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REVIEW

Efficacy of topical drug application to manage in-office bleaching sensitivity: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Objectives To answer whether the topical drug application can reduce in-office tooth bleaching sensitivity without impairing the color change.

Materials and methods This review was registered on PROSPERO (CRD42024524171). Two reviewers screened PubMed, Web of Science, Scopus, Embase, and clinicaltrials.gov in March 2024 independently for randomized clinical trials investigating the efficacy of topical drug application to manage in-office tooth bleaching sensitivity. The risk of bias was assessed using Cochrane's Risk of Bias tool (RoB2). Certainty of the evidence was assessed using the Grading of Recommendations: Assessment, Development, and Evaluation tool (GRADE). The meta-analyses evaluated the bleaching sensitivity and color change with RevMan 5.4 software.

Results 334 articles were retrieved. The final sample was composed of four articles. Tested drugs were Otosporin, Eugenol, Ibuprofen with arginine, and Dipyrone. The meta-analysis evidenced no difference in bleaching sensitivity up to 1 h (MD, -0.39; 95% CI, -0.89, 0.11), 24 h (MD, -0.26, 95% CI, -0.71, 0.18), or 48 h (MD, 0.00, 95% CI, -0.16, 0.16). Meta-analysis for color change evidenced no difference for color change (MD, 0.03; 95% IC, -0.56, 0.61). The risk of bias was low. The certainty of the evidence was rated moderate for bleaching sensitivity and high for color change.

Conclusions Although topical drug application did not impair color change, it was ineffective in reducing in-office tooth bleaching sensitivity.

Clinical relevance topical drug application on dental enamel is not an effective approach in reducing bleaching sensitivity, but several modifications can be made in future studies to possibly achieve a better outcome.

Keywords In-office bleaching · Sensitivity · Medication use · Topical application to the enamel

Introduction

Tooth bleaching is effective in changing the color of the teeth, being a very satisfactory, conservative, safe treatment, and improving the patient's self-confidence [1]. It can be performed by using different techniques: at-home bleaching, in-office bleaching, or the combined method, which uses both techniques together [2]. Although a statistically significant difference was not obtained, previous reviews show a tendency for higher sensitivity in the in-office bleaching technique, since a much higher bleaching agent concentration is used [3, 4]. Thus, more painless in-office bleaching protocols are necessary.

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Since the inflammatory infiltrate due to in-office tooth bleaching with hydrogen peroxide is the most common cause associated with bleaching sensitivity [5], previous investigations evaluated the efficacy of oral anti-inflammatory drugs to decrease pulp inflammation and bleaching sensitivity. However, recent systematic reviews all concluded that the use of several oral anti-inflammatory drugs promoted no reduction in the risk and intensity of bleaching sensitivity [6–8]. One of the primary causes behind these findings originates from the restricted ability of drugs to penetrate the pulp chamber when administered orally [8]. Therefore, the ineffectiveness of oral drugs in reducing sensitivity caused by in-office bleaching suggests the need to explore alternative routes of administration.

Existing literature corroborates that administering drugs topically offers numerous advantages over the oral route, such as controlled application, avoidance of the first-pass metabolism in the liver, and reduction of gastrointestinal side effects [9, 10]. Drug topical administration is the first choice of treatment for noninvasive oral lesions of candidiasis [11]. The drug topical administration route, already explored in other fields of research for pain management, can achieve the targeted site directly while having a limited systemic absorption percentage [9, 12]. Therefore, a topical drug application over the dental surface could promote pulp absorption if the drug permeates through enamel and dentine, acting directly on the inflamed tissue.

Recent animal studies tested the efficacy of topical drug application to the enamel surface and showed positive results in reducing the inflammatory infiltrate, which suggests that this course of treatment could be effective in humans [13–16]. Likewise, randomized clinical trials have been carried out aiming to answer if the topical drug application would reduce in-office tooth bleaching sensitivity without impairing color change [17–19]. However, the diversity of the primary study results demands a comprehensive synthesis of the evidence to analyze, summarize, and establish the level of evidence on the efficacy of topical drug application in reducing in-office bleaching-mediated tooth sensitivity.

Therefore, this systematic review and meta-analysis aimed to answer whether topical drug application to the enamel surface can reduce in-office bleaching-mediated tooth sensitivity. In addition, this paper will also answer if this novel treatment will impair the color change. The following PICOS guided this article: (P) patients undergoing in-office tooth bleaching. (I) topical drug application. (C) control groups or placebo application. (O) bleaching sensitivity and color change. (S) randomized clinical trials.

Methods

This systematic review and meta-analysis were conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [20] and reported using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21]. The protocol was registered on the PROSPERO platform under the identifier CRD42024524171.

Eligibility criteria

This review followed the PICOS question below.

P(opulation): patients undergoing in-office tooth bleaching.

I(ntervention): topical drug application.

C(omparison): control groups or placebo application.

O(utcomes): bleaching sensitivity and color change.

S(tudy design): randomized clinical trials.

Inclusion criteria: randomized clinical trials investigating the efficacy of topical drug application to the enamel surface to treat or prevent in-office tooth bleaching sensitivity and the effect on color change. No restriction was made regarding language or year of publication to comprehend an ample search in the literature.

Exclusion criteria: studies with systemic drug administration and studies with no control group.

Information sources

The electronic databases PubMed, Web of Science, Scopus, Embase, and clinicaltrials.gov were last searched in March 2024, comprehending articles published in any year. All searches were exported to the Rayyan (https://www.rayyan.ai) platform with the Ris or BibTex format.

Search strategy

The following search strategy was applied in all databases. Adaptations were made following the databases' directions.

(sensitivity OR pain OR "pain management" OR ache OR discomfort)

AND.

((bleaching OR whitening) AND (in-office OR "in office" OR professional))

AND.

("administration, topical" OR "topical drug administration" OR "topical administration" OR "topical administrations" OR "topical drug administrations" OR "administration buccal" OR "buccal drug administration" OR "buccal administration" OR "buccal administrations" OR "topical drug" OR "topical medication" OR "topical medicine" OR

"topical application" OR gel OR nanogel OR nano-gel OR "nano gel" OR emulsion OR solution OR cream OR paste OR nanoemulsion OR nano-emulsion OR "nano emulsion")

AND.

(NSAIDs OR corticosteroids OR antibiotics OR anti-inflammatory OR "anti-inflammatory" OR antinflammatory OR analgesic OR hydrocortisone OR acetaminophen OR paracetamol OR Ibuprofen OR Otosporin™ OR Carvedilol OR Dipyrone OR Eugenol OR diclofenac OR dexamethasone OR betamethasone OR tramal OR tramadol OR nimesulide OR opioids OR opioid OR codeine OR medication OR medications OR drugs OR medicine OR remedy)

Selection process

Two previously calibrated reviewers (FJDO and MJFC) conducted the selection process independently. Calibration was made using approximately 10% of the initial sample (30 articles) (k = 0.88).

After exportation to the Rayyan platform, the platform initially detected duplicates, and a reviewer (FJDO) assessed if the detection was accurate, solving the duplicate exclusion phase. Studies were then selected in a two-step independent evaluation: first, articles were selected by reading the title and abstract. Studies approved in this initial selection were then submitted to a second selection by full-text reading. Only the studies approved in the second selection were included in the final sample. Any disagreement between reviewers was solved by discussion or intervention from a third reviewer (BCDB), if necessary.

Data collection process

Studies were screened by one reviewer for the following information: drug used, product composition, study design, sample size, groups tested, bleaching technique, method and time of drug application, outcome assessed and evaluation time, and main results. This information is organized in Table 1.

Meta-analysis

The meta-analyses were conducted with the software Review Manager version 5.4 to evaluate bleaching sensitivity, and color change. In the primary studies, bleaching sensitivity was measured using a Visual Analog Scale (VAS) filled out by the patients, while color change was measured in ΔE using digital devices. Therefore, data extracted from the primary studies consisted of continuous variables: mean pain per VAS for bleaching sensitivity, and ΔE results for color change. The mean difference was the effect measure chosen to perform the meta-analysis because there were no methodological differences in the assessment of variables. The random-effects model was chosen. Analyses were made with a 95% confidence interval (CI). The statistical significance for the variable tested was considered when the meta-analysis resulted in $p < 0.05$.

The heterogeneity analysis was also performed from the Review Manager 5.4 using the value of the I^2 test.

Risk of bias assessment

Two independent reviewers (FJDO and MJFC) conducted the risk of bias assessment using the Cochrane Collaboration tool (Rob 2) [22]. The assessment criteria comprised five domains: sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting. The analysis was made for the two evaluated outcomes, bleaching sensitivity and color change. Throughout data selection and quality assessment, any disagreements between the reviewers were resolved through discussion, and if necessary, a third reviewer (BCDB) was consulted.

Certainty of evidence assessment

Two independent reviewers (FJDO and MJFC) evaluated the certainty of evidence for each outcome across studies using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) [23]. The GRADE approach initially assigns a high level of evidence for randomized clinical trials, but this can be downgraded by one or two levels due to five criteria (methodological limitations, imprecision, inconsistency, indirectness of evidence, and publication bias). In addition, evidence can also be elevated by three criteria (high magnitude of effect, residual confounders, and dose-response gradient). The analysis was made for the two evaluated outcomes, bleaching sensitivity and color change. Throughout the process of certainty of evidence assessment, any disagreements between the reviewers were resolved through discussion, and if necessary, a third reviewer (BCDB) was consulted.

Results

General characteristics

The database search initially resulted in 334 articles. After two-step selection, four articles were selected to compose the final sample. The selection process is detailed in the flowchart in Fig. 1.

The published data of the selected articles varied between 2018 and 2024. All articles were published in English.

Table 1 Data extraction from primary studies

	Favoreto et al. (2022)	HortKoff et al. (2024)	Rezende et al. (2018)	Vilela et al. (2021)
Medication used	Otosporin™	Ibuprofen + Arginine	Dipyrone	Eugenol
Product Composition	Solution containing: Hydrocortisone 10 mg + neomycin sulfate 5 mg + polymyxin B sulfate 10,000 IU) along with the following excipients: sulfuric acid, cetostearyl alcohol, methylparaben, sorbitan laurate, polysorbate 20, and water	Gel containing: Propylene glycol and hydroxyethyl cellulose as thickening agents, with methylparaben as a preservative	Gel containing: Dipyrone (500 milligrams per milliliter), thickening agents (propylene glycol and hydroxyethylcellulose)	Nanogel containing: Natrosol (9 g), nipagin (0.15 g), propylene glycol (7.5 g) and distilled water (133.35 mL). For the nanocapsule, 33.3 g of base gel was weighed, and 66.7 mL of nanosuspension was added; for the 1% pure Eugenol gel, 33.3 g of base gel was weighed, 1 g of Eugenol oil was added and 65.7 mL of distilled water
Study design	Split-mouth	Split-mouth	Split-mouth	Split-mouth
Sample (n)	20 participants	62 participants	120 participants	56 participants
Groups	1 - Otosporin™ 2 - Placebo	1 - Ibuprofen + Arginine 2 - Placebo	1 - Dipyrone 2 - Placebo	1- Eugenol 2- Placebo
Bleaching technique	In-office tooth bleaching with 35% HP (Whiteness HP Automixx, FGM, Joinville, SC, Brazil)	In-office tooth bleaching with 35% HP (Whiteness HP Automixx, FGM)	In-office tooth bleaching with HP 35% (Whiteness HP Maxx, FGM, Joinville, SC, Brazil)	In-office tooth bleaching at 35% HP (Whiteness HP 35% AutoMixx, FGM, Joinville, SC, Brazil)
Method and time of drug application	Before each bleaching session, the authors applied a placebo on one side of the hemi-arch and Otosporin™ on the other for 10 min. The application of 35% HP occurred in two sessions with a 1-week interval	Before each bleaching session, the authors applied a placebo on one side of the hemi-arch and Ibuprofen + Arginine on the other for 20 s and then left undisturbed on the surface for 10 min. The application of 35% HP occurred in two sessions with a 1-week interval	Before each bleaching session, the authors applied a placebo on one side and Dipyrone on the other for 10 min, followed by active application of the gels for 20 s with a disposable microbrush and removal with gauze. The application of 35% HP occurred in two sessions with a 1-week interval	Before each bleaching session, the authors applied nanoencapsulated Eugenol gel to one hemi-arch and placebo gel to the other for 10 min. The application of 35% HP occurred in two sessions with a 1-week interval
Outcome assessed and time of evaluation	1 - **BS absolute risk and intensity** using the NRS and VAS . **Time of evaluation**: 1 h after, 24 h after; and 48 h after each bleaching session 2 - **Tooth color change** by subjective (VITA Classical and VITA 3D-MASTER) and objective analysis (VITA Easyshade)	1 - **BS absolute risk and intensity** using the NRS and VAS . **Time of evaluation**: 1 h after, 24 h after; and 48 h after each bleaching session 2 - **Tooth color change** by subjective (VITA Classical and VITA 3D-MASTER) and objective analysis (VITA Easyshade)	1 - **BS absolute risk and intensity** using the NRS and VAS . **Time of evaluation**: 1 h after, 24 h after; and 48 h after each bleaching session 2 - **Tooth color change** by subjective (VITA Classical and VITA 3D-MASTER) and objective analysis (VITA Easyshade)	1 - **BS absolute risk and intensity** using the NRS and VAS . **Time of evaluation**: 1 h after, 24 h after; and 48 h after each bleaching session 2 - **Tooth color change** by subjective (VITA Classical and VITA 3D-MASTER) and objective analysis (VITA Easyshade)
Main results	1- There was no statistically significant difference in the absolute risk ($p = 1.0$) and intensity of BS ($p > 0.59$ for VAS and $p = 1.00$ for NRS) between groups 2- There was no statistically significant difference for both groups ($p < 0.39$)	1 – There was a statistically significant difference for both absolute risk and intensity of BS between groups ($p < 0.05$) 2- There was no statistically significant difference for both groups ($p > 0.05$)	1- There was no statistically significant difference in the absolute risk or intensity of BS between groups ($P = 0.09$), except from the period up to 1 h, when a significant difference favoring the Dipyrone group ($p = 0.02$) was detected 2- There was no statistically significant difference for both groups ($p > 0.05$)	1- There was no statistically significant difference in the absolute risk or intensity of BS between the two groups ($p > 0.05$) 2- There was no statistically significant difference for both groups ($p > 0.05$)

BS: Bleaching Sensitivity. HP: Hydrogen Peroxide. RH: Right hemimaxilla: LH: Left Hemimaxilla. NRS: Numerical Rating Scale. VAS: Visual Analog Scale

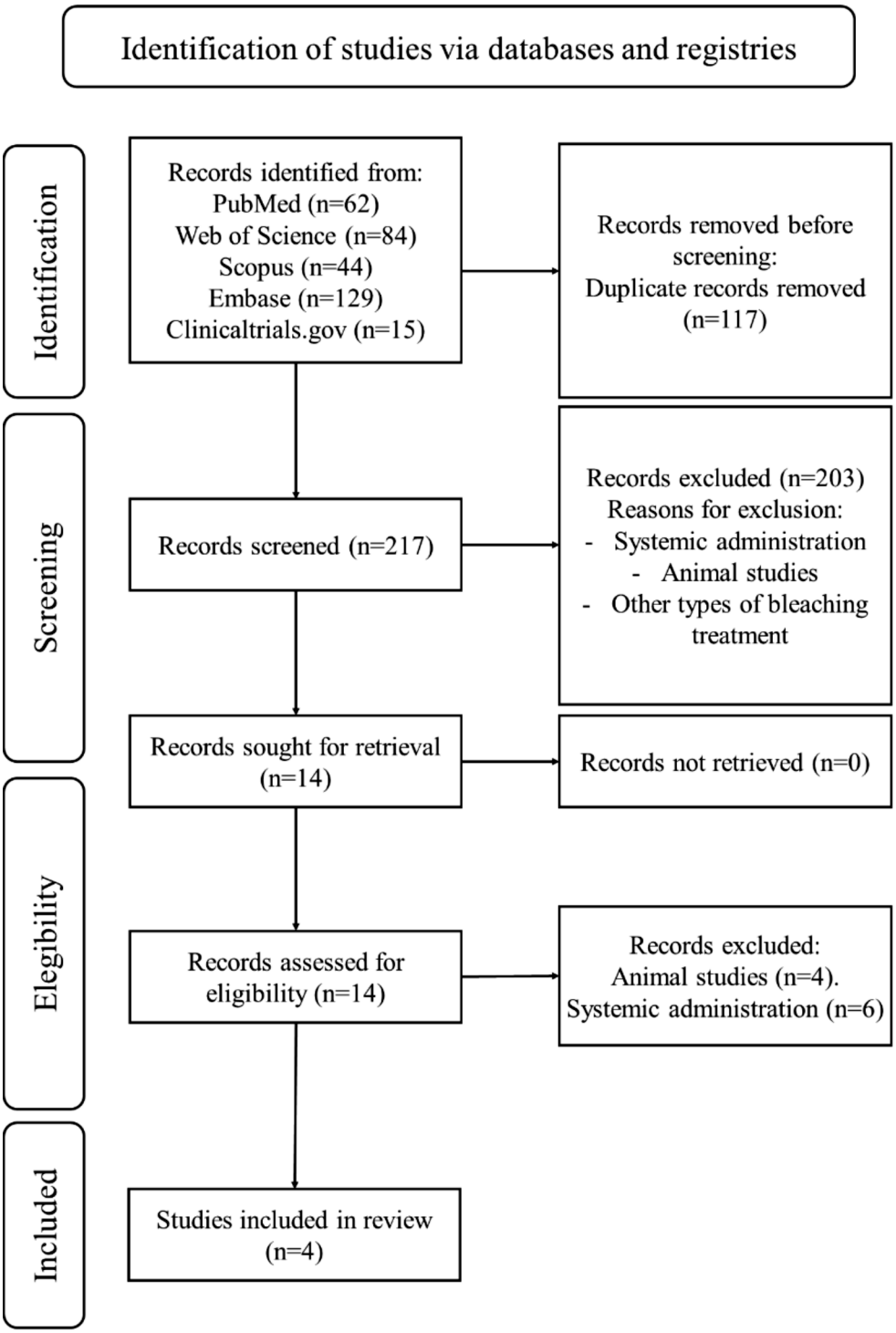

Fig. 1 Flowchart of the studies selection process according to PRISMA checklist 2020

Regarding the country of the studies, all studies were from Brazil.

All studies were performed in a split-mouth design. In total, 258 patients were evaluated, resulting in 516 hemi-arches.

Drugs evaluated

The studies evaluated Otosporin, Ibuprofen in combination with arginine, dipyrone, and eugenol. The first was used as a solution, whereas all remaining three were used as a gel. In the study by Vilela et al. (2021) [18] they used a nanogel formulation.

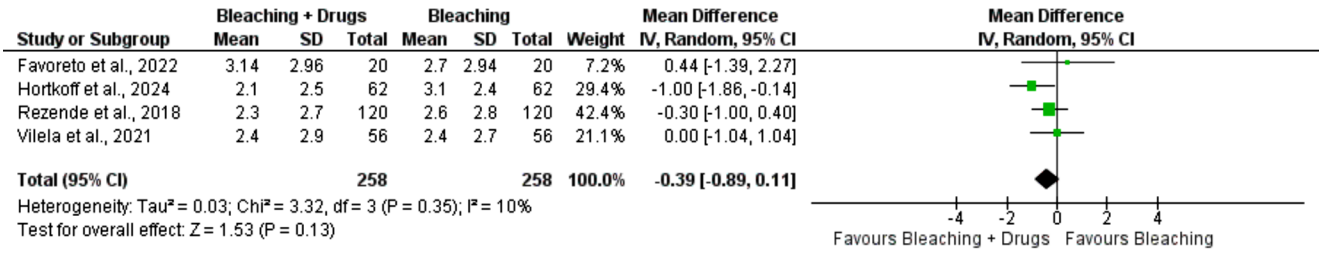

Fig. 2 Meta-analysis for bleaching sensitivity up to 1 h

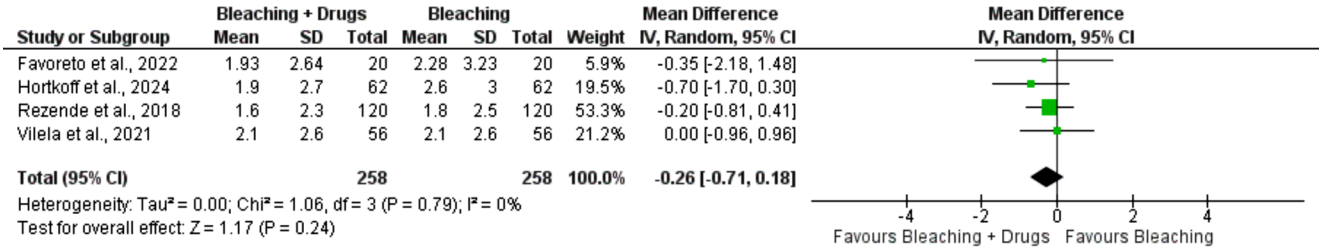

Fig. 3 Meta-analysis for bleaching sensitivity up to 24 h

All studies applied the drug before the bleaching session. The application was made for 10 min. HortKoff et al. (2024) [24] applied the gel for 20 s before leaving undisturbed for 10 min. Rezende et al. (2018) [19] actively applied the drug for 20 s after leaving undisturbed for 10 min.

Bleaching technique

All studies performed bleaching treatment in two sessions with a 1-week interval. The product was the same in all studies: 35% hydrogen peroxide (Whiteness HP Automixx, FGM, Joinville, SC, Brazil).

Bleaching sensitivity

All studies reported the absolute risk and intensity of bleaching sensitivity using the visual analog scale and the numeric rating scale at 1 h, 24 h, and 48 h after each bleaching session.

Two studies [17, 18] reported no statistically significant difference in the absolute risk or intensity of bleaching sensitivity between experimental and control groups. One study [19] reported a difference only at 1 h after favoring the experimental group. The study by Hortkoff et al. (2024) [24] reported a statistically significant reduction for both absolute risk and intensity of bleaching sensitivity, favoring the experimental group.

Color change

The color change was evaluated through both subjective and objective measurements. The first was performed with the value-oriented shade guide Vita Classical and the Vita Bleachedguide, and the latter through the spectrophotometer Vita Easyshade.

All studies reported no statistically significant difference between experimental and control groups regarding tooth color change.

Meta-analysis

Bleaching sensitivity

All studies were included in the meta-analysis for sensitivity evaluation up to 1 h, 24 h, and 48 h after bleaching. The results from all meta-analyses, shown in Figs. 2 and 3, and 4, respectively, evidence no statistically significant difference in bleaching sensitivity between experimental and control groups up to 1 h (MD, -0.39; 95% CI, -0.89, 0.11), 24 h (MD, -0.26, 95% CI, -0.71, 0.18), or 48 h (MD, 0.00, 95% CI, -0.16, 0.16).

Color change

All studies were included in the meta-analysis for color change evaluation. The results shown in Fig. 5 evidence no statistically significant difference in color change between experimental and control groups (MD, 0.03; 95% IC, -0.56, 0.61).

Risk of bias assessment

All studies evaluated were judged to have a low risk of bias for all domains analyzed and an overall bias for bleaching

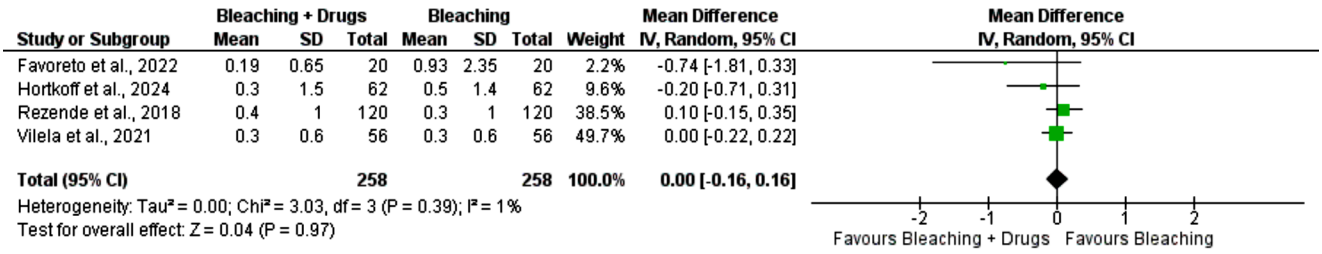

Fig. 4 Meta-analysis for bleaching sensitivity up to 48 h

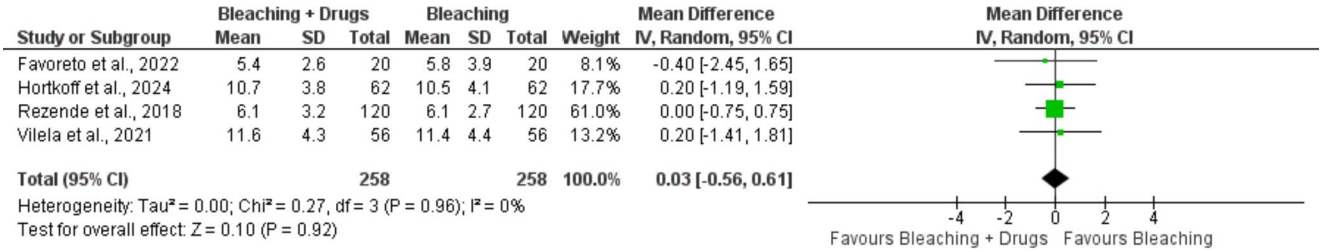

Fig. 5 Meta-analysis for color change evaluation

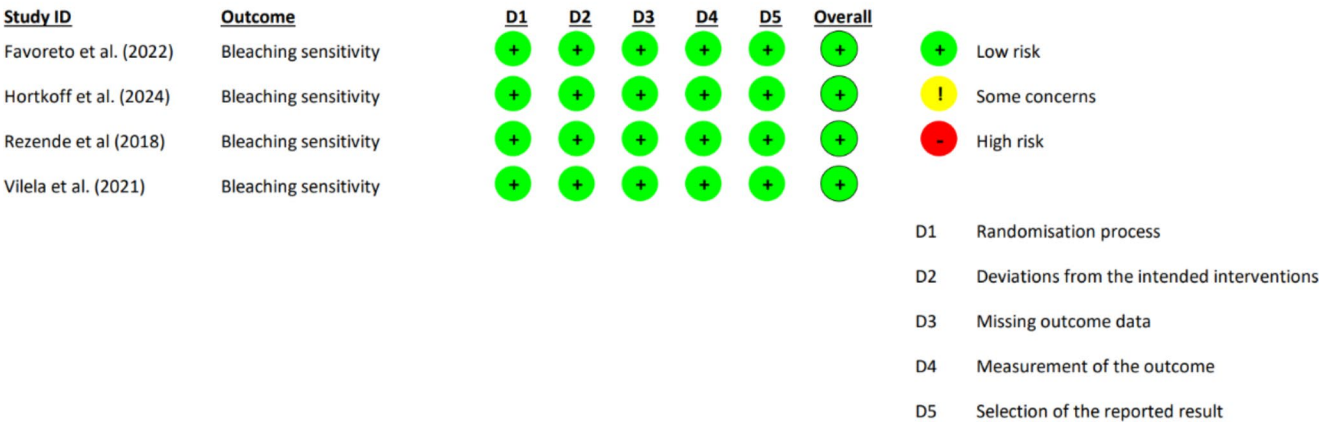

Fig. 6 Risk of bias assessment for bleaching sensitivity

sensitivity and color change. The analysis considered information in the primary publication and the trial protocols. All studies demonstrated good methodological descriptions of the studies; hence, the overall bias was low. Judgment for all criteria is available in Figs. 6 and 7 for bleaching sensitivity and color change, respectively.

Certainty of the evidence

The overall certainty of the evidence was graded moderate for bleaching sensitivity and high for color change. Although initially graded high because of the design of the studies being randomized clinical trials, the evidence was reduced in one level for imprecision in bleaching sensitivity. No methodological limitations were pointed out since no bias was judged to be significantly present among primary studies. No indirectness was identified because all studies directly compared the intended intervention and the control. No inconsistency was judged because the heterogeneity, evaluated through I^2 test, was low. No publication bias was suspected since a broad search was made, and negative and positive outcome trials were identified and included in the review. A funnel plot was not made to identify publication bias further because the meta-analysis included less than 10 articles. Regarding imprecision, evidence was downgraded one level for bleaching sensitivity evaluation because, even though confidence intervals were fairly narrow, the clinical recommendation would be significantly different considering the upper and lower end of the confidence interval since the result of the meta-analyses crossed the line of no effect. This judgment was made following GRADE guidelines for rating imprecision [25]. The color change evaluation was

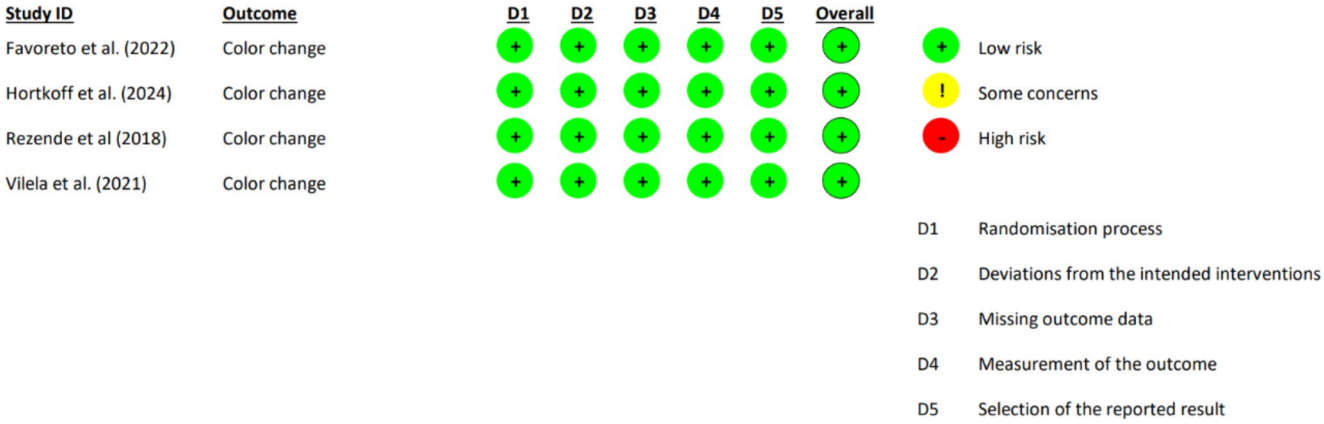

Fig. 7 Risk of bias assessment for color change

Table 2 Certainty of evidence assessment for bleaching sensitivity

Studies	Design	Methodological limitations	Indirectness	Imprecision	Publication bias	Effect	Number of participants	Certainty
4	Randomized Clinical Trials	Not serious	Not serious	Serious	Not suspected	MD -0.39 [-0.89, 0.11] MD -0.26 [-0.71, 0.18] MD -0.00 [-0.16, 0.16]	258 (516 hemiarches)	Moderate ⊕⊕⊕◯

Table 3 Certainty of evidence assessment for color change

Studies	Design	Methodological limitations	Indirectness	Imprecision	Publication bias	Effect	Number of participants	Certainty
4	Randomized Clinical Trials	Not serious	Not serious	Not serious	Not suspected	MD 0.03 [-0.56, 0.61]	258 (516 hemiarches)	High ⊕⊕⊕⊕

not downgraded for imprecision because the absence of difference between the two groups presents a positive effect for the tested intervention since the topical drug application should not interfere with color change. There was no upgraded level because of the high magnitude of effect, residual confounders, and dose-response gradient since none of these criteria was observed in the articles. The certainty of evidence assessment is detailed in Tables 2 and 3 for bleaching sensitivity and color change, respectively.

Discussion

To the author's knowledge, this is the first systematic review evaluating the efficacy of topical drug application in reducing or preventing in-office tooth bleaching sensitivity, and whether this approach would impair color change. According to our results, the proposed course of treatment had no statistically significant efficacy in reducing bleaching sensitivity up to 1 h, 24 h, and 48 h. The application of drugs also caused no impairment in the color change. Given the benefits of topical application, the adverse outcomes reported demand a thorough analysis of potential causes of ineffectiveness.

Enamel structure is known to be a highly mineralized tissue that partially enables the passage of ions and molecules [26]. The diameter of the tunnels evidenced in enamel structure ranges from 1 to 3 µm, a very narrow space that makes difficult passage through this hard tissue [27]. Enamel organization must be considered when a new drug is proposed to pass through this challenging pathway and reach the pulp chamber.

Factors related to the drug composition can also affect its permeability into the dental tissues to reach the pulp. Low molecular weight and low affinity for the tissue are desired to increase the drug permeability [19, 28]. Hydrogen peroxides present a low molecular weight and minimal interaction with the organic matrix in enamel, which results in a homogenous distribution [19, 28]. Following data from PubChem, the molecular weight of the tested drugs is: Ibuprofen (206 g/mol), Dipyrone (311 g/mol), Eugenol (164 g/mol), and Hydrocortisone (362.5 g/mol), the anti-inflammatory present in Otosporin. All tested drugs present a higher molecular weight than hydrogen peroxide (34 g/mol), and no information is available regarding the specific

interactions and affinity with dental tissue that can reduce penetration. All these factors combined can impair penetration and reduce the amount of drug reaching the pulp chamber, which may not be enough to act on inflammation properly.

Two studies in the present review used commercially available drugs that were not manipulated to sustain such tasks better. Although it is not possible to affirm that this was the cause, it is valid to suggest that future investigations involve testing of nanostructured drugs, because nanosized drugs have advantages such as controlled release, reduced toxicity, longer action time, and overall better permeability [29], an ideal characteristic for the challenge imposed by enamel penetration. In addition, the drug characteristics need to be considered to use the pharmacokinetics in favor of better outcomes.

It is well known that hydrogen peroxide enhances tooth permeability, especially when used in high concentrations, such as the ones used in-office bleaching [30]. All four studies applied the drugs for 10 min before in-office bleaching. Still, considering hydrogen peroxide's effect on dental enamel, suggesting that an application after the procedure could have better positive outcomes in future trials is valid.

Regarding possible causes for bleaching sensitivity, it is important to emphasize that the exact mechanism behind this type of pain is yet to be uncovered. Theories for this phenomenon cover, firstly, a possible association with reversible pulpitis, since bleaching agents penetrate the pulp chamber, causing irritation [31]. Second, a negative effect from the osmotic gradient caused by the water content on the bleaching product, drying the tooth structure [31]. Third, a possibility that bleaching sensitivity may be a form of dentin hypersensitivity, which is more acceptably explained by the hydrodynamic theory, in which several stimuli can activate intradental nerve endings, causing pain [31]. The uncertainty that covers the exact cause of bleaching sensitivity makes treatment difficult.

Previous animal studies reported that topical drug application to the enamel surface reduced inflammation [13–16]. The inflammatory process is one of the causes attributed to the in-office bleaching-mediated sensitivity. Of course, the findings of animal studies cannot be carelessly extrapolated, but if these drugs reduce inflammation, it is valuable to consider other causes for bleaching sensitivity. In this context, the transient receptor potential ankyrin 1 (TRPA1) is believed to play a critical role in bleaching sensitivity because the procedure increased the protein levels of hyperalgesia factors (TRPA1 and PANX1) [32]. Only one study had statistically significant results favoring experimental treatment with an Ibuprofen gel [24]. The study by De Logu et al. (2019) [33] pointed out that an ibuprofen metabolite, ibuprofen-acyl glucuronide, selectively antagonizes TRPA1, which can help understand why this drug was the most efficient [29].

As general limitations identified by this systematic review, it is important to highlight that, although an ample literature search was made, all identified studies were conducted in Brazil. Other countries should conduct similar clinical studies so researchers can understand if ethnic heterogeneity can influence different outcomes. Current literature already supports that pain is an individual experience that is possibly influenced by numerous demographic factors, such as sex, age, and ethnicity [34]. For example, a cohort study showed that several suprathreshold orofacial pain measures had significant racial differences, likely related to variances in central nociceptive processing among different ethnicities [34]. Therefore, the perception of bleaching sensitivity can be influenced by such ethnic differences.

Another limitation regarding methodological heterogeneity concerns the variety of the drugs tested, which can lead to variation in the results presented by each primary study. In addition, as the topical drug application approach to manage in-office bleaching sensitivity is new, a few studies are still available in the literature. The limited number of studies calls for careful consideration when extrapolating the findings of the present review to the proposed population.

In light of the present results, future studies should consider developing nanostructured drugs with nanotechnology with a high affinity for the TRPA1. A recent study [35] evaluating the in-silico affinity of several drugs with TRPA1 suggested that codeine and dexamethasone showed high binding affinity to TRPA1. Thus, further investigations might test nanostructured topical drugs based on codeine or dexamethasone regarding their permeability into the tooth and protective biological effect in cell cultures. In addition, such drugs should be applied before and after bleaching treatment when the enamel permeability, one of the biggest challenges with this course of treatment, is enhanced. This way, it is possible to improve further the potential of the drug to reach the pulp chamber and maybe obtain a more desirable effect on bleaching sensitivity. Therefore, considering the estimated effect favoring the experimental group, although a statistically significant difference was not reached, this promising field of research needs to be further explored with the feasible modifications highlighted previously.

Based on the evidence available in the literature, this work's findings have proposed several directions for future studies. Dental care providers worldwide would benefit greatly from understanding the new proposed courses of treatment and whether they are, in fact, effective. Moreover, shedding light on a new research topic can provide visibility to better studies on a novel treatment strategy.

Conclusion

Based on the evidence in the literature, it can be concluded that topical drug application is ineffective in reducing or preventing in-office tooth bleaching sensitivity and does not impair the efficacy of color change. However, this novel treatment modality requires further investigation. Future research should consider working with nanostructured drug formulations with affinity for the TRPA1 receptor.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval Not Applicable.

Informed consent Not applicable.

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