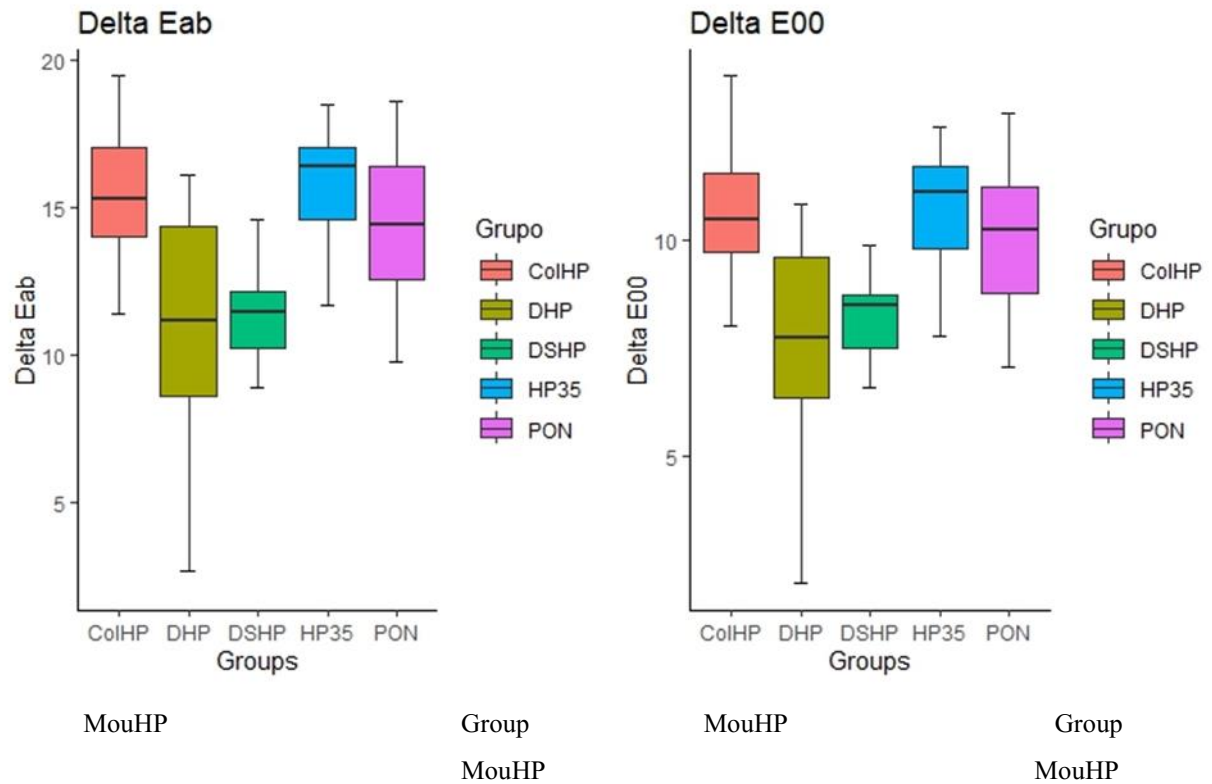
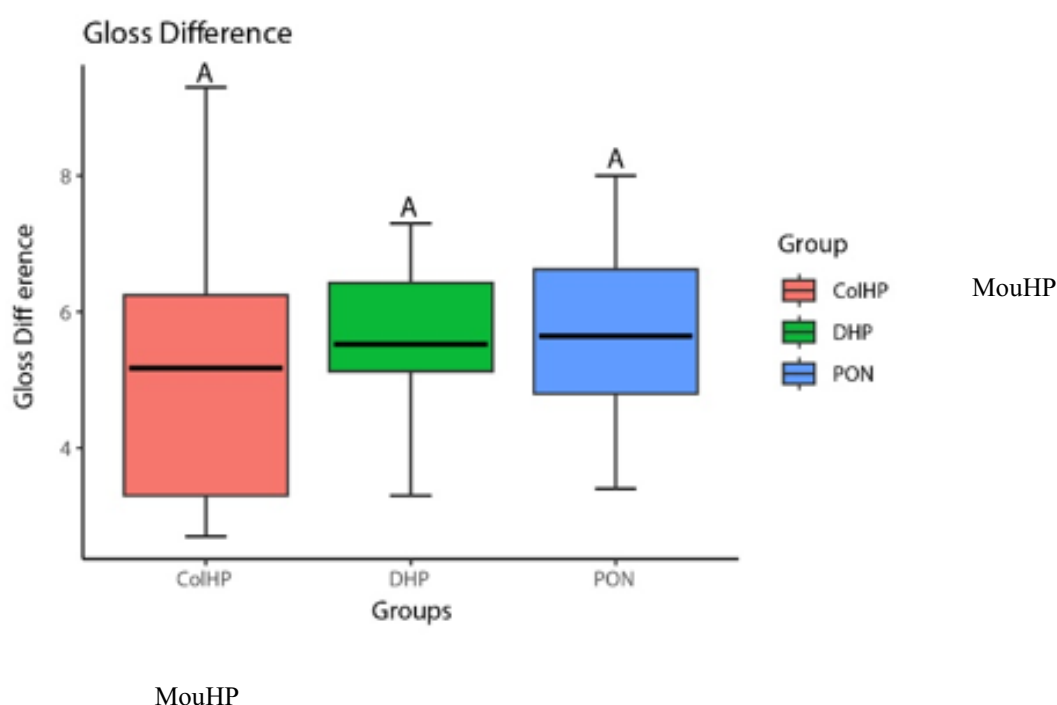


Table 2. Comparison between groups for gloss values.

Groups	Gloss change (mean $\pm$ standard deviation)
HP35	6.39 $\pm$ 1.20 ^A
MouHP	5.17 $\pm$ 2.06 ^A
DSHP	5.76 $\pm$ 1.14 ^A
DHP	5.52 $\pm$ 1.32 ^A
PON	5.64 $\pm$ 1.84 ^A

Figure 4. Boxplots of the comparisons between groups for gloss values.

DISCUSSION

Considering the limitations of this study, the initial color change showed a better outcome for groups applying in-office bleaching (35% HP) and mouthwash (2.5% HP) than those using dentifrice (2% HP and without peroxide). This difference may be due to the higher hydrogen peroxide concentration in groups HP35 and MouHP than in DHP and DSHP. The literature indicates a tendency for higher color change in teeth exposed to more concentrated agents ^{15,16} and a higher propensity for sensitivity ^{17,15}. Further clinical trials and a tooth sensitivity assessment should be performed with these products to validate the results.

The color change outcomes were close to other *in vitro* studies using over-the-counter (OTC) products but without orthodontic brackets ^{18,19}. Other *in vitro* studies corroborate these findings, showing that an orthodontic bracket bonded on the buccal surface did not interfere with tooth color change ²⁰. However, the color change between the margins and under the bracket may present statistically significant results, although that difference seems clinically imperceptible ^{21,22}.

It is worth noting that, despite the statistical difference in color change outcomes, the mean of all groups was higher than the color change tolerance index ($\Delta E_{00} > 1.77$) ²³. This finding may be associated with the potential of dentifrices to remove the teeth extrinsic staining, changing the color even without hydrogen peroxide action ²⁴, which shows that the performed treatments were satisfactorily effective for color change, even in the placebo group (DSHP).

Gloss change is related to the light reflected on the enamel surface, and increasing this value benefits esthetic perception because it may give the impression of a bleached tooth ^{25,26}. All groups showed a positive color change in sample gloss without statistical differences between the groups, favoring the color change findings. Gloss is directly related to surface roughness ²⁷, so the increase in sample gloss suggests that the tested bleaching agents did not cause adverse effects on tooth enamel morphology.

A limitation of laboratory studies with OTC products is the impossibility of evaluating gingival irritation caused by these agents. Considering the absence of follow-up by a dentist, the bleaching protocol is not customized, promoting the risk of inadequate product application. The direct contact between the bleaching agent and soft tissues may cause inflammatory reactions because hydrogen peroxide is toxic to the fibroblasts of the gingival tissue, leading to an inflammatory reaction ²⁸. Future clinical studies should also evaluate different bracket materials because metallic brackets may accumulate more plaque than ceramic brackets, potentially causing adverse effects, such as gingival irritation ²⁹.

This study verified several bleaching agents with different application methods, commercialized online, freely, and without requiring follow-up by a dental professional, making it impossible to test all products. We suggest more regulation in commercializing these agents to evaluate the scientific proof of each one before they become available to patients.

Lastly, the agents effectively changed the color of samples, indicating the possibility of further clinical studies, even in patients undergoing orthodontic treatment

who wish to perform tooth bleaching, to correctly map the occurrence of potential adverse effects and allow the assessment of patient satisfaction.

CONCLUSION

Except for dentifrices, the color change outcomes of the evaluated over-the-counter bleaching treatments were as satisfactory as in-office bleaching, without differences between groups for gloss change.

REFERENCES

1. Kawamoto K, Tsujimoto Y. Effects of the hydroxyl radical and hydrogen peroxide on tooth bleaching. *J Endod*. 2004 Jan;30(1):45-50. doi: 10.1097/00004770-200401000-00010. PMID: 14760908.
2. Majeed A, Farooq I, Grobler SR, Rossouw RJ. Tooth-Bleaching: A Review of the Efficacy and Adverse Effects of Various Tooth Whitening Products. *J Coll Physicians Surg Pak*. 2015 Dec;25(12):891-6. PMID: 26691365.
3. Wiegand A, Drebenstedt S, Roos M, Magalhães AC, Attin T. 12-month color stability of enamel, dentine, and enamel-dentine samples after bleaching. *Clin Oral Investig*. 2008 Dec;12(4):303-10. doi: 10.1007/s00784-008-0195-7. Epub 2008 Mar 28. PMID: 18369668.
4. Majeed A, Farooq I, Grobler SR, Rossouw RJ. Tooth-Bleaching: A Review of the Efficacy and Adverse Effects of Various Tooth Whitening Products. *J Coll Physicians Surg Pak*. 2015 Dec;25(12):891-6. PMID: 26691365.
5. Leite TC, Dias KRHC. Efeitos dos agentes clareadores sobre a polpa dental: revisão de literatura. *Rev Bras Odontol*. 2011 Sep;67(2):203.
6. Silva MFR, Tomo S, Oliveira CV, Alves DP, Lima DP, Pires HC. Avaliação in vitro da eficácia de dentifrícios de ação clareadora. *ARCHIV HEALTH INVESTIG*. 2015 Mar-Apr;4(2).
7. Marco FF, Meireles SS, Masotti AS. Over-the-counter whitening agents: a concise review. *Braz Oral Res*. 2009 Jun;23:64-70. doi: 10.1590/s1806-83242009000500010. PMID: 19838560.
8. Greenwall-Cohen J, Francois P, Silikas N, Greenwall L, Le Goff S, Attal JP. The safety and efficacy of 'over the counter' bleaching products in the UK. *Br Dent J*. 2019 Feb;226(4):271-276. doi: 10.1038/s41415-019-0011-6. PMID: 30787399.

9. Freitas MR, de Carvalho MM, Liporoni PCS, Fort ACB, Moura RDME, Zanatta RF. Effectiveness and adverse effects of over-the-counter whitening products on dental tissues. *Front Dent Medic*. 2021 Jun;2:687507.
10. Consolaro A, Francischone LA, Consolaro RB. Tooth whitening products in toothpastes and mouthwashes may act as co-carcinogens in the oral mucosa: how to advise orthodontic patients and how to avoid undesirable effects. *Dent Press J Orthodont*. 2011 Apr;16:28-35.
11. Consolaro A, Consolaro RB, Francischone L. Clarifications, guidelines and questions about the dental bleaching "associated" with orthodontic treatment. *Dental Press J Orthod*. 2013 Sep-Oct;18(5):4-10. doi: 10.1590/s2176-94512013000500002. PMID: 24352384.
12. Jadad E, Montoya J, Arana G, Gordillo LA, Palo RM, Loguercio AD. Spectrophotometric evaluation of color alterations with a new dental bleaching product in patients wearing orthodontic appliances. *Am J Orthod Dentofacial Orthop*. 2011 Jul;140(1):e43-7. doi: 10.1016/j.ajodo.2010.11.021. PMID: 21724070.
13. Krithikadatta J, Gopikrishna V, Datta M. CRIS Guidelines (Checklist for Reporting In-vitro Studies): A concept note on the need for standardized guidelines for improving quality and transparency in reporting in-vitro studies in experimental dental research. *J Conserv Dent*. 2014 Jul;17(4):301-4. doi: 10.4103/0972-0707.136338. PMID: 25125839; PMCID: PMC4127685.
14. Torres CR, Perote LC, Gutierrez NC, Pucci CR, Borges AB. Efficacy of mouth rinses and toothpaste on tooth whitening. *Oper Dent*. 2013 Jan-Feb;38(1):57-62. doi: 10.2341/11-360-L. Epub 2012 Jul 7. PMID: 22770430.
15. Peixoto AC, Vaez SC, Pereira NAR, Santana CNDS, Soares KDA, Romão ACTR, Ferreira LF, Martins-Filho PRS, Faria-E-Silva AL. High-concentration carbamide peroxide can reduce the sensitivity caused by in-office tooth bleaching: a single-blinded randomized controlled trial. *J Appl Oral Sci*. 2018;26:e20170573. doi: 10.1590/1678-7757-2017-0573. Epub 2018 May 7. PMID: 30084472; PMCID: PMC6007969.
16. Lima SNL, Ribeiro IS, Grisotto MA, Fernandes ES, Hass V, de Jesus Tavares RR, Pinto SCS, Lima DM, Loguercio AD, Bandeca MC. Evaluation of several clinical parameters after bleaching with hydrogen peroxide at different concentrations: A randomized clinical trial. *J Dent*. 2018 Jan;68:91-97. doi: 10.1016/j.jdent.2017.11.008. Epub 2017 Nov 21. PMID: 29169968.

17. Maran BM, Matos TP, Castro AS, Vochikovski L, Amadori AL, Loguercio AD, Reis A, Berger SB. In-office bleaching with low/médium vs. High concentrate hydrogen peroxide: A Systematic review and meta-analysis. *J Dentist*. 2020 Oct;103:103499.
18. Lima FG, Rotta TA, Penso S, Meireles SS, Demarco FF. In vitro evaluation of the whitening effect of mouth rinses containing hydrogen peroxide. *Braz oral res*. 2012 May;26(3):269–74. Available from: <https://doi.org/10.1590/S1806-83242012000300014>
19. Karadas M, Duymus ZY. In Vitro Evaluation of the Efficacy of Different Over-the-Counter Products on Tooth Whitening. *Braz Dent J*. 2015Jul;26(4):373–7. Available from: <https://doi.org/10.1590/0103-64402013x0111>
20. Oliveira LGS, Francisconi-Dos-Rios LF, Martins LM, Nahsan FPS. Can the efficacy of in-office tooth bleaching change in the presence of orthodontic brackets? An in vitro study. *Resear Soc and Develop*. 2021 Apr;10(4):e12410413513. DOI: 10.33448/rsd-v10i4.13513.
21. Lunardi N, Correr AB, Rastelli AN, Lima DA, Consani RL. Spectrophotometric evaluation of dental bleaching under orthodontic bracket in enamel and dentin. *J Clin Exp Dent*. 2014 Oct 1;6(4):e321-6. doi: 10.4317/jced.51168. PMID: 25593650; PMCID: PMC4282895.
22. Pinzan-Vercelino CRM, Lima SNL, Pereira FFJV, Gurgel JA, Silva GRD, Freitas KMSD. Efficacy of products for bleaching and whitening under orthodontic brackets. *Dental Press J Orthod [Internet]*. 2022 Nov;27(5):e2220325. Available from: <https://doi.org/10.1590/2177-6709.27.5.e2220325.oa>
23. Paravina RD, Ghinea R, Herrera LJ, Bona AD, Igiel C, Linninger M, Sakai M, Takahashi H, Tashkandi E, Perez Mdel M. Color difference thresholds in dentistry. *J Esthet Restor Dent*. 2015 Mar-Apr;27 Suppl 1:S1-9. doi: 10.1111/jerd.12149. Epub 2015 Apr 17. PMID: 25886208.
24. Shinde SV, Patil Y, Madhu PP, Bhatnagar A, Khurana C, Bhargava A. An overview: insight of dental bleaching agents. *J Med Pharmaceu Allied Sci*. 2021 Jul-Aug;10(4):3182-6.
25. Scrinzi E, Rossi S. (2010). The aesthetic and functional properties of enamel coatings on steel. *Mater & Design*. 2010 Oct;31(9):4138-4146.
26. Alshali RZ, AlQahtani MA, Bukhary DM, Alzahrani MA, Alsoraihi SS, Alqahtani MA. The effect of bleaching on surface roughness and gloss of different CAD/CAM

- ceramic and hybrid ceramic materials. *J Appl Biomater Funct Mater*. 2023 Jan-Dec;21:22808000231152566. doi: 10.1177/22808000231152566. PMID: 36785513.
27. Rocha RS, Fagundes TC, Caneppele T, Bresciani E. Perceptibility and Acceptability of Surface Gloss Variations in Dentistry. *Oper Dent*. 2020 Mar/Apr;45(2):134-142. doi: 10.2341/18-184-C. Epub 2019 Aug 2. PMID: 31373888.
 28. Furukawa M, K-Kaneyama JR, Yamada M, Senda A, Manabe A, Miyazaki A. Cytotoxic Effects of Hydrogen Peroxide on Human Gingival Fibroblasts In Vitro. *Oper Dent*. 2015 Jul-Aug;40(4):430-9. doi: 10.2341/14-059-L. Epub 2015 Jan 9. PMID: 25575199.
 29. Lindel ID, Elter C, Heuer W, Heidenblut T, Stiesch M, Schwestka-Polly R, Demling AP. Comparative analysis of long-term biofilm formation on metal and ceramic brackets. *Angle Orthod*. 2011 Sep;81(5):907-14. doi: 10.2319/102210-616.1. Epub 2011 May 4. PMID: 21542722; PMCID: PMC8916195.

**Artigo 3 - Artigo a ser submetido na revista Dental Press Journal of Orthodontics
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**Impact of over-the-counter bleaching products on teeth with orthodontic brackets:
an *in vitro* assessment of mechanical properties - part II**

ABSTRACT

This *in vitro* study evaluated the impact of over-the-counter (OTC) products on the mechanical properties (surface roughness and shear bond strength) of tooth enamel. Thus, 80 bovine teeth were selected and subjected to a staining protocol and initial surface roughness assessment. Then, orthodontic brackets were bonded on the center of the clinical crown of each sample, and teeth underwent the bleaching protocols. The samples were allocated to five groups (n=16): Conventional in-office bleaching 35% Hydrogen peroxide (HP) - positive control; Dentifrice with 2% HP; Mouthwash with 2.5% HP; Paint-on with 6% HP; Conventional dentifrice without HP - negative control. After receiving the bleaching protocol, the samples underwent the shear strength test for orthodontic bracket removal. The remaining resin was then removed from the sample surfaces using multi-blade burs, and the final roughness was assessed under the sample center. The statistical assessment did not detect a significant difference between the experimental groups for shear assessment ($p = 0.14$). As for surface roughness, the statistical test detected a significant difference between group means ($p = 0.007$). Pairwise comparisons with Tukey's post hoc test identified a significant difference only between groups DSHP and HP35 ($p = 0.008$). The group using dentifrice without peroxide presented higher surface roughness change. The study suggests that the evaluated OTC products did not influence the bond strength of orthodontic brackets to teeth or enamel roughness change.

INTRODUCTION

Over-the-counter (OTC) products appeared in the early 2000s in the United States as an alternative for patients who could not afford a dentist but sought bleaching treatments ¹. These products have a low hydrogen peroxide concentration and may be sold without a prescription from a dental professional, depending on the legislation of each country ².

The association between whiter teeth and the image of an ideal smile, associated with the increasing esthetic pressure, directly affects psychological factors and patients' quality of life, also potentially affecting patients whose self-esteem might be already affected, such as during orthodontic treatments ³⁻⁵. The easy acquisition of these products online, combined with intense advertisement, makes these patients attracted to the possibility of tooth bleaching during treatment, even though the literature reports that the optimal time to perform a bleaching protocol is after ending orthodontics ^{6,7}.

Another concern related to bleaching treatment without professional supervision is the morphological change of tooth enamel, as studies indicate an association between bleaching agents and enamel surface roughness changes ^{8,9}. Although these changes are usually reversible through natural saliva remineralization ¹⁰, the outcomes from OTC bleaching agents without scientific proof, combined with their unrestrained use without the supervision of a dental professional, remain uncertain.

Another factor for consideration is the influence of bleaching agents on orthodontic bracket adhesion ¹¹. Although the literature remains unclear about the clinical relevance of the lower adhesion potentially caused by bleaching agent action on the bonding interface ^{12,13}, studies are still scarce regarding the effects of OTC bleaching agents on the adhesion of brackets cemented on the dental structure.

Hydrogen peroxide (H₂O₂) is the primary tooth-bleaching agent. Tooth bleaching is little invasive, well accepted by most patients, and presents satisfactory color change outcomes with few adverse effects when correctly supervised by a dentist ^{14,15}. The success of these bleaching agents depends on their concentration and action time in contact with the dental surface ¹⁶.

Our study considers that patients using conventional orthodontic appliances seek OTC products because of their easy access. Therefore, we performed an *in vitro* assessment of the changes in mechanical properties (roughness and shear) of different OTC products containing hydrogen peroxide in bovine tooth samples with orthodontic brackets bonded on their buccal surface, simulating a conventional fixed appliance treatment. The study used the null hypothesis that the groups would not statistically differ.

METHODOLOGY

Study design and sample size:

The study design followed the CRIS (Checklist for Reporting *In vitro* Studies) tool guidelines ¹⁷, according to the recommendations for *in vitro* studies. The bovine tooth

samples originated from slaughterhouse donations, exempting them from the ethical committee approval for animal testing. All tests followed the scientific requirements and research protocols established by the World Medical Association Declaration of Helsinki. The sample size calculation was based on the experimental design, using the following parameters: 5% two-tailed significance level ($\alpha = 0.05$), 95% confidence interval, 90% statistical power ($\beta = 0.10$), 1:1 sample allocation ratio to experimental groups, and a large estimated effect size ($d = 0.80$), indicating the need for including at least 16 samples in each group, totaling 80 samples, based on Torres et al. (2013).

Sample selection and preparation:

After extraction, the bovine incisors were cleaned with periodontal curettes and stored in distilled water. Teeth selection followed the eligibility criteria: 1. Healthy permanent incisors; 2. Teeth without fractures in the coronal region; 3. The absence of macroscopically visible enamel cracks. The excluded teeth were discarded properly as biological materials. The initial color assessment had the samples cleaned, polished with pumice, and extrinsically stained by black coffee immersion for three days, replacing the solution every 24 hours and preparing it according to the manufacturer's instructions by diluting two teaspoons of powder (Nescafé®, Nestlé, São Paulo, SP, Brazil) in 100 ml of boiling water (Torres et al., 2013). After finishing the staining protocol, the samples were cleaned in running water to remove the excess coffee and dried at room temperature for six hours. A diamond disc (American Burrs, Palhoça, SC, Brazil) helped remove the roots, and the samples were stabilized by the palatal surface in a colorless acrylic resin base (VIPI FLASH, Pirassununga, SP, Brazil) made with a polyvinyl chloride (PVC) tube (Conexões Tigre, Joinville, SC, Brazil) of 12 mm in diameter, completely exposing the buccal aspect of the crown. **Figure 1** shows the samples.

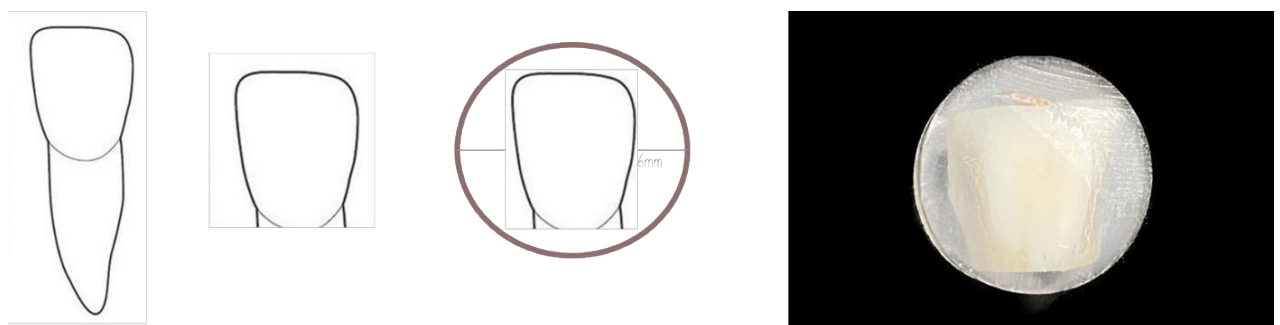


Figure 1: Samples prepared before bracket bonding.

Surface roughness assessment:

A contact roughness meter (Mitutoyo, Aurora, IL, USA) analyzed the surface roughness of each sample at baseline (T0) and 72 hours after finishing the bleaching treatment and removing the brackets (T1); the samples were stored in distilled water during this period. Mean roughness (Ra) was measured with a 5N static load and speed of 0.5 mm/s. The cutoff value was 0.25 μm in sequence, and the measurement distance was 1 mm. Each sample was read three times, at each time, from the sample center in the enamel region where the bracket was bonded. The arithmetic mean of the values was calculated and tabulated.

Bracket bonding:

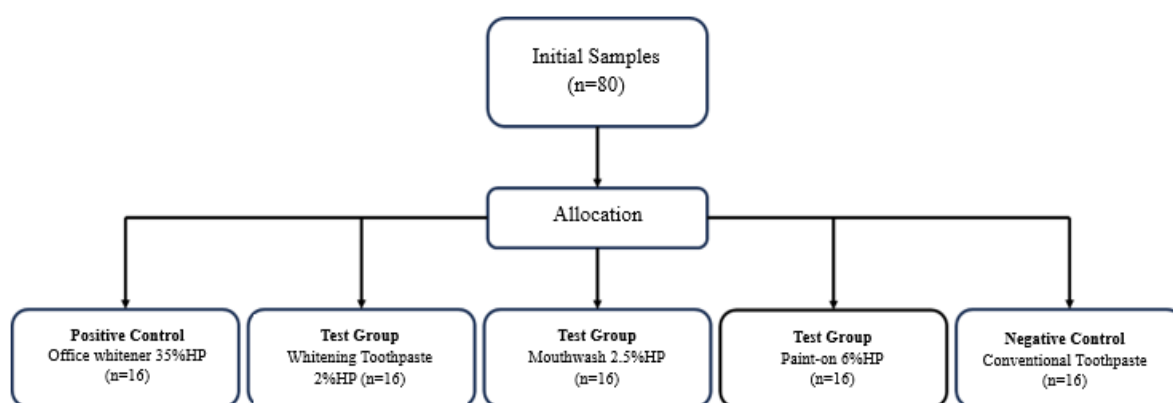
Eighty metal brackets with an area of 6 mm² (Kirium U1R Roth 022; Abzil 3M, São José do Rio Preto, SP, Brazil) were cemented on the center of the samples. The region delimited by the mold was etched with 37% phosphoric acid (Alpha-Etch; Nova DFL, Rio de Janeiro, RJ, Brazil) for 30 seconds according to the manufacturer's specifications, then washed with water for 30 seconds and dried by air spray. Next, an adhesive layer (Scotchbond; 3M Unitek, Sumaré, SP, Brazil) was light-cured for 20 seconds according to the manufacturer's instructions (Valo – Ultradent, Indaiatuba, SP, Brazil) and applied. A composite resin layer (Transbond™ XT, Sumaré, SP, Brazil) was then spread under the metal bracket base placed on the tooth surface aided by orthodontic tweezers. After a quick three-second light-curing, the excess resin was removed from the dental surface aided by a spatula (Golgran, São Caetano do Sul, SP, Brazil). Then, a final light-curing was performed for 20 seconds.

Bleaching treatment:

A blind evaluator allocated the samples to five groups using randomization software (www.random.org). Group HP35 underwent an in-office bleaching simulation using 35% hydrogen peroxide gel (Whiteness HP – FGM, Joinville, SC, Brazil) applied on the buccal surface of the sample with the help of a brush. Three 45-minute sessions (three 15-minute applications according to the product manufacturer's recommendations) occurred with a 48-hour interval between sessions, establishing the positive control group. Group DHP experienced bleaching with a dentifrice containing 2% hydrogen peroxide (Colgate Luminous White Advanced - Colgate - São Paulo, SP, Brazil). The samples were taken to the toothbrushing machine programmed to perform 60 reciprocating brushing movements per minute with a 200g load. This process

accomplished 850 cycles, simulating approximately 180 toothbrushing days using soft-bristle toothbrushes (Colgate Classic – Colgate, São Paulo, SP, Brazil). Group MouHP underwent a simulated treatment with a mouthwash containing 2.5% hydrogen peroxide (Listerine Whitening Extreme – Johnson and Johnson, São José dos Campos, SP, Brazil). The samples were immersed in a recipient with mouthwash for 12 hours. The mouthwash was replaced every hour, and the samples were washed in running water at each exchange. Group PON underwent treatment using paint-on gel containing 6% hydrogen peroxide (Whitening Pen – Dazzling White, Guangzhou, China). The samples received the product in daily 10-minute applications for 14 days. Group DSHP underwent treatment using a conventional dentifrice (Colgate Total 12 - Colgate - São Paulo, SP, Brazil) without hydrogen peroxide. The samples were taken to a toothbrushing machine under the same settings of group DHP, simulating a 180-day treatment, establishing the negative control. The samples were stored in distilled water while not subjected to bleaching agents. Figure 2 exemplifies the allocation of samples.

Figure 2: Flowchart of sample allocations.



Initial samples (n=80) / Allocation / **Positive control** – 35% HP in-office bleaching (n=16) / **Test group** – 2% HP bleaching dentifrice (n=16) / **Test group** – 2.5% HP mouthwash (n=16) / **Test group** – 6% HP paint-on (n=16) / **Negative control** – Conventional dentifrice (n=16).

Bracket removal and bond strength assessment:

All samples were subjected to a mechanical shear test in a machine (EMIC DL-1000, Uberlândia, MG, Brazil). This equipment used a 1kN cell and an active chiseled tip placed between enamel and resin, and the speed was 0.5 mm/min. The maximum force for rupture was recorded in Newtons (N). The mechanical test is shown in **figure 3**.



Figure 3. Sample positioned for the shear bond strength test.

Data analysis:

A blinded participant performed the statistical analysis. The data were analyzed with R software, version 4.3.0, aided by the stats, rstatix, and ggplot2 packages. The Shapiro-Wilk and Bartlett tests evaluated the normality and homogeneity of data variance, respectively. The data from shear analyses presented a non-normal distribution ($p < 0.05$); hence, Kruskal-Wallis with Dunn post-hoc test and Bonferroni correction compared the groups. ANOVA and Welch with Games-Howell post hoc test analyzed the roughness change means of each experimental group due to the absence of variance homogeneity ($p < 0.5$). All analyses used a 5% significance level.

RESULTS

Shear test:

The shear test excluded six specimens from the analysis due to technical failure. The Kruskal-Wallis test did not detect significant differences between the experimental groups ($p = 0.14$) (Table 1, Figure 2).

Table 1. Comparison between groups for shear values.

Groups	Shear (median, minimum-maximum value)
HP35	202 (65 – 357) ^A
MouHP	185 (96 - 364) ^A
DSHP	188 (66 – 421) ^A
DHP	126 (79 – 449) ^A
PON	168.5 (74 – 335) ^A

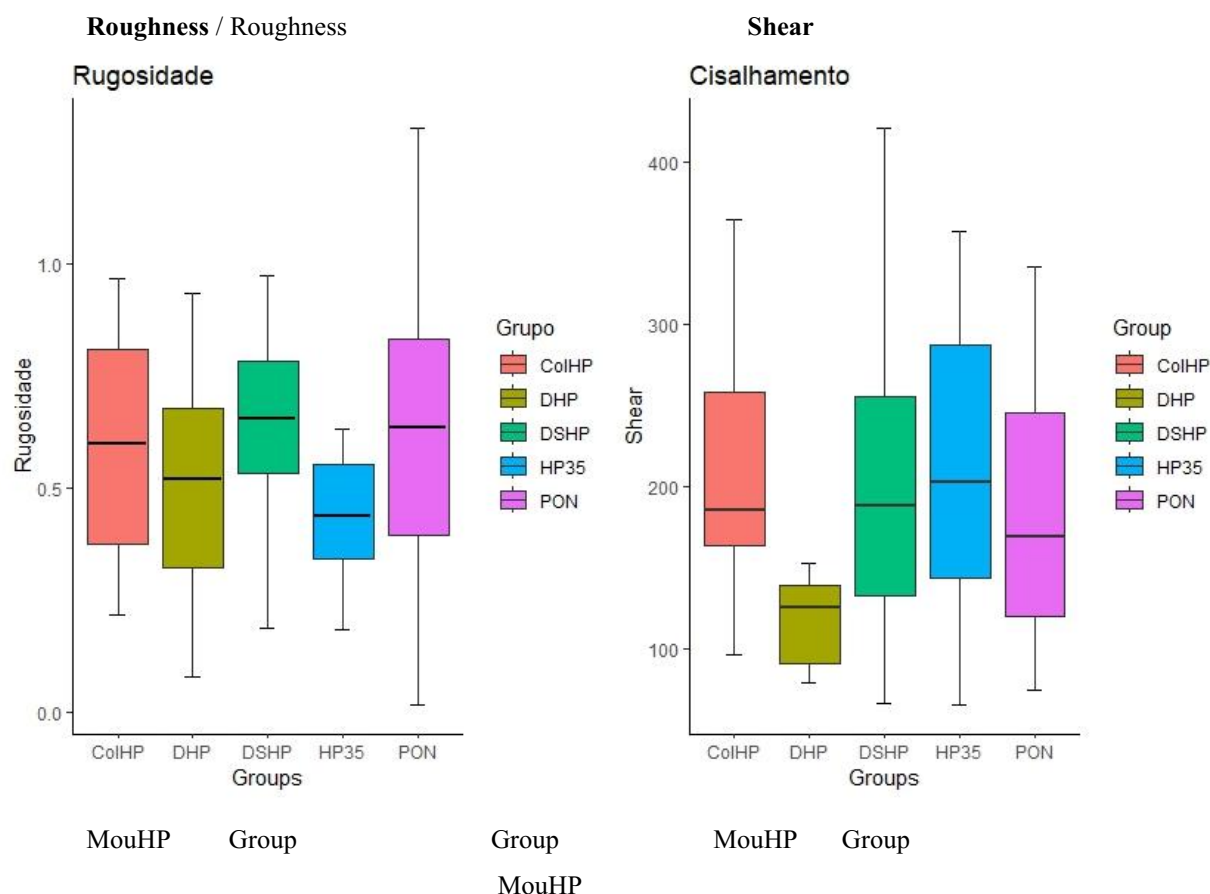
Surface roughness assessment:

The analysis of post-bleaching roughness change included all specimens. Welch ANOVA detected a significant difference between the group means ($p = 0.007$). Pairwise comparisons with Tukey's post hoc test identified a significant difference only between groups DSHP and HP35 ($p = 0.008$) (Table 2, Figure 2).

Table 2. Comparison between groups for roughness values.

Groups	Surface roughness (median, minimum-maximum value)
HP35	0.44 ± 0.13A
MouHP	0.60 ± 0.25AB
DSHP	0.65 ± 0.19B
DHP	0.52 ± 0.33AB
PON	0.63 ± 0.31AB

Figure 4. Boxplots of the comparisons between groups for roughness change and shear strength values.



DISCUSSION

The shear assessment did not show statistical differences between the groups, confirming the null hypothesis and suggesting that the evaluated bleaching agents did not harm the bond strength of brackets. These findings agree with other *in vitro*^{18,19}; however, the present investigation treated the teeth for a controlled time, which would not necessarily occur if patients purchased these products indiscriminately and used them without professional supervision.

The decreased bond strength of brackets with orthodontic cement may cause their detachment, promoting patient discomfort and the need for additional repair and bonding sessions²⁰. However, the means obtained in all groups reached the minimum adhesion results recommended in the literature: 50-70 N²¹. The findings suggest that bleaching agent action cannot harm adhesion to the point of clinically impairing orthodontic treatment development. We also suggest further studies to evaluate whether the prolonged use of these agents may cause adverse effects on material shear bond strength.

As for surface roughness values, the only statistical difference occurred between the positive control (in-office bleaching) and the negative control (dentifrice without

hydrogen peroxide). That suggests the tested OTC products did not influence enamel roughness more than a regular dentifrice, although the surface roughness tests rejected the null hypothesis due to the statistical difference.

Despite the surface morphology change after bleaching, studies indicate that roughness variations between 0.4 and 0.6 μm presented remineralization potential when applying remineralizing dentifrices²². Therefore, the study suggested that, during the protocol time, OTC bleaching agents would not cause irreversible changes in tooth enamel morphology.

Another factor that may influence the surface roughness analysis results is the technique to remove the dental surface resin. Laboratory investigations indicate that bladed burs, such as those used in this study, present better roughness and enamel preservation results than other techniques, such as diamond points or Er:YAG laser. However, surface roughness still changes, with values agreeing with our study^{23,24}. We emphasize that the results suggest that roughness change is reversible and has no significant clinical implications; however, the roughness increase may be more related to bracket bonding and removal than the bleaching agent.

Lastly, it is worth noting the relevance of professional supervision for bleaching treatments due to the toxicity of hydrogen peroxide, which may cause gingival irritation if the agent directly contacts the gingiva (Furukawa et al., 2015) or inflammatory reactions in the digestive tract if the product is accidentally ingested²⁶.

CONCLUSION

The present *in vitro* study suggests that the evaluated over-the-counter products did not influence the shear bond strength of orthodontic brackets to teeth or enamel roughness changes.

REFERENCES

1. Demarco FF, Meireles SS, Masotti AS. Over-the-counter whitening agents: a concise review. *Braz Oral Res.* 2009;23 Suppl 1:64-70. doi: 10.1590/s1806-83242009000500010. PMID: 19838560.
2. Ghalili KM, Khawaled K, Rozen D, Afsahi V. Clinical study of the safety and effectiveness of a novel over-the-counter bleaching tray system. *Clin Cosmet Investig Dent.* 2014 Feb 21;6:15-9. doi: 10.2147/CCIDE.S59292. PMID: 24591847; PMCID: PMC3937104.
3. 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 Aug;27(4):349-57. PMID: 17726991.
4. Carey CM. Tooth whitening: what we now know. *J Evid Based Dent Pract.* 2014 Jun;14 Suppl:70-6. doi: 10.1016/j.jebdp.2014.02.006. Epub 2014 Feb 13. PMID: 24929591; PMCID: PMC4058574.
5. Freitas MR, de Carvalho MM, Liporoni PCS, Fort ACB, Moura RDME, Zanatta RF. Effectiveness and adverse effects of over-the-counter whitening products on dental tissues. *Front Dent Medic.* 2021 Jun;2:687507.
6. Jadad E, Montoya J, Arana G, Gordillo LA, Palo RM, Loguercio AD. Spectrophotometric evaluation of color alterations with a new dental bleaching product in patients wearing orthodontic appliances. *Am J Orthod Dentofacial Orthop.* 2011 Jul;140(1):e43-7. doi: 10.1016/j.ajodo.2010.11.021. PMID: 21724070.
7. Consolaro A, Consolaro RB, Francischone L. Clarifications, guidelines and questions about the dental bleaching "associated" with orthodontic treatment. *Dental Press J Orthod.* 2013 Sep-Oct;18(5):4-10. doi: 10.1590/s2176-94512013000500002. PMID: 24352384.
8. Pinto CF, Oliveira Rd, Cavalli V, Giannini M. Peroxide bleaching agent effects on enamel surface microhardness, roughness and morphology. *Braz Oral Res.* 2004 Oct-Dec;18(4):306-11. doi: 10.1590/s1806-83242004000400006. PMID: 16089261.
9. Dudea D, Florea A, Mihiu C, Câmpeanu R, Nicola C, Benga G. The use of scanning electron microscopy in evaluating the effect of a bleaching agent on the enamel surface. *Rom J Morphol Embryol.* 2009;50(3):435-40. PMID: 19690771.
10. Kutuk ZB, Ergin E, Cakir FY, Gurgan S. Effects of in-office bleaching agent combined with different desensitizing agents on enamel. *J Appl Oral Sci.* 2018 Nov

8;27:e20180233. doi: 10.1590/1678-7757-2018-0233. PMID: 30427477; PMCID: PMC6223786.

11. Boccuzzi M, Nota A, Cosola S, De Simone G, Iozzo R, Pittari L, Hwang MH, Bosco F, Polizzi E, Tecco S. Effect of bleaching treatments on the adhesion of orthodontic brackets: a systematic review. *BMC Oral Health*. 2023 Oct 13;23(1):758. doi: 10.1186/s12903-023-03418-9. PMID: 37833672; PMCID: PMC10576373.

12. Mishima FD, Valentim RG, Araújo MT, Ruellas AC, Sant'Anna EF. The effect of tooth bleaching on the enamel surface and the tensile force to debond orthodontic brackets. *J Orthod*. 2009 Dec;36(4):236-42. doi: 10.1179/14653120723265. PMID: 19934241.

13. Sardarian A, Malekpour B, Roshan A, Danaei SM. Bleaching during orthodontic treatment and its effect on bracket bond strength. *Dent Res J (Isfahan)*. 2019 Jul-Aug;16(4):245-250. PMID: 31303879; PMCID: PMC6596175.

14. Wiegand A, Drebenstedt S, Roos M, Magalhães AC, Attin T. 12-month color stability of enamel, dentine, and enamel-dentine samples after bleaching. *Clin Oral Investig*. 2008 Dec;12(4):303-10. doi: 10.1007/s00784-008-0195-7. Epub 2008 Mar 28. PMID: 18369668.

15. Majeed A, Farooq I, Grobler SR, Rossouw RJ. Tooth-Bleaching: A Review of the Efficacy and Adverse Effects of Various Tooth Whitening Products. *J Coll Physicians Surg Pak*. 2015 Dec;25(12):891-6. PMID: 26691365.

16. Leite TC, Dias KRHC. Efeitos dos agentes clareadores sobre a polpa dental: revisão de literatura. *Rev Bras Odontol*. 2011 Sep;67(2):203.

17. Krithikadatta J, Gopikrishna V, Datta M. CRIS Guidelines (Checklist for Reporting In-vitro Studies): A concept note on the need for standardized guidelines for improving quality and transparency in reporting in-vitro studies in experimental dental research. *J Conserv Dent*. 2014 Jul;17(4):301-4. doi: 10.4103/0972-0707.136338. PMID: 25125839; PMCID: PMC4127685.

18. Rego MV, dos Santos RM, Leal LM, Braga CG. Evaluation of the influence of dental bleaching with 35% hydrogen peroxide in orthodontic bracket shear bond strength. *Dental Press J Orthod*. 2013 Mar-Apr;18(2):95-100. doi: 10.1590/s2176-94512013000200020. PMID: 23916438.

19. Akin M, Aksakalli S, Basciftci FA, Demir A. The effect of tooth bleaching on the shear bond strength of orthodontic brackets using self-etching primer systems. *Eur J Dent*. 2013 Jan;7(1):55-60. PMID: 23408777; PMCID: PMC3571510.

20. Pithon MM, Oliveira MV, Ruellas AC, Bolognese AM, Romano FL. Shear bond strength of orthodontic brackets to enamel under different surface treatment conditions. *J Appl Oral Sci.* 2007 Apr;15(2):127-30. doi: 10.1590/s1678-77572007000200010. PMID: 19089115; PMCID: PMC4327243.
21. Reynolds IR, von Fraunhofer JA. Direct bonding in orthodontics: a comparison of attachments. *Br J Orthod.* 1977 Apr;4(2):65-9. doi: 10.1179/bjo.4.2.65. PMID: 346056.
22. Attia RM, Kamel MM. Changes in surface roughness of bleached enamel by using different remineralizing agents. *Tanta Dent J.* 2016 Oct-Dec;13(4):179-186.
23. Ahrari F, Akbari M, Mohammadipour HS, Fallahrastegar A, Sekandari S. The efficacy and complications of several bleaching techniques in patients after fixed orthodontic therapy: A randomized clinical trial. *SWISS DENTAL JOURNAL SSO–Sci Clin Top.* 2020 May;130(6):493-501.
24. Degrazia FW, Genari B, Ferrazzo VA, Santos-Pinto AD, Grehs RA. Enamel Roughness Changes after Removal of Orthodontic Adhesive. *Dent J (Basel).* 2018 Aug 6;6(3):39. doi: 10.3390/dj6030039. PMID: 30082662; PMCID: PMC6162712.
25. Furukawa M, K-Kaneyama JR, Yamada M, Senda A, Manabe A, Miyazaki A. Cytotoxic Effects of Hydrogen Peroxide on Human Gingival Fibroblasts In Vitro. *Oper Dent.* 2015 Jul-Aug;40(4):430-9. doi: 10.2341/14-059-L. Epub 2015 Jan 9. PMID: 25575199.
26. Martin JV, Sugawa C. Hydrogen peroxide ingestion with injury to upper gastrointestinal tract. *World J Clin Cases.* 2017 Oct 16;5(10):378-380. doi: 10.12998/wjcc.v5.i10.378. PMID: 29085828; PMCID: PMC5648999.

4. Considerações Finais

Apesar da baixa certeza de evidência, os resultados dos estudos obtidos na revisão sistemática sugerem que produtos clareadores over-the-counter apresentaram resultados clínicos satisfatórios, tanto em alteração de cor, quanto em ocorrência de efeitos adversos. Porém, devemos ressaltar cautela durante a utilização desses produtos, já que nos estudos clínicos avaliados, havia supervisão do cirurgião-dentista durante a utilização dos agentes clareadores, o que reforça a importância do acompanhamento profissional em procedimentos clareadores.

Foi observado através de estudo in-vitro, a eficácia na alteração de cor e de brilho dos produtos over-the-counter em dentes bovinos submetidos a tratamento ortodôntico supervisionado, sugerindo também que os produtos OTC avaliados não influenciariam na rugosidade superficial das amostras ou na força de união dos bráquetes ao dente.

Porém, devido às limitações de estudos in-vitro, não é possível avaliar possíveis efeitos adversos que esses agentes poderiam causar em pacientes. Outra limitação é a grande variedade de produtos disponíveis para vendas online de agentes contendo peróxido de hidrogênio, o que impossibilita uma avaliação de todos os produtos disponíveis no mercado. Assim, o paciente se torna suscetível a utilizar produtos que não possuam comprovação científica de sua eficácia.

REFERÊNCIAS

- ALTINIŞIK, H.; AKGÜL, S.; NEZIR, M.; ÖZCAN, S.; ÖZYURT, E. The effect of in-office bleaching with different concentrations of hydrogen peroxide on enamel color, roughness, and color stability. **Materials**, v. 16, n. 4, p. 1389, 2023. doi: 10.3390/ma16041389. PMID: 36837018; PMCID: PMC9961799.
- BIZHANG, M.; CHUN, Y.H.; DAMERAU, K.; SINGH, P.; RAAB, W.H.; ZIMMER, S. Comparative clinical study of the effectiveness of three different bleaching methods. **Operative dentistry**, v. 34, n. 6, p. 635-641, 2009.. doi: 10.2341/08-069-C. PMID: 19953771.
- BRUNTON, P.A.; BURKE, F.J.; SHARIF, M.O.; CREANOR, S.; HOSEY, M.T.; MANNOCCI, F.; WILSON, N.H. Contemporary dental practice in the UK in 2008: aspects of direct restorations, endodontics and bleaching. **British Dental Journal**, v. 212, n. 2, p. 63-67, 2012. doi: 10.1038/sj.bdj.2012.46. PMID: 22281627.
- CALDAS, A.; VASCONCELOS, D.; SAMPAIO, G.; CAMPOS, J.; ARAGÃO, L.; CAVALCANTI, A.N. PRODUTOS CLAREADORES OVER THE COUNTER: UMA REVISÃO DE LITERATURA. **Journal of Dentistry & Public Health (inactive/archive only)**, v. 6, n. 2, 2015. <https://doi.org/10.17267/2596-3368dentistry.v6i2.586>
- CAREY, C.M. Tooth whitening: what we now know. **Journal of Evidence Based Dental Practice**, v. 14, p. 70-76, 2014. doi: 10.1016/j.jebdp.2014.02.006. Epub 2014 Feb 13. PMID: 24929591; PMCID: PMC4058574.
- CONSOLARO, A.; CONSOLARO, R.B.; FRANCISCHONE, L. Clarifications, guidelines and questions about the dental bleaching" associated" with orthodontic treatment. **Dental Press Journal of Orthodontics**, v. 18, p. 4-10, 2013. doi: 10.1590/s2176-94512013000500002. PMID: 24352384.
- DE FREITAS, M.R.; DE CARVALHO, M.M.; LIPORONI, P.C.S.; FORT, A.C.B.; MOURA, R.D.M.E.; ZANATTA, R.F. Effectiveness and adverse effects of over-the-counter whitening products on dental tissues. **Frontiers in Dental Medicine**, v. 2, p. 687507, 2021.
- DE GEUS, J.L.; WAMBIER, L.M.; KOSSATZ, S.; LOGUERCIO, A.D.; REIS, A. At-home vs in-office bleaching: a systematic review and meta-analysis. **Operative dentistry**, v. 41, n. 4, p. 341-356, 2016. doi: 10.2341/15-287-LIT. PMID: 27045285.
- DEMARCO, F.F.; MEIRELES, S.S.; MASOTTI, A.S. Over-the-counter whitening agents: a concise review. **Brazilian oral research**, v. 23, p. 64-70, 2009. doi: 10.1590/s1806-83242009000500010. PMID: 19838560.
- EPPLÉ, M.; MEYER, F.; ENAX, J. A critical review of modern concepts for teeth whitening. **Dentistry journal**, v. 7, n. 3, p. 79, 2019. doi: 10.3390/dj7030079. PMID: 31374877; PMCID: PMC6784469.

FÉLIZ-MATOS, L.; HERNÁNDEZ, L.M.; ABREU, N. Dental bleaching techniques; hydrogen-carbamide peroxides and light sources for activation, an update. Mini review article. **The open dentistry journal**, v. 8, p. 264, 2014. doi: 10.2174/1874210601408010264. PMID: 25646134; PMCID: PMC4311381.

GHALILI, K.M.; KHAWALED, K.; ROZEN, D.; AFSABI, V. Clinical study of the safety and effectiveness of a novel over-the-counter bleaching tray system. **Clinical, cosmetic and investigational dentistry**, p. 15-19, 2014. doi: 10.2147/CCIDE.S59292. PMID: 24591847; PMCID: PMC3937104.

HASSON, H.; ISMAIL, A.I.; NEIVA, G.; MEYERS, I. Home-based chemically-induced whitening of teeth in adults. **Cochrane Database Syst Rev**, v. 4, 2006. doi: 10.1002/14651858.CD006202. PMID: 17054282.

HATTAB, F.N.; QUDEIMAT, M.A.; AL-RIMAWI, H.S. Dental discoloration: an overview. **Journal of Esthetic and Restorative Dentistry**, v. 11, n. 6, p. 291-310, 1999. doi: 10.1111/j.1708-8240.1999.tb00413.x. PMID: 10825865.

HÖFEL, L.E.A.; LANGE, M.; JACOBSEN, T. Beauty and the teeth: perception of tooth color and its influence on the overall judgment of facial attractiveness. **International Journal of Periodontics & Restorative Dentistry**, v. 27, n. 4, 2007. PMID: 17726991.

JADAD, E.; MONTOYA, J.; ARANA, G.; GORDILLO, L.A.; PALO, R.M.; LOGUERCIO, A.D. Spectrophotometric evaluation of color alterations with a new dental bleaching product in patients wearing orthodontic appliances. **American Journal of Orthodontics and Dentofacial Orthopedics**, v. 140, n. 1, p. e43-e47, 2011. doi: 10.1016/j.ajodo.2010.11.021. PMID: 21724070.

JIANG, N.; ZHANG, C.; AGINGU, C.; ATTIN, T.; CHENG, H.; YU, H. Comparison of whitening dentifrices on the effectiveness of in-office tooth bleaching: a double-blind randomized controlled clinical trial. **Operative Dentistry**, v. 44, n. 2, p. 138-145, 2019. doi: 10.2341/17-333-C. Epub 2018 Aug 14. PMID: 30106335.

KIHN, P.W. Vital tooth whitening. **Dental Clinics of North America**, v. 51, n. 2, p. 319-331, 2007. doi: 10.1016/j.cden.2006.12.001. PMID: 17532915.

KIM, Y.M.; HA, A.N.; KIM, J.W.; KIM, S.J. Double-blind randomized study to evaluate the safety and efficacy of over-the-counter tooth-whitening agents containing 2.9% hydrogen peroxide. **Operative Dentistry**, v. 43, n. 3, p. 272-281, 2018. doi: 10.2341/16-379-C. Epub 2018 Mar 7. PMID: 29513635.

LIMA, A.F.; FONSECA, F.M.; FREITAS, M.S.; PALIALOL, A.R.; AGUIAR, F.H.; MARCHI, G.M. Effect of bleaching treatment and reduced application time of an antioxidant on bond strength to bleached enamel and subjacent dentin. **J Adhes Dent**, v. 13, n. 6, p. 537-42, 2011. doi: 10.3290/j.jad.a19813. PMID: 21246074.

NAIDU, A.S.; BENNANI, V.; BRUNTON, J.M.A.P.; BRUNTON, P. Over-the-counter tooth whitening agents: a review of literature. **Brazilian dental journal**, v. 31, p. 221-235, 2020. doi: 10.1590/0103-6440202003227. Epub 2020 Jul 13. PMID: 32667517.

PEIXOTO, A.C.; VAEZ, S.C.; PEREIRA, N.A.R.; SANTANA, C.N.D.S.; SOARES, K.D.A.; ROMÃO, A.C.T.R.; FERREIRA, L.F.; MARTINS-FILHO, P.R.S.; FARIA-E-

SILVA, A.L. 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**, v. 26, p. e20170573, 2018. doi: 10.1590/1678-7757-2017-0573. Epub 2018 May 7. PMID: 30084472; PMCID: PMC6007969.

SULIEMAN, M. An overview of tooth discoloration: extrinsic, intrinsic and internalized stains. **Dental update**, v. 32, n. 8, p. 463-471, 2005. doi: 10.12968/denu.2005.32.8.463. PMID: 16262034.

TOSTES, N.E.; BAPTISTA, N.B.; CARVALHO JÚNIOR, O.B.D.; FRANCISCONI, P.A.S.; PIRES, H.C. Avaliação do desgaste produzido em esmalte por cremes dentais clareadores. **Rev Odontol Araçatuba (Impr.)**, p. 9-13, 2009.