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REVIEW

Topical application of a desensitizing agent containing potassium nitrate before dental bleaching: a systematic review and meta-analysis

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Abstract

Objectives To conduct a systematic review and meta-analysis to evaluate the risk and intensity of tooth sensitivity (TS) after topical application of desensitizers containing potassium nitrate before dental bleaching.

Methods We searched PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library, and SIGLE. We also surveyed gray literature without restrictions. We meta-analyzed the data using the random-effects model to compare potassium nitrate and placebo in terms of risk and intensity of TS and color change (ΔSGU or ΔE). The quality of the evidence was rated using the GRADE approach. The risk of bias (RoB) of the included studies was analyzed using the Cochrane RoB tool.

Results After the database screening, 24 articles remained. A significant 12% lower risk for the groups where desensitizing agents were applied (p = 0.02), with a risk ratio of 0.88 (95% CI 0.78 to 0.98). About the intensity of TS, a significant average mean difference of − 0.77 units of VAS units (95%CI − 1.34 to − 0.19; p = 0.01) in favor of the desensitizer group. In the NRS scale, a significant average mean difference of − 0.36 (95% CI − 0.61 to − 0.12; p value = 0.004) in favor of the desensitizer group. No significant difference was observed in color change (p > 0.28) in ΔSGU and ΔE.

Conclusions Although a significant reduction in the risk and intensity of TS was observed in groups treated with a potassium nitrate at some point during the bleaching, the clinical significance of this reduction is subtle and clinically questionable. Color change is not affected by the use of agents.

Clinical relevance The reduction in the risk and intensity of TS with the topical application of potassium nitrate–based desensitizing agents in dental bleaching is subtle and maybe clinically questionable.

Keywords Tooth bleaching · Dentin sensitivity · Hydrogen peroxide · Dentin desensitizing agents · Randomized clinical trials · Systematic review

Introduction

Patients' facial appearance is affected by the smile and, when within esthetic standards, can improve self-esteem and social relationships [1, 2]. Although the attractiveness of a smile is related to the shape and position of the teeth, tooth color has a strong effect on the social perceptions, as brighter teeth are usually associated with good oral health status [3]. These factors are the reasons why tooth bleaching has been desired for many patients.

Currently, there are two dentist-supervised techniques available for dental bleaching: at-home bleaching [4, 5] and in-office bleaching [5, 6]. Although both techniques provide similar results [6–9], some patients prefer the in-office bleaching as they need faster bleaching results and are not willing to use bleaching trays for prolonged periods.

In a recent study, the authors reported that the risk of TS for in-office bleaching and at-home bleaching was quite similar [8]; however, the TS intensity was much higher for in-office bleaching (2.8 ± 2.9) than at-home (0.5 ± 0.9) when measured in a 0–4 pain scale [8].

This common and inconvenient adverse effect of TS has encouraged researches to investigate protocols to prevent or

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minimize its occurrence. Some of the approaches include the reduction of the concentration and usage time of the bleaching gel [10, 11], the application of topical desensitizing agents [12–14], the administration of systemic drugs [15–18], and the incorporation of desensitizing agents, into the formulation of the bleaching gels [19, 20].

Among all these approaches, the topical application of desensitizing agents showed promising results for the reduction of the risk and intensity of TS [21–23], but there are recent reports that do not reach the same conclusions [14, 22, 24].

Although a systematic review of the literature concluded that the application of desensitizing agents based on potassium nitrate and sodium fluoride reduces the bleaching-induced TS [25], there are significant methodological differences when compared to the present systematic review. Besides, other randomized controlled trials (RCTs) on this topic were published in the most recent years, and this systematic review requires updating.

Therefore, this systematic review aimed to answer the focused research question, based on the PICO acronym (Participant-Intervention-Comparator-Outcome): "Are the risk and intensity of TS lower when potassium nitrate–based desensitizers are applied before dental bleaching in adults, compared to a placebo?"

Methods

Protocol and registration

This study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO - CRD 42018104598), and the present report follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for report [26].

Information sources and search strategy

We used controlled vocabulary (MeSH terms) and free keywords for the concepts Participants and Intervention to define the search strategy for the following databases: Cochrane Library, MEDLINE via PubMed, Latin American and Caribbean Health Sciences Literature database (LILACS), and Brazilian Library in Dentistry (BBO). We also searched for some citation databases, such as Scopus and Web of Science. No restrictions on publication date or languages were made. Table 1 depicts the search strategies employed.

Some sources of gray literature were investigated: (1) abstracts of the annual conference of the International Association for Dental Research (1990–2020), (2) System for Information on Grey Literature in Europe (SIGLE), (3) dissertations and theses in ProQuest, (4) Periodicos Capes Theses database, and (5) clinical trial registries (current controlled trials, International Clinical Trials Registry Platform, ClinicalTrials.gov, ReBEC, and EU Clinical Trials Register).

Eligibility criteria

We included parallel and split-mouth randomized clinical trials (RCTs) that evaluated the application of potassium nitrate as a topical desensitizing agent on the risk and intensity of TS during in-office and at-home dental bleaching in adult patients. We excluded RCTs if studies (1) incorporated the potassium nitrate only into the bleaching gel; (2) evaluated dentifrices containing potassium nitrate; (3) evaluated desensitizing agents other than potassium nitrate; (4) did not have a placebo or no-desensitizing agent group for comparison; and (5) included both groups but did not compare bleaching gels with equivalent concentrations.

Initially, review authors removed duplicates and non-relevant articles by screening titles and abstracts. The full-text paper of the relevant articles was obtained, and subsequently, four reviewers (E.M., M.F., J.L.G., and M.R.) classified those that met the inclusion criteria. Each study received a study ID, combining the first author and the year of publication.

Details about study methods, designs and settings, participant's characteristics, bleaching protocol, and desensitizing protocol were extracted from the eligible studies using customized extraction forms.

Risk of bias in individual studies

Four reviewers assessed, independently, the risk of bias of the eligible studies using the Cochrane Collaboration tool for assessing risk of bias in randomized trials [27]. This tool contains seven items: sequence generation, allocation concealment, blinding of the participants and the outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (not used in the present study). Any disagreements between the reviewers were resolved through discussion and, if necessary, by consulting a fifth reviewer (A.R.).

Each domain from the risk of bias tool was scored following recommendations as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). The judgment for each entry involves the judgments of low risk of bias, high risk of bias, or unclear risk, indicating either lack of information or uncertainty over the potential for bias.

Summary measures and synthesis of the results

As the RCTs usually report TS intensity in different time assessments, we collected data from the worst scenario.

Table 1 Electronic database and search strategy. Search performed on February 22, 2019, and last updated on March 11, 2020

PUBMED 11/March/2020		
#1 ((((Tooth discoloration[MeSH Terms] OR "tooth staining"[Title/Abstract] OR "teeth staining"[Title/Abstract] OR "tooth stain"[Title/Abstract] OR "teeth stain" [Title/Abstract] OR "stained tooth"[Title/Abstract] OR "stained teeth" [Title/Abstract] OR "tooth discoloration"[Title/Abstract] OR "teeth discoloration"[Title/Abstract] OR "tooth discolouration"[Title/Abstract] OR "tooth discolouration" [Title/Abstract] OR "discolored tooth"[Title/Abstract] OR "discolored teeth"[Title/Abstract] OR "discoloured tooth"[Title/Abstract] OR "discoloured teeth"[Title/Abstract] OR "dental discoloration"[Title/Abstract] OR "dental discolouration"[Title/Abstract] OR "tooth color"[Title/Abstract] OR "tooth colour"[Title/Abstract] OR "teeth color"[Title/Abstract] OR "teeth colour"[Title/Abstract])))**	#2 ((Tooth Bleaching[MeSH Terms] OR Tooth Bleaching agents[MeSH Terms]) OR Carbamide peroxide[Supplementary Concept] OR Hydrogen peroxide[MeSH Terms] OR dentin desensitizing agents[MeSH Terms] OR Potassium nitrate[MeSH Terms] OR Glutaral[MeSH Terms] OR Sodium Fluoride[MeSH Terms] OR Gluma desensitizer[Supplementary Concept] OR bleaching[Title/Abstract]) OR whitening[Title/Abstract] OR "potassium oxalate"[Title/Abstract] OR "GLUMA Desensitizer"[Title/Abstract] OR desensitization[Title/Abstract] OR glutaraldehyde[Title/Abstract] OR "potassium nitrate"[Title/Abstract] OR "hydrogen peroxide"[Title/Abstract] OR "carbamide peroxide"[Title/Abstract] OR "sodium fluoride"[Title/Abstract]) OR "calcium phosphates"[Title/Abstract] OR "calcium phosphate"[Title/Abstract] OR "desensitizing agents"[Title/Abstract] OR "CPP-ACP"[Title/Abstract])))**	#3 ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))
#1 AND #2 AND #3		
SCOPUS 11/March/2020		
#1 TITLE-ABS-KEY ("tooth stain*") OR TITLE-ABS-KEY ("stained t??th") OR TITLE-ABS-KEY ("tooth discoloration*") OR TITLE-ABS-KEY ("tooth discolouration") OR TITLE-ABS-KEY ("discolored t??th") OR TITLE-ABS-KEY ("discoloured t??th") OR TITLE-ABS-KEY ("teeth discoloration") OR TITLE-ABS-KEY ("teeth discolouration") OR TITLE-ABS-KEY ("dental discoloration") OR TITLE-ABS-KEY ("t??th color") OR TITLE-ABS-KEY ("t??th colour") OR TITLE-ABS-KEY ("dental discolouration")	**#2** TITLE-ABS-KEY (bleaching) OR TITLE-ABS-KEY (whitening) OR TITLE-ABS-KEY ("tooth sensitivity") OR TITLE-ABS-KEY ("potassium oxalate") OR TITLE-ABS-KEY ("GLUMA Desensitizer") OR TITLE-ABS-KEY (desensitization) OR TITLE-ABS-KEY (glutaraldehyde) OR TITLE-ABS-KEY ("potassium nitrate") OR TITLE-ABS-KEY ("dentin sensitivity") OR TITLE-ABS-KEY ("hydrogen peroxide") OR TITLE-ABS-KEY ("carbamide peroxide") OR TITLE-ABS-KEY ("sodium fluoride") OR TITLE-ABS-KEY ("calcium phosphate*") OR TITLE-ABS-KEY ("desensitizing agents") OR TITLE-ABS-KEY ("CPP-ACP")	**#3** (LIMIT-TO (SUBAREA , "DENT"))
#1 AND #2 AND #3		
WEB OF SCIENCE 11/March/2020		
#1 TS=("tooth stain$") OR TS=("stained t??th") OR TS=("tooth discoloration$") OR TS=("tooth discolouration") OR TS=("discolored t??th") OR TS=("discoloured t??th") OR TS=("teeth discoloration") OR TS=("teeth discolouration") OR TS=("dental discoloration") OR TS=("dental discolouration") OR TS=("t??th color") OR TS=("t??th colour")	**#2** TS=(bleaching) OR TS=(whitening) OR TS=("tooth sensitivity") OR TS=("potassium oxalate") OR TS=("GLUMA Desensitizer") OR TS=(desensitization) OR TS=(glutaraldehyde) OR TS=("potassium nitrate") OR TS=("dentin sensitivity") OR TS=("hydrogen peroxide") OR TS=("carbamide peroxide") OR TS=("sodium fluoride") OR TS=("calcium phosphate$") OR TS=("desensitizing agents") OR TS=("CPP-ACP")	
#1 AND #2		
LILACS AND BBO 11/March/2020		
#1 (mh:(Tooth discoloration)) OR (mh:(Dentition, Permanent)) OR (tw:("tooth color")) OR (tw:("tooth colour")) OR (tw:("teeth	**#2 (**mh:(Tooth Bleaching)) OR (mh:(Tooth Bleaching agents)) OR (mh:(Peroxides)) OR (mh:(Hydrogen peroxide)) OR (mh:(dentin desensitizing	**#3** db: ("LILACS" OR "BBO")

When more than one experimental or placebo group was evaluated in the primary study, we merged the corresponding groups. In case medians and interquartile ranges were provided, the medians were used as the best estimates of means, and the interquartile ranges converted to standard deviation [SD] (the width of the interquartile range corresponds to approximately 1.35 SD for normally distributed data). Data provided in a numerical rating scale (NRS) and visual analog scale (VAS) were collected and evaluated separately.

In some cases, standard deviations were not reported in the primary articles. As standard deviations of pain scales usually range between half of the reported mean and the mean itself, we imputed a standard deviation equal to the mean in the missing cases. To evaluate the impact of such imputation, we conducted a sensitivity analysis to check if other imputations such as half of the mean could affect the overall conclusions.

Data were analyzed using Revman 5.3 (Review Manager Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark). The risk of TS from the eligible studies was summarized by the risk ratio and the 95% confidence interval, while the intensity of TS was summarized by the mean difference and the 95% confidence interval.

Color change was also evaluated. Data from studies using the same color measurement tool was evaluated separately. The same approaches used for missing cases for the TS were applied for color change data.

For all meta-analysis, we used the random-effects models as this is the most appropriate model for studies performed in different populations. Subgroup analyses based on the type of bleaching (at-home and in-office) were performed. We evaluated the heterogeneity in all meta-analysis with at least four studies. For this purpose, we used the Cochran Q test (which test the null hypothesis that all studies share the same effect size), I^2 statistics (which describe the proportion of the observed heterogeneity is due to real variation of the true effect sizes), and the 95% prediction interval (which is the dispersion of the observed effect sizes). Sensitivity analyses were conducted to investigate the reasons for high heterogeneity, whenever detected.

Assessment of the quality of the evidence using GRADE

We graded the quality of the evidence for primary outcomes across the studies (body of evidence) by using the Grading of

color")) OR (tw:("teeth colour")) OR (tw:("tooth staining")) OR (tw:("tooth stain")) OR (tw:("stained tooth")) OR (tw:("stained teeth")) OR (tw:("tooth discoloration")) OR (tw:("tooth discolouration")) OR (tw:("discolored tooth")) OR (tw:("discoloured tooth")) OR (tw:("discolored teeth")) OR (tw:("discoloured teeth")) OR (tw:("teeth discoloration")) OR (tw:("teeth discolouration")) OR (tw:("dental discoloration")) OR (tw:("dental discolouration")) OR (tw:("tooth discolorations")) OR (tw:("color del diente")) OR (tw:("Color de los dientes")) OR (tw:("Manchas en los dientes")) OR (tw:("Manchas dentales")) OR (tw:("Diente manchado")) OR (tw:("dientes manchados")) OR (tw:("Descoloración de los dientes")) OR (tw:("Dientes descoloridos")) OR (tw:("Dientes de descoloración")) OR (tw:("Descoloración dental")) OR (tw:("descoloraciones de los dientes")) OR (tw:("cor dental")) OR (tw:("Cor dos dentes")) OR (tw:("Dente escurecido")) OR (tw:("Dentes escurecidos")) OR (tw:("Dente manchado")) OR (tw:("Dentes manchados")) OR (tw:("Descoloração dos dentes")) OR (tw:("Descoloração dentária")) OR (tw:("Dente descolorido")) OR (tw:("Descoloração dental")) OR (tw:("descolorações dos Dentes"))	agents)) OR (mh:(dentin sensitivity)) OR (mh:(Glutaral)) OR (mh:(Sodium Fluoride)) OR (tw:(bleaching)) OR (tw:(Clareamiento)) OR (tw:(blanqueamiento)) OR (tw:("Clareamento dental")) OR (tw:(whitening)) OR (tw:("tooth sensitivity")) OR (tw:("Sensibilidad dental")) OR (tw:("Sensibilidade dental")) OR (tw:("potassium oxalate")) OR (tw:("Oxalato de potasio")) OR (tw:("Oxalato de potássio")) OR (tw:("GLUMA Desensitizer")) OR (tw:("Desensibilizante GLUMA")) OR (tw:("Dessensibilizante GLUMA")) OR (tw:(desensitization)) OR (tw:(desensibilización)) OR (tw:(dessensibilização)) OR (tw:(glutaraldehyde)) OR (tw:(glutaraldehído)) OR (tw:(glutaraldeído)) OR (tw:("potassium nitrate")) OR (tw:("nitrato de potasio")) OR (tw:("Nitrato de potássio")) OR (tw:("dentin sensitivity")) OR (tw:("sensibilidad dentinaria")) OR (tw:("Sensibilidade da dentina")) OR (tw:("hydrogen peroxide")) OR (tw:("peróxido de hidrógeno")) OR (tw:("peróxido de hidrogênio")) OR (tw:("carbamide peroxide")) OR (tw:("Peróxido de carbamida")) OR (tw:("sodium fluoride")) OR (tw:("fluoruro de sodio")) OR (tw:("fluoreto de sódio")) OR (tw:("calcium phosphates")) OR (tw:("fosfatos de calcio")) OR (tw:("fosfatos de cálcio")) OR (tw:("calcium phosphate")) OR (tw:("Fosfato de calcio")) OR (tw:("fosfato de cálcio")) OR (tw:("desensitizing agents")) OR (tw:("agentes desensibilizantes")) OR (tw:("Agente desensibilizante")) OR (tw:("CPP-ACP"))	
#1 AND #2		
COCHRANE LIBRARY 11/March/2020		
#1 MeSH descriptor: [Tooth Discoloration] explode all trees #2 MeSH descriptor: [Dentition, Permanent] explode all trees #3 (stain next teeth*):ti,ab,kw (Word variations have been searched) #4 (tooth next stain*):ti,ab,kw (Word variations have been searched) #5 (tooth* next discoloration):ti,ab,kw (Word variations have been searched) #6 (discoloration next tooth*):ti,ab,kw (Word variations have been searched) #7 (tooth* next color):ti,ab,kw (Word variations have been searched) #8 (teeth* next discoloration*):ti,ab,kw (Word variations have been searched) #9 (color next tooth*):ti,ab,kw (Word variations have been searched) #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #11 MeSH descriptor: [Tooth Bleaching] explode all trees #12 MeSH descriptor: [Tooth Bleaching Agents] explode all trees #13 MeSH descriptor: [Peroxides] explode all trees #14 MeSH descriptor: [Dentin Desensitizing Agents] explode all trees #15 MeSH descriptor: [Dentin Sensitivity] explode all trees #16 MeSH descriptor: [Nitrates] explode all trees #17 MeSH descriptor: [Glutarates] explode all trees #18 MeSH descriptor: [Sodium Fluoride] explode all trees #19 (bleaching):ti,ab,kw (Word variations have been searched)	#20 (whitening):ti,ab,kw (Word variations have been searched) #21 (tooth* next sensitivity):ti,ab,kw (Word variations have been searched) #22 (potassium next oxalate):ti,ab,kw (Word variations have been searched) #23 (GLUMA next Desensitizer):ti,ab,kw (Word variations have been searched) #24 (desensitization):ti,ab,kw (Word variations have been searched) #25 (glutaraldehyde):ti,ab,kw (Word variations have been searched) #26 (potassium next nitrate):ti,ab,kw (Word variations have been searched) #27 (dentin next sensitivity):ti,ab,kw (Word variations have been searched) #28 (carbamide next peroxide):ti,ab,kw (Word variations have been searched) #29 (hydrogen next peroxide):ti,ab,kw (Word variations have been searched) #30 (sodium next fluoride):ti,ab,kw (Word variations have been searched) #31 (calcium next phosphate*):ti,ab,kw (Word variations have been searched) #32 (desensitizing* next agent*):ti,ab,kw (Word variations have been searched) #33 ("CPP-ACP"):ti,ab,kw (Word variations have been searched) #34 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 #35 #10 and #34	

Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) to determine the overall strength of the evidence for each meta-analysis [28]. The GRADE pro Guideline Development Tool (available online at www.gradepro.org) was used to create a summary-of-findings table, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2 (http://handbook.cochrane.org) for the primary outcomes in two study follow-ups.

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

Results

Study selection

The search strategy was conducted initially on February 22, 2019, and updated twice (in December 14, 2019, and March 11, 2020). After database screening and duplicate removal, 4896 studies were identified (Fig. 1). After title screening, 206 studies remained, and after abstract screening, 34 studies remained. This number was reduced to 24 after careful examination of the full texts.

From the 34 studies, a total of ten studies were excluded since (1) they did not have a placebo group [13, 14, 29, 30]; (2) they did not use a desensitizer based on potassium nitrate [31, 32]; (3) they were not a RCT, but a clinical case report [33]; (4) they incorporated potassium nitrate only in dentifrices [34, 35]; and (5) they were ongoing studies without results [36].

Characteristics of the included studies

The characteristics of the 24 selected studies are listed in Table 2. The split-mouth design was used in six studies [37–42]. The parallel design was used in 18 studies [12, 21–24, 43–55]. VAS pain scale [21, 23, 37, 39, 40, 42, 46–48, 51–53, 55], and NRS pain scale [12, 21–24, 37, 38, 40, 41, 44, 45, 50] were the ones mostly employed. The study of Leonard [49] assessed patients' risk of sensitivity through a questionnaire applied before and during bleaching.

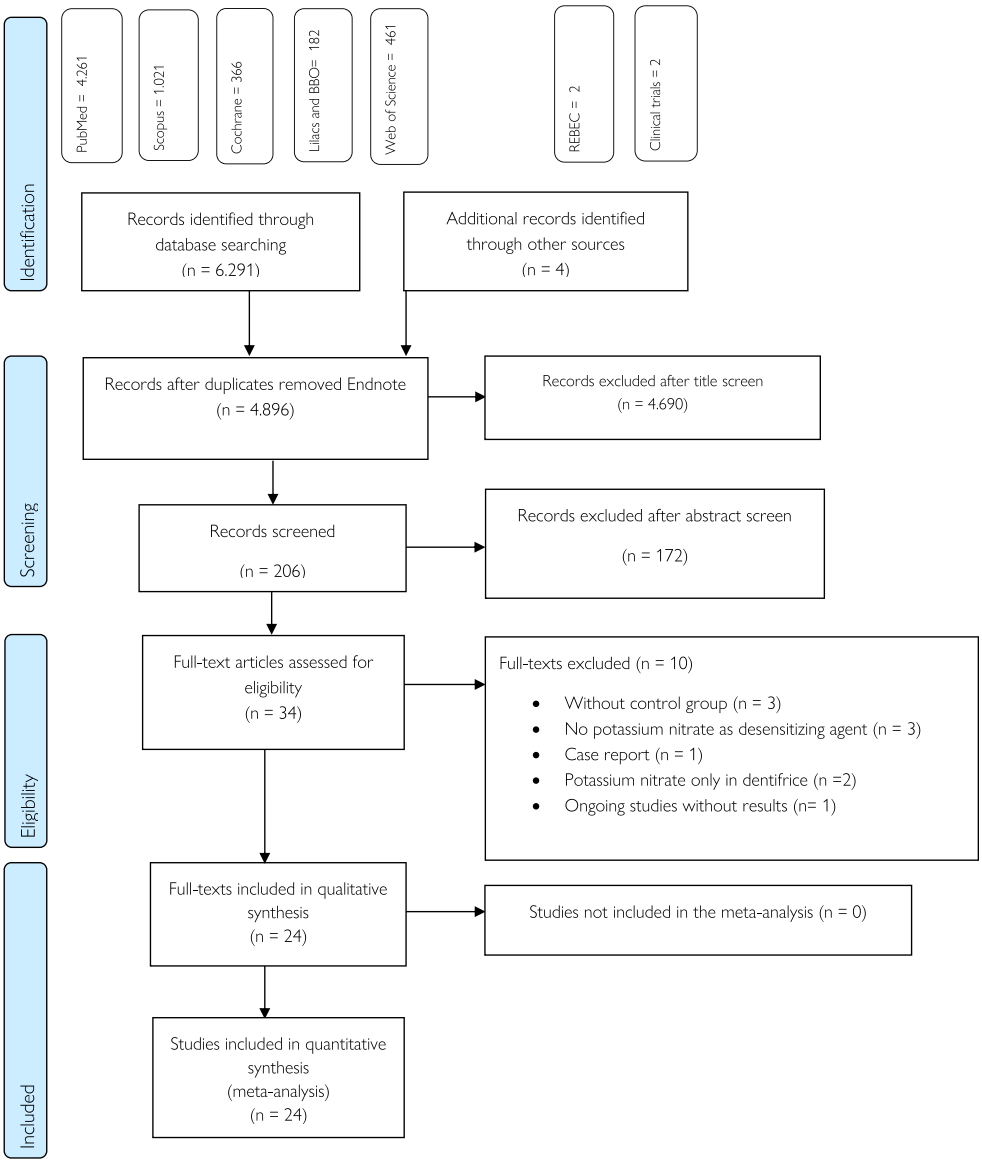

Fig. 1 Flow diagram of study identification. Search date: February 22, 2019; update on December 14, 2019, and March 11, 2010

For color evaluation, eight studies used only shade guides [12, 21, 23, 24, 42, 46, 50, 53], and six studies used shade guides and objective color measure instruments (spectrophotometer or colorimeter) [22, 37, 39, 40, 43, 55]. In two studies, only spectrophotometer was used [38, 52]. In other eight studies [41, 44, 45, 47–49, 51, 54], the authors did not evaluate color change.

The number of patients per group included in these studies ranged from 15 to 58. The mean age of all participants included in the clinical trials was approximately 25 ± 3 years, and the minimum age to participate in the study was 18. In six out of the twenty-four studies, most of the participants were female [22, 38, 41, 47, 49, 53]. Only one study reported that gender distribution was similar [12], and in other 12 studies, this information was not reported [21, 23, 37, 39, 42, 44, 46, 48, 50, 51, 54, 55].

Regarding the bleaching protocol, in 22 out of 24 studies, HP gels were employed [21–24, 37–48, 50–55] with HP concentrations varying from 20 to 35%. Two RCTs used 10% CP [49] and 16% carbamide peroxide (CP) [12]. The most used protocol with HP was two sessions with three applications of 15 min each [21–24, 37, 40, 41, 52, 53, 55]. However, other protocols were also employed. The use of CP ranged from 4 to 6 h daily for 2 to 5 weeks [12, 49]. Two studies used LED activation during HP bleaching [23, 55].

About the desensitizing protocol, 5% potassium nitrate was the most used, applied for 10 min before bleaching [12, 21–24, 37, 38, 41–43, 45–47, 50–52, 54], and 30 min before bleaching [49, 55]. Other concentrations and application times were also observed. For instance, a study applied 6% potassium nitrate for 30 min before bleaching [39], and another one applied 10% potassium nitrate 10 min before bleaching [40].

Table 2 Summary of the studies selected for qualitative analysis this systematic review

Study ID	Study design	Subject's age in mean ± SD [range] (years)	Male/total number of participants	Bleaching protocol	Desensitizing protocol	Outcomes		
						Color evaluation criteria [time assessment]	Pain evaluation criteria [time assessment]	Gingival irritation
Abbud 2018 [39]	Split-mouth	26.9 ± n.r. [20 ± 54]	n.r./31	35% HP[d] ; three 8-min applications/2 sessions/1-week interval	6% potassium nitrate and 0.11% sodium fluoride[s] [30 min before each bleaching session]	ΔSGU (Vita Classical[n], Vita Bleachedguide)[q] and ΔE (Easyshade)[n] [baseline, after 1 and 2 weeks and 1 month post-bleaching]	Risk and intensity with VAS and NRS [during/up to 1 h, 24 h, and 48 h post-bleaching]	Not evaluated
Araujo 2012 [44]	Parallel	n.r. ± n.r. [n.r.]	40/30	35% HP[n.r.]; one 40-min application/3 sessions; 1-week interval	n.r.% potassium nitrate and n.r.% sodium fluoride [10 min before the bleaching session]	Not evaluated	Risk and intensity with NRS scale [before and immediately after the 1st and 2nd session]	Not evaluated
Barbosa 2015 [38]	Split-mouth	26 [18 ± 41]	12/30	35% HP[a]; three 15-min applications/3 sessions/1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before the bleaching]	ΔE (Easyshade)[o] [baseline, after 1st week of bleaching, after 2nd week, after 21 days, after 1 week of end, and 1 month of end of bleaching]	Risk and intensity with NRS [at the end of each bleaching session]	Not evaluated
Bonafé et al. 2014 [22]	Parallel	24.8 ± 4.3 [18 ± 35]	10/30	35% HP[a] three 15-min applications/2 sessions; 1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before each bleaching session]	ΔSGU (Vita Classical)[n] and ΔE (Easyshade)[o] [1 week and 6 months after bleaching]	Risk and intensity with NRS [during/up to 24 h post-bleaching]	Not evaluated
Calheiros 2015 [45]	Parallel	28.7 ± 8.5 [18 ± 40]	37/60	35% HP[a]; three 15-min applications/ three sessions/1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before and 10 min after the bleaching]	Not reported	Intensity with NRS [before and after each bleaching session for 7 days]	Not evaluated
Cerqueira et al. 2013 [46]	Parallel	n.r. [18 ± 40]	n.r./30	20% HP[t]; one 50-min application/2 sessions; 1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before the bleaching]	ΔSGU (Vita Classical)[n] [baseline, after 1 and 2 weeks post-bleaching]	Risk and intensity with VAS and NRS [up to 48 h post-bleaching]	Not evaluated
Crescente et al. 2016 [47]	Parallel	22.7 [18 ± 46]	7/32	35% HP[u]; one 40-min application/3 sessions; 1-week interval	5% potassium nitrate and 2% sodium fluoride[g]; 5% potassium nitrate and 0.2 % sodium fluoride[v] [10 min before the bleaching]	Not evaluated	Risk and intensity with VAS and NRS [immediately after each session]	Not evaluated
De Paula et al. 2019a [41]	Split-mouth	24.0 ± n.r. [18 ± 30]	22/100	35% HP[a]; three 15-min applications/two sessions/1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before the bleaching] 5% potassium nitrate and 2% sodium fluoride[g] [10 min before the bleaching] + laser[r] [16 s]	Not evaluated	Risk and intensity with NRS [during/up to 21 days post-first session of bleaching]	Not evaluated
De Paula et al. 2019b [43]	Parallel	21.8 ± 2.9 [18 ± n.r.]	60/115	35% HP[w]; one 50-min applications/2 sessions/1-week interval	5% potassium nitrate and 0.2% sodium fluoride[g] [10-min for 10 days before the 4 bleaching, in the week interval and 2 days after the second session]	ΔSGU (Vita Classical[m], Vita Bleachedguide)[q] and ΔE (Easyshade)[n] [baseline and 1-month post-bleaching]	Risk with VAS [during/up to 48 h post-bleaching]	Not evaluated
Dias 2017 [48]	Parallel	n.r. [18 ± 40]	n.r./60	35% HP[n.r.]; 45-min applications/ 2 sessions/1-week interval	5% potassium nitrate and 2 % sodium fluoride[n.r.] [n.r.]	Not evaluated	Intensity with VAS [during, up to 6 days post-bleaching]	Not evaluated
Godoy 2016 [42]	Split-mouth	22.5 ± n.r. [20 ± 25]	n.r./20	35 % HP[a]; two 15-min applications/one session	5% potassium nitrate and 2% sodium fluoride[g] [10 min before the bleaching]	ΔSGU (Vita Classical[n]) [baseline and 1 week after the bleaching treatment ends]	Risk and intensity with VAS and NRS [during, up to 1 h, 24 h, and 48 h	Not evaluated

Table 2 (continued)

Study ID	Study design	Subject's age in mean ± SD [range] (years)	Male/total number of participants	Bleaching protocol	Desensitizing protocol	Outcomes		
						Color evaluation criteria [time assessment]	Pain evaluation criteria [time assessment]	Gingival irritation
							post-bleaching]	
Kose et al. 2011 [12]	Parallel	24 ± n.r. [18 ± 30]	30/60	16% CP[b] at least 6h/night [until it reaches color B1 or A1 (5 weeks average)]	5% potassium nitrate and 2% sodium fluoride[g] [10 min before each daily bleaching]	ΔSGU (Vita Classical)[n] [after 30 days]	Risk and intensity with NRS [daily evaluation]	Not evaluated
Leonard et al. 2004 [49]	Parallel	n.r. [19 ± 53]	EXP: 4/40 PL: 1/40	10% CP[c] for 14 days (time of bleaching not reported)	3% potassium nitrate and 0.11% fluoride[h] [30 min before daily bleaching]	Not evaluated	Risk of TS	Risk of GI
Loguercio et al. 2015[24]	Parallel	23.3 ± 5.4 [18 - n.r.]	22/40	35% HP[a] three 15-min applications/2 sessions [10 min before the bleaching]	5% potassium nitrate and fluoride 9000 ppm[z] [10 min before the bleaching]	ΔSGU (Vita Classical)[n] [baseline, after 1 and 2 weeks]	Risk and intensity with NRS [during sessions and 48h post-bleaching]	Not evaluated
Martins et al. 2011 [50]	Parallel	n.r. [18 ± 40]	n.r./30	35% HP[u]; one 40-min application/2 sessions; 1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before each daily bleaching]	ΔSGU (Vita Classical)[n] [baseline, after each bleaching session]	Risk and intensity with NRS scale [daily, did not report for how long]	Not evaluated
Nanjundassetty et al. 2016[51]	Parallel	n.r. [18 ± 30]	n.r./69	35% HP[d] three 15-min applications/1 session	5% potassium nitrate and 0.7% sodium monofluorophosphate[i] [10 min after bleaching]	Not evaluated	Risk and intensity with VAS [after 24 h and 7 days post-bleaching]	Not evaluated
Palé et al. 2014 [55]	Parallel	n.r. [n.r. ± n.r.]	n.r./32	28% HP[e] Three 15-min applications with LED 15-min activation/1 session	5% potassium nitrate[j] [30 min before the bleaching]	ΔSGU (Vita Classical)[n] and ΔE (MHT Optic Research SpectroShade)[p] [immediately after 2 weeks and 3 months]	Risk and intensity with VAS [baseline and 24 h post-bleaching]	Not evaluated
Parreiras et al. 2018 [37]	Split-mouth	22.1 ± n.r. [18 ± 52]	n.r./42	35% HP[a]; three 15-min applications/2 sessions/1-week interval	5% glutaraldehyde and 5% potassium nitrate[l] [10 min before each bleaching session]	ΔSGU (Vita Classical[n], Vita Bleachedguide)[p] and ΔE (Easyshade)[o] [baseline, after 1 and 2 weeks and 1 month post-bleaching]	Risk and intensity with VAS and NRS [immediately, up to 24 h and 48 h post-bleaching]	Not evaluated
Pierote 2019 [52]	Parallel	n.r. [18 ± 30]	58/108	35% HP[a]; three 15-min applications/2 sessions/1-week interval	5% potassium nitrate and 2% sodium fluoride[g] ; 5% potassium nitrate and 8% plus arginine (experimental desensitizer) [10 min before each bleaching session]	ΔE (Easyshade)[o] [baseline, after 4 weeks and 24 weeks after starting bleaching]	Intensity with VAS [immediately, up to 24 h and 24 weeks after starting bleaching]	Not evaluated
Reis et al. 2011 [23]	Parallel	n.r. [18 ± n.r.]	n.r./30	35% HP[a]; three 15-min applications with LED 5-min activation/2 sessions/1-week interval	5% potassium nitrate and 2% sodium fluoride[g] [10 min before each bleaching session]	ΔSGU (Vita Classical)[n] [baseline, after 1 and 2 weeks post-bleaching]	Risk and intensity with VAS and NRS [immediately, up to 24 h and 48 h post-bleaching]	Not evaluated
Rezende et al. 2019 [40]	Split-mouth	24.3 ± n.r. [18 ± 51]	29/43	35% HP[a]; three 15-min applications/2 sessions/1-week interval	10% potassium nitrate[n.r.] [10 min before the bleaching]	ΔSGU (Vita Classical[n], Vita Bleachedguide)[q] and ΔE (Easyshade)[n] [baseline, after 1 and 2 weeks and 1 mouth post-bleaching]	Risk and intensity with VAS and NRS [during, up to 1 h, 24 h and 48 h post-bleaching]	Not evaluated
Santos 2017 [54]	Parallel	n.r. [18 ± 40]	n.r./60	35% HP[a]; 45-min applications/one session	5% potassium nitrate and 2 % sodium fluoride[g] [10 min before the bleaching session]	Not evaluated	Intensity with VAS [during, up to 6 days post-bleaching]	Not evaluated
Tawfik et al. 2019 [53]	Parallel	32.1± 5.3 [18 ± 40]	6/36		5% potassium nitrate + 0.22% sodium fluoride and 0.75%	ΔSGU (Vita Classical)[n] [baseline, after 24 hours		Not evaluated

Table 2 (continued)

Study ID	Study design	Subject's age in mean ± SD [range] (years)	Male/total number of participants	Bleaching protocol	Desensitizing protocol	Outcomes		
						Color evaluation criteria [time assessment]	Pain evaluation criteria [time assessment]	Gingival irritation
				30% HP[x]; three 15-min applications/2 sessions/1-week interval	amorphous calcium phosphate (ACP)[y] [before; after or before + after]	and 1 week each session and 6 months]	Intensity with VAS [immediately and 24 h, 1 week and 1 month after]	
Tay et al. 2009 [21]	Parallel	n.r. [18 ± n.r.]	n.r./30	35 % HP[a]; three 15-min applications/2 sessions/1-week interval	5% potassium nitrate and 2 % sodium fluoride[g] [10 min before each bleaching session]	ΔSGU (VITA Classical)[n] [baseline, after 1 and 2 weeks post-bleaching]	Risk and intensity with VAS and NRS [immediately and up to 24 h post-bleaching]	Not evaluated

Abbreviations: *CP* carbamide peroxide; *HP* hydrogen peroxide; *n.r.* not reported; *ΔSGU* shade guide units; *ΔE* color difference measured with a spectrophotometer; *VAS* visual analog scale, *NRS* numeric rating scale; *GI* gingival irritation; *EXP* experimental group; *PL* placebo group

[a] Whiteness HP Maxx 35%, FGM, Joinville, SC, Brazil

[b] Whiteness Perfect CP 16%, FGM, Joinville, SC, Brazil

[c] Opalescence CP 10%, Ultradent, South Jordan, UT, USA

[d] Pola office HP 35%, SDI Innovative Dental Products, Australia

[e] Flashwhite HP 28%, Corpora®, Barcelona, Spain

[f] Whiteness class with Calcium 4%, FGM, Joinville, Santa Catarina, Brazil

[g] Desensibilize KF 2%, FGM Dental Products, Joinville, SC, Brazil

[h] UltraEZ—3% potassium nitrate and 0.25% by weight fluoride ion, Ultradent, South Jordan, UT, USA

[i] Potassium nitrate 5% and sodium monofluorophosphate 0.7%, Sensodent KF, Indoco Remedies Ltd. (Warren) Mumbai, India

[j] 5% potassium nitrate, Flashwhite Corpora®, Barcelona, Spain

[k] Sensodyne® (potassium nitrate 5% and 1187 ppm monofluorophosphate), GSK, Glaxo Smith Kline, Brazil

[l] Experimental gel composed of 5% glutaraldehyde and 5% potassium nitrate (pharmaceutical laboratory at the local university)

[m] Colgate-Palmolive®, New York, USA

[n] VITAPAN classical, VITA Zahnfabrik, Bad Säckingen, Germany

[o] Vita Easyshade Advance 4.0 ®; Vita Zahnfabrik, Bad Säckingen, Germany

[p] MHT Optic Research AG SpectroShade spectrophotometer, Zurich, Switzerland

[q] VITA Bleachedguide 3D-MASTER, Vita Zahnfabrik, Bad Säckingen, Germany

[r] PBM-LLLT. Photon Laser III infrared DMC Equipments (São Carlos, SP, Brazil)

[s] Soothe® 6%, SDI Limited, Bayswater, Victoria, Australia

[t] Whiteness HP Blue 20%, FGM, Joinville, SC, Brazil

[u] Whiteness HP Blue 35%, FGM, Joinville, SC, Brazil

[v] Desensibilize KF 0,2 %, FGM Dental Products, Joinville, SC, Brazil

[w] Whiteness HP Automixx, FGM Dental Products, Joinville, SC, Brazil

[x] Discus dental, Culver City, 91761 USA

[y] Relief® ACP (Discus Dental, Culver City, 91761 USA)

[z] Nano-P paste, FGM, Joinville, SC, Brazil

Assessment of the risk of bias

Regarding randomization, 16 out of the 24 studies evaluated reported the randomization method used [12, 21–24, 37, 39–43, 45, 50–53]. Only eight of the 24 studies reported the allocation concealment [22, 24, 37, 39, 40, 43, 52, 53].

Blinding was reported in 13 studies [12, 21–24, 37–43, 53]. At the study level, 17 studies [12, 21, 23, 24, 38, 41, 42, 44, 46–52, 54, 55] were judged as having an unclear risk of bias. One study was judged as having a high risk of bias [45] for selective outcome reporting. The authors reported that color change would be measured, but they did not present the results (Fig. 2).

Meta-analysis

Tooth sensitivity

The risk of TS was calculated from a total of 16 studies. This systematic review of the literature showed that desensitizing application produced a relative ratio reduction (RRR) of 12% in the risk of having TS (p = 0.02), with a risk ratio of 0.88 (95%CI 0.78 to 0.98) (Fig. 3). Heterogeneity was detected (p = 0.003), and more than half of the observed variability was due to variation in the true effect sizes (I^2 = 59%).

To make this easier to understand, we can put it in other words. The RRR can be applied to different baseline risks of having TS. For example, approximately 80% of the participants who have their teeth bleached with in-office bleaching gels suffer from TS. If we apply this RRR of 12% over the baseline risk of 80% risk, we end up with an absolute reduction of 9.6%. This gives us the number needed to treat (NNT) of 10 (100/9.6), meaning that 10 patients will need to be treated for one patient to benefit from it. If we apply the same calculations to lower baseline risk of TS, such as for at-home bleaching, which has an approximately 50% risk, we end up with an absolute reduction of 6%, which is equivalent to a NNT of 17.

The intensity of TS was meta-analyzed using two different pain scales. In the VAS scale (Fig. 4), ten studies were included, giving a significant average mean difference of − 0.77 units of VAS units (95%CI − 1.34 to − 0.19; p = 0.01) in favor of the desensitizer group. Heterogeneity was detected (p = 0.01), and it was attributed mainly to variations in the true effect sizes (I^2 = 57%).

To make the understanding of the reported reduction in the intensity of TS more familiar, we can rewrite it in other terms. The non-weighted average of the intensity of TS in the control groups of the eligible studies in this systematic review was approximately 4 units in a 0–10 VAS scale. The present meta-analysis showed that the use of a desensitizer can reduce this mean TS by an average of 0.77, which means that the desensitizer-treated patients would have a mean VAS pain of 3.23 units.

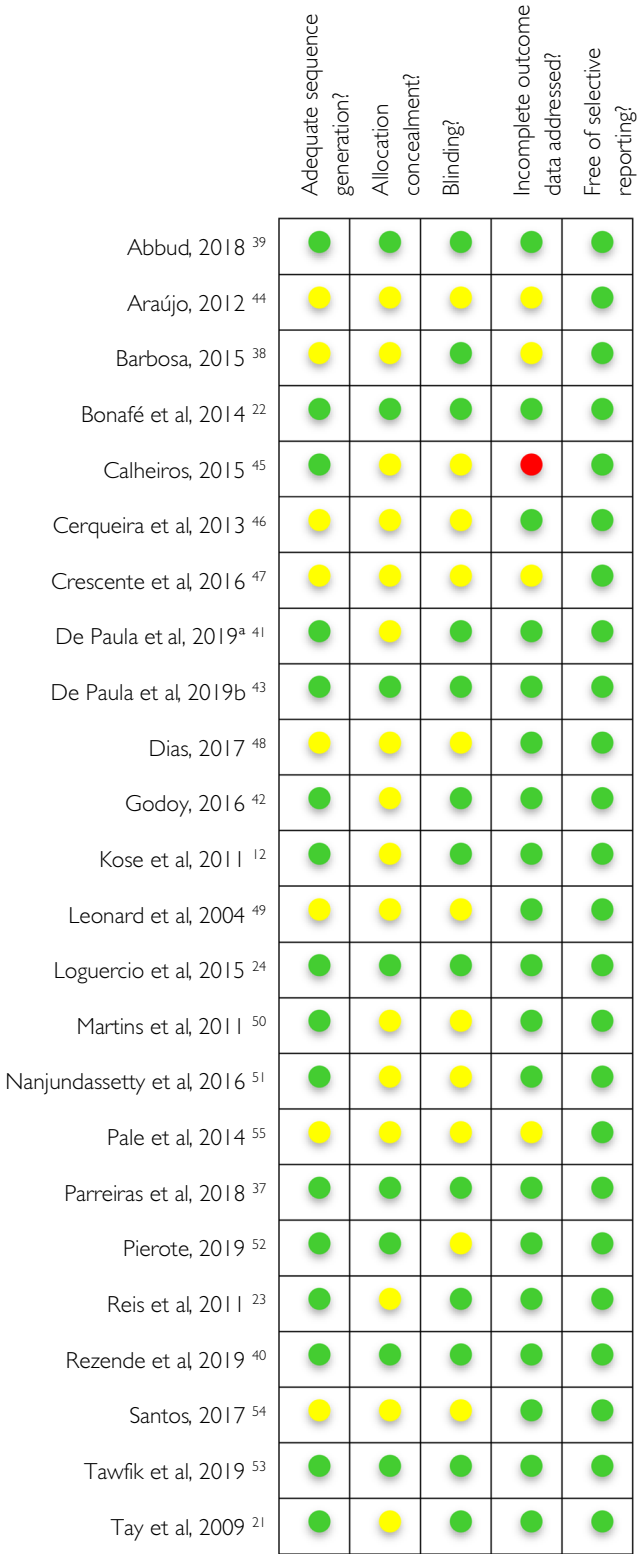

Fig. 2 Summary of the risk of bias assessment according to the Cochrane Collaboration tool

In the NRS scale (Fig. 5), a total of 14 studies were included, with a significant average mean difference of − 0.36 (95% CI − 0.61 to − 0.12; p = 0.004) in favor

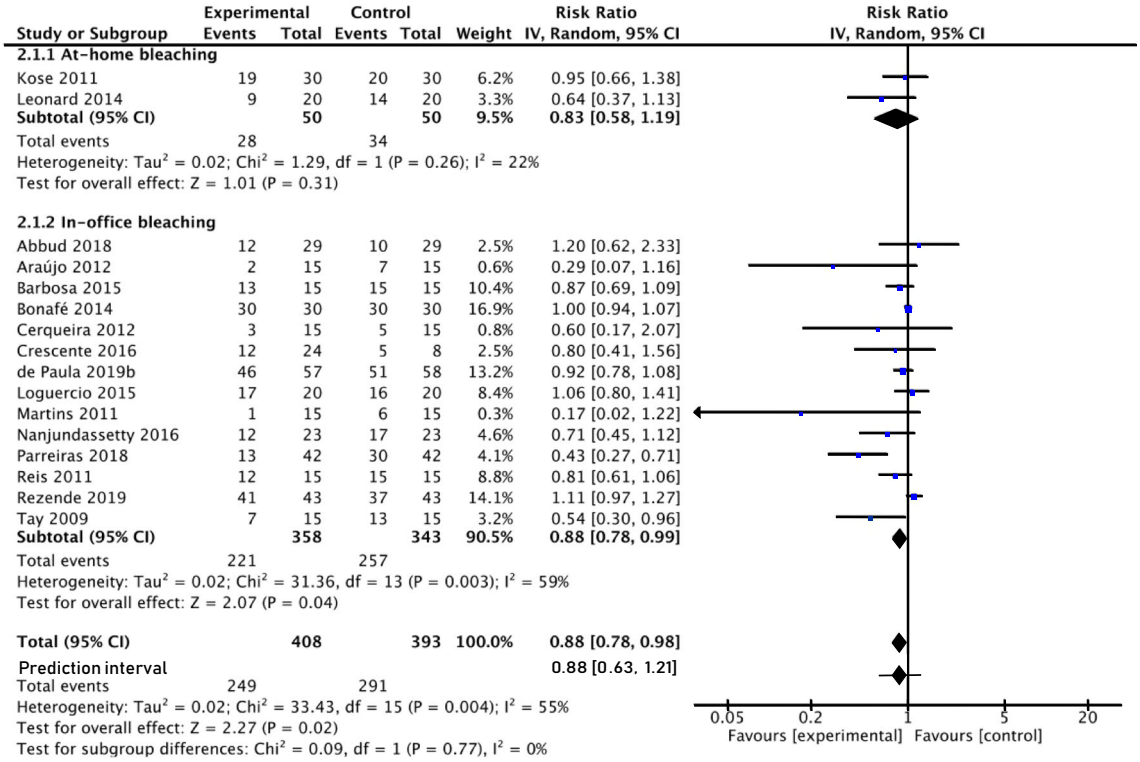

Fig. 3 Forest plot of the risk of TS for dental bleaching with desensitizer vs without desensitizer

of the desensitizer group. Heterogeneity was detected (p value < 0.001), and it was mainly due to variations in the true effect sizes (I^2 = 66%).

Color change

Data from color change were meta-analyzed in ΔSGU Vita Classical (six studies; MD = 0.14; 95% CI − 0.21 to 0.48), final SGU Vita Classical (six studies; MD = − 0.02; 95% CI − 0.29 to 0.24), ΔSGU Vita Bleachedguide (four studies; MD = 0.10; 95% CI − 0.35 to 0.54), and ΔE (seven studies; MD = − 0.22; 95% CI − 0.62 to 0.18). In all cases, no significant difference was observed in color change (p > 0.28). Heterogeneity was not detected in none of the meta-analysis (p > 0.25, Figs. 6, 7, 8, and 9).

Subgroup analysis

We performed subgroup analysis based on the type of bleaching protocol employed (at-home or in-office bleaching), as can be seen in the forest plots of the outcomes. The bleaching protocol did not explain the heterogeneity detected in the data for TS.

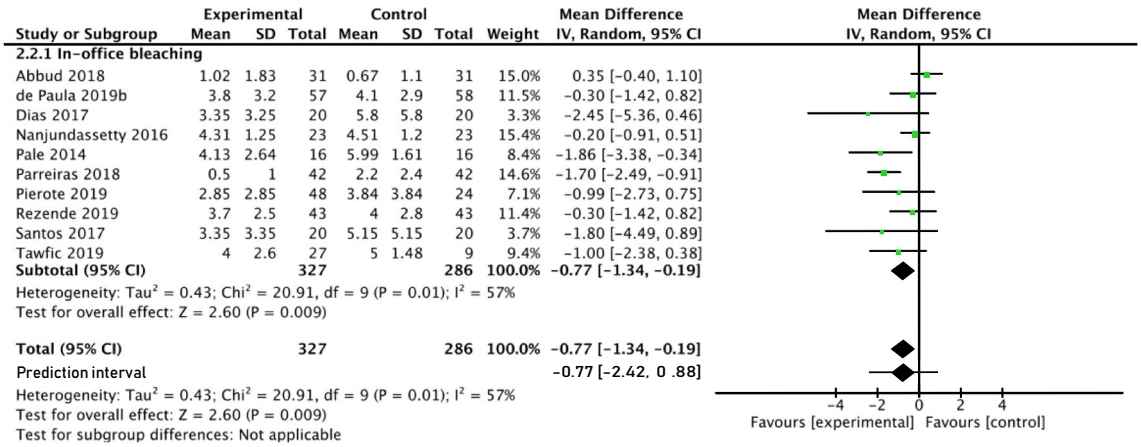

Fig. 4 Forest plot of the intensity of TS using the VAS scale for dental bleaching with desensitizer vs without desensitizer

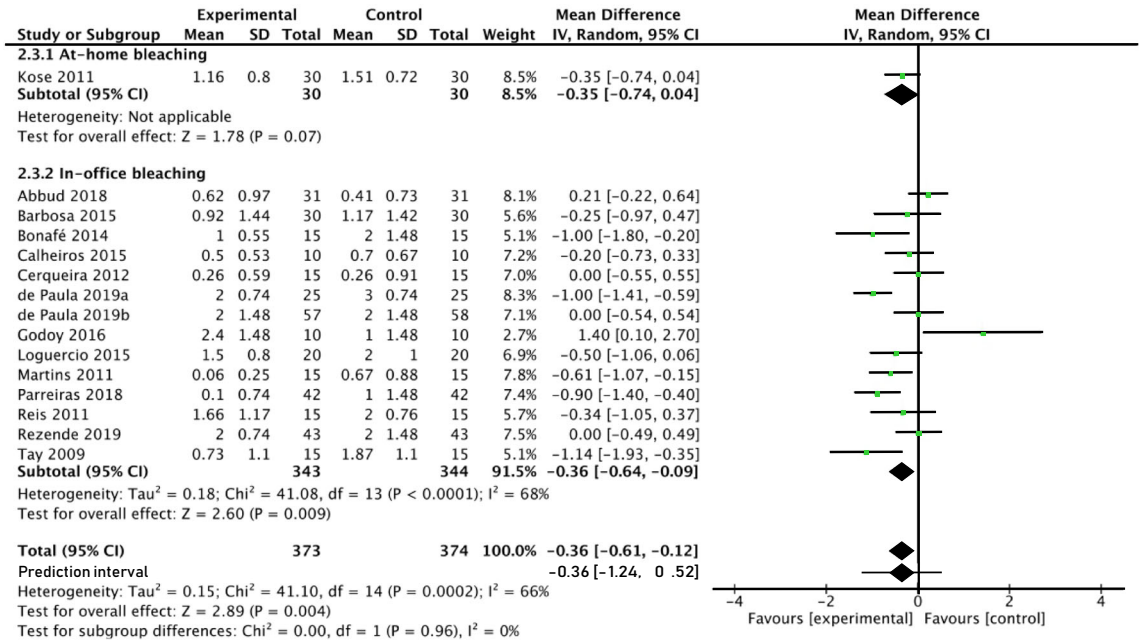

Fig. 5 Forest plot of the intensity of TS using the NRS scale for dental bleaching with desensitizer vs without desensitizer

Sensitivity analysis

Imputations had to be made in some cases where standard deviations were not reported in the full texts, both in data from intensity of TS in VAS scale [48, 52, 54], intensity of TS in NRS scale [24], and color change in ΔE [55]. Sensitivity analysis using more extreme values of imputations were performed, but the overall conclusions were not affected.

Additionally, we suspected that the study of Dias [48] and Santos [54] shared the same experimental group with different comparators. In a sensitivity analysis, we excluded one or the other in the meta-analysis where they were included, but the conclusions remained the same.

Certainty of the evidence

A total of three outcomes for TS (risk of TS, intensity of TS in VAS scale, and intensity of TS in NRS scale) and four outcomes for color change (ΔSGU Vita Classical, Final SGU Vita Classical, ΔSGU Bleachedguide, and ΔE) were evaluated. The certainty of evidence for all these outcomes is summarized in Table 3. Regarding TS, all outcomes were graded as low certainty of the evidence due to the fact that most articles included in the meta-analysis were at unclear risk of bias and due to unexplained heterogeneity. Data from the color change was graded as high (in the meta-analysis composed mostly with studies at low risk of bias) or moderate (when most of the studies included were at unclear risk of bias).

Discussion

Dental bleaching protocols employ hydrogen peroxide (HP) as the oxidizing agent. HP has a low molecular weight and thus penetrates the dental substrates fast and easily. However,

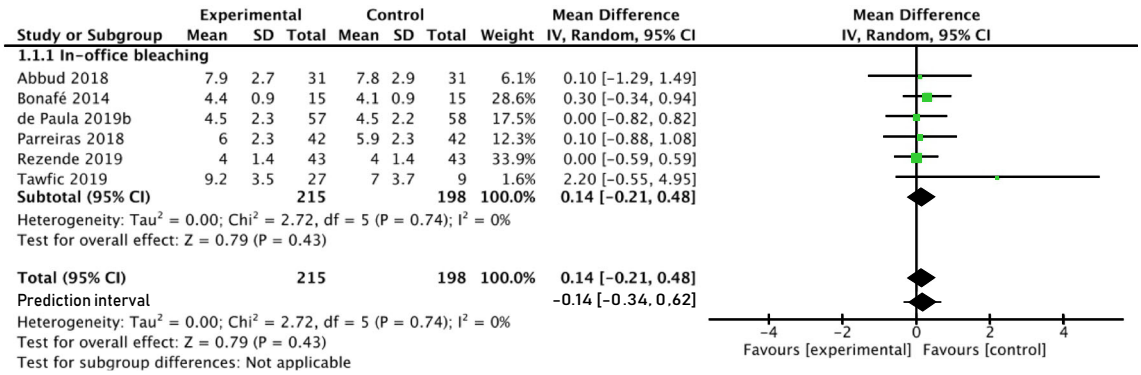

Fig. 6 Forest plot of the color change in shade guide units (ΔSGU Vita Classical) for dental bleaching with desensitizing vs without desensitizing

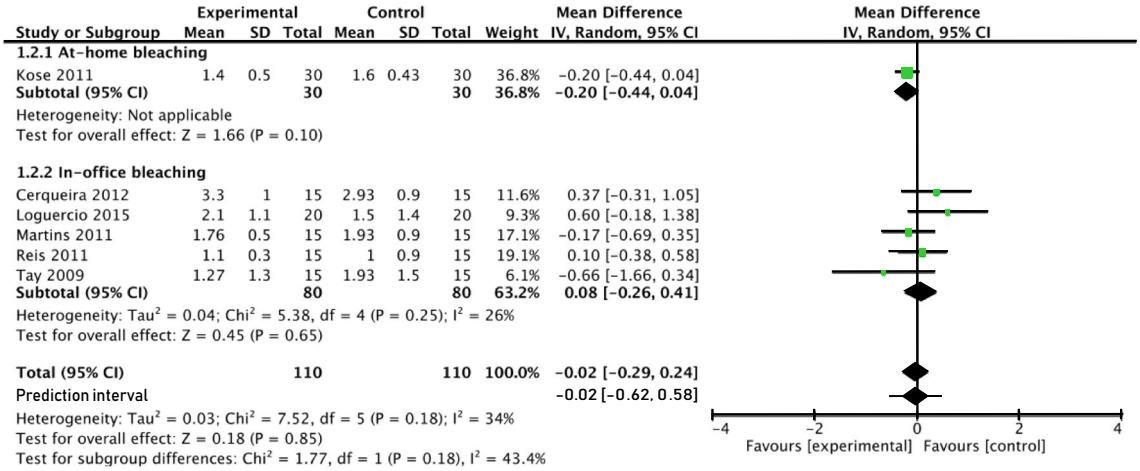

Fig. 7 Forest plot of the color change in shade guide units (Final ΔSGU Vita Classical) for dental bleaching with desensitizing vs without desensitizing

this penetration is not only restricted to the dental hard tissues. HP can reach the pulp chamber within few minutes [56–58] and may cause inflammatory reaction [59, 60], oxidative stress, and cell damage.

This penetration is facilitated by factors such as the patient's age, the concentration of the bleaching gel, the application time, the presence of restorations, and the end pH of the bleaching product [61–64]. Consequently, inflammatory mediators and stimulating nociceptors are released, causing pain transmission [65].

The presence of this undesirable side effect is the reason why topically applied desensitizing agents have been studied as preventive measures to avoid the undesirable bleaching-induced TS. Among these agents, potassium nitrate has been described as an alternative to minimize this side effect [25], although its exact mechanism of action to reduce TS in the dental bleaching is not well known [66].

As well as HP, potassium nitrate can penetrate the dental hard tissues and reach the pulp chamber [67, 68], and this penetration is considered time-dependent [68]. Theoretically, in the pulp tissue, potassium nitrate is believed to reduce dentinal sensory nerve activity by preventing nerve repolarization due to excess of K+ ions outside the nerve membrane. Without nerve repolarization, pain impulse does not progress through the length of the nerve fibers, and the patient may not feel the bleaching-induced TS [69–71].

Not included in this review, studies using toothpastes containing potassium nitrate in the composition, because the contact time and the concentration of the active ingredient is very different from the desensitizing potassium nitrate used for topical applications. In the majority of the studies, potassium-based desensitizers are usually applied for 10 min, while in the best scenario, dentifrices do not stay longer than 3 min in the buccal cavity. When included in desensitizers, potassium nitrate is incorporated in concentrations that range from 3 to 10% [40]; in dentifrices these concentrations are not superior to 5% [34]. Additionally, potassium nitrate–based dentifrices are leached out by the contact with saliva, which does not occur in professionally topical application of a desensitizer.

We also decided to exclude from this systematic review studies that included potassium nitrate in the bleaching agent. When incorporated into the gel, the potassium nitrate stays longer in contact with the dental structure, but it is delivered simultaneously to the hydrogen peroxide, differently to what occur to potassium nitrate desensitizers applied in a preventive

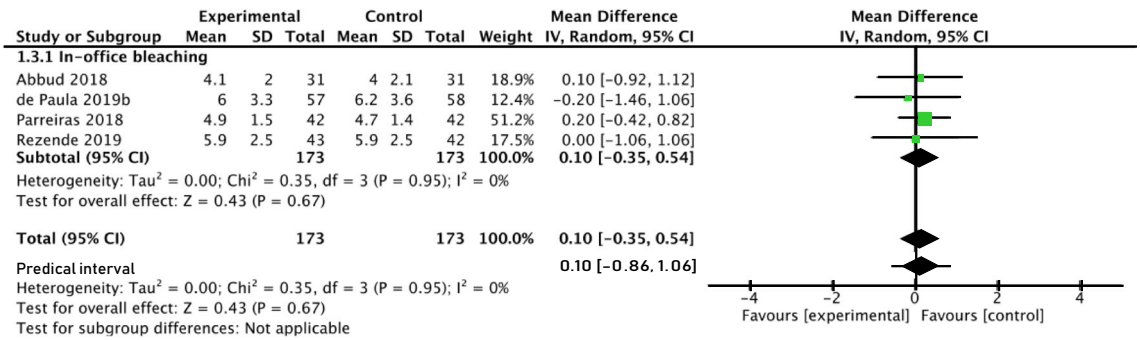

Fig. 8 Forest plot of the color change in shade guide units (ΔSGU Vita Bleachedguide) for dental bleaching with desensitizing vs without desensitizing

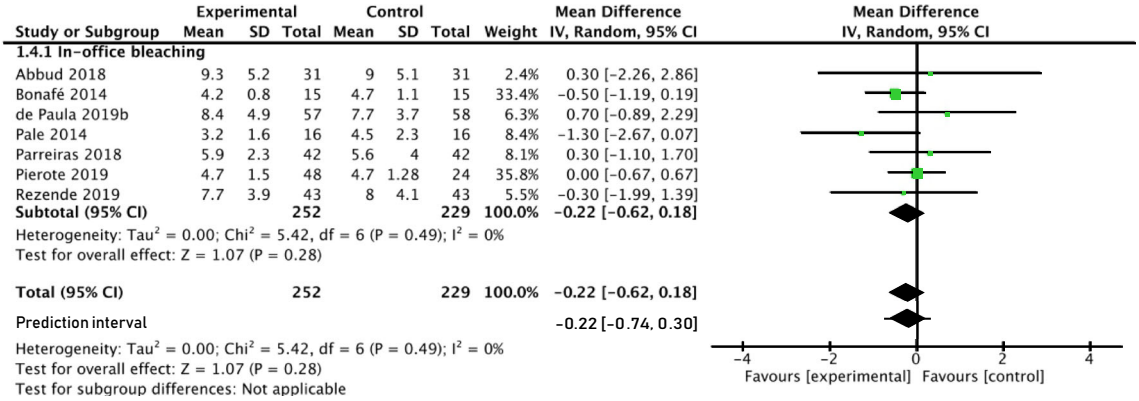

Fig. 9 Forest plot of the color change in (ΔE*) for dental bleaching with desensitizing vs without desensitizing

manner [72]. The universe of eligible studies included in a systematic review should be narrow enough to collect studies with similar populations, treatment protocol, and comparator group to avoid a high heterogeneity of the data [73, 74].

Table 3 Summary of findings with the certainty of the evidence using the GRADE approach

Outcomes	№ of participants(studies)	Certainty of the evidence(GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with potassium nitrate–based desensitizer
Color change in Delta SGU Vita Classical assessed with: Vita Classical shade guide	413(6 RCTs)	⊕⊕⊕⊕HIGH	-	The mean color change in Delta SGU Vita Classical was 0 units	MD 0.14 Delta SGU higher(0.34 lower to 0.62 higher)
Color change in Final SGU Vita Classical assessed with: Vita Classical shade guide	220(6 RCTs)	⊕⊕⊕○MODERATE [a]	-	The mean color change in Final SGU Vita Classical was 0 units	MD 0.02 Final SGU lower(0.29 lower to 0.24 higher)
Color change in Delta SGU Bleachedguide assessed with: Vita Bleachedguide shade guide	346(4 RCTs)	⊕⊕⊕⊕HIGH	-	The mean color change in Delta SGU Bleachedguide was 0 units	MD 0.1 Delta SGU higher(0.35 lower to 0.54 higher)
Color change in Delta E assessed with: Spectrophotometer	613(7 RCTs)	⊕⊕⊕⊕HIGH	-	The mean color change in Delta E was 0 units	MD 0.83 units of Delta E lower(1.46 lower to 0.2 lower)
Risk of tooth sensitivity assessed with: dichotomous scale (yes/no)	801(16 RCTs)	⊕⊕○○LOW [a,b]	RR 0.88(0.7-8 to 0.98)	740 per 1,000	89 fewer per 1,000(163 fewer to 15 fewer)
Intensity of tooth sensitivity using VAS scale assessed with: VAS scale	613(10 RCTs)	⊕⊕○○LOW [a,b]	-	The mean intensity of tooth sensitivity using VAS scale was 0 units	MD 0.83 VAS units lower(1.46 lower to 0.2 lower)
Intensity of tooth sensitivity using NRS scale assessed with: NRS scale	747(14 RCTs)	⊕⊕○○LOW [a,b]	-	The mean intensity of tooth sensitivity using NRS scale was 0 units	MD 0.36 NRS units lower(0.61 lower to 0.12 lower)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI* confidence interval; *MD* mean difference; *RR* risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Explanations: [a.] The majority of the studies are at unclear risk of bias; [b.] Unexplained heterogeneity

Another systematic review was recently published addressing specifically the addition of desensitizers into the bleaching gels [72]; this study concluded that incorporating desensitizers in the bleaching gel did not reduce the risk of TS, and the quality of this evidence was considered moderate. On the other hand, the intensity of TS, color change, and risk of gingival irritation were similar between groups, but the quality of the evidence was graded as low or very low.

An earlier systematic review of the literature addressing this issue reported that potassium nitrate agents are effective in reducing the bleaching-induced TS [25]. In this systematic review, review authors included studies that evaluated the association of potassium nitrate with fluorides. It is claimed that fluorides can obliterate the dentinal tubules by precipitation of fluorine crystals, preventing the HP from reaching the pulp [75].

However, in most of the primary studies, patients with exposed dentin surfaces, where fluorides could have a beneficial effect, were excluded from the sample. Therefore, the benefit of fluorides in these cases is questionable, explaining why, in the present study, we included studies that evaluated potassium nitrate alone or in association with other agents.

It is also important to note that the systematic review published [25] presents flaws, and discussion about them is crucial to avoid these common mistakes in future systematic reviews. The data replicated from the same study population many times [22, 76, 77] overestimate the reported effect size in the study and increases the power of the systematic review unequivocally.

Additionally, the authors use a fixed-effect model for the meta-analysis, which is not the most appropriate to use [76, 78]. This fixed-effect model assumes that there is a single effect size, common to all studies. This assumption is unlikely to be true due to variations in the populations, bleaching protocols, and composition of the desensitizing agents. By using the fixed-effect model, the confidence intervals for the summary effect are smaller than under the random-effect model, which is the most appropriate statistical model [79]. Thus, the chances of finding statistically significant results are increased under the fixed-effect model. Finally, from the time this study was published until today, several new studies on the topic have been published, the reason why this study was conducted. In this case, we assume that each study is estimating different, yet related, intervention effects, and we want to know the average of all these different and related effect sizes along with the heterogeneity of these estimates.

In the present systematic review, we observed that potassium nitrate has a positive benefit in preventing the development of bleaching-induced TS. On average, patients treated with potassium nitrate–based agents have a 12% lower risk of presenting TS. In terms of pain intensity, the average reduction was less than 1 unit in VAS, and around 0.35 units in the 0-10 NRS scale. However, these figures should be interpreted with caution. Although these positive findings were statistically significant, they represent small effect sizes, with questionable clinical importance. An average of one unit in a VAS 0–10 or 0.35 unit in a 0–4 NRS scale does not represent a clinically relevant reduction in the intensity of the bleaching induced TS.

Although we could not identify, from a statistical perspective, the reasons for the heterogeneity that was observed in the meta-analysis, from a clinical view, the observed heterogeneity must be due to the different bleaching protocols and the different compositions of the potassium nitrate–based desensitizers. Although all studies applied potassium nitrate, the composition of these desensitizers varied. Changes in the concentration of the potassium nitrate and inclusion of other products, such as fluorides, as in most cases [12, 21–24, 38, 39, 41–48, 50, 52–54], glutaraldehyde [37], sodium monofluorophosphate [51], and nano-calcium phosphate crystals [24, 49], were observed. Additionally, variations of the bleaching protocols (varied HP concentrations, application times, frequency of application as well as number of clinical sessions) may also affect the overall bleaching-induced TS [6], and therefore, may impact the results.

We are confident to state that color change is not affected by the application of potassium nitrate–based agents. This conclusion was reached in the four meta-analyses of color change, and it is robust enough not to be affected by the type of color change instrument used. The HP and the potassium nitrate can penetrate the pulp tissue, but they do not compete for the same sites in the hard tissues, as each one has different mechanisms of action [14].

Most of the studies included in the present investigation were considered at unclear risk of bias in the domains sequence generation and allocation concealment, which agrees to what was previously reported in other bleaching studies [8, 80]. Adequate random sequence generation and allocation concealment are crucial to prevent selection bias, so that we can be confident that studies have comparable known and unknown characteristics at baseline. Thus, the differences obtained after the implementation of the treatments can only be attributed to the treatment itself. The fact that most studies were classified as unclear highlights the need for significant improvements in the conduction and report of future RCTs.

Future RCTs should focus on the investigation of other types of desensitizing agents and their combination to prevent or reduce the undesirable side effect of bleaching-induced TS. Apart from potassium nitrate, which has neural action, other types of desensitizing agents such as fluorides, bioactive agents, amorphous calcium phosphate, nano-hydroxyapatite, bioglass, or even their association could be the focus of further randomized controlled trials.

Conclusions

Although a significant reduction in the risk and intensity of TS was observed in groups treated with a potassium nitrate before

dental bleaching, the clinical significance of this reduction is subtle, and it may be clinically questionable. Color change is not affected by the preliminary use of a potassium nitrate–based agent.

Declarations

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 that there is no conflict of interest.

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