Review Article

EFFECTIVENESS OF DIFFERENT DESENSITIZING AGENTS ON IN-OFFICE TOOTH WHITENING - A SYSTEMATIC REVIEW AND META-ANALYSIS

Abstract

Objective: To summarize the available evidence on the efficacy of desensitizing agents on dentin sensitivity following tooth whitening. Sources: On September 04, 2021, a comprehensive search of MEDLINE via PubMed, EMBASE, LILACS (Latin American and Caribbean Health Sciences Literature), LIVIVO, SCOPUS, Web of Science, and the gray literature by Google Scholar was performed. Study selection: After removal of duplicates, title, and abstract screening by two reviewers (performed in the Rayyan tool for systematic reviews), 13 articles were included, selected only blinded randomized clinical trials, which present patients with discolored teeth submitted to in-office and/or home tooth whitening and desensitizing agents used. The following data were collected: authors, year of publication, objectives or research questions, desensitizing agent, number of participants, number of groups, control group description, study group description, whitening approach, outcomes evaluated, main results, main conclusions, the scale used for outcome measurement, risk of tooth sensitivity (outcome), statistical test used, odds ratio/IC results, dentin sensitivity intensity analysis (intergroup statistical test), dentin sensitivity intensity analysis (intragroup statistical test), and maximum analysis time. Conclusion: Based on the findings of this study, it was possible to verify that the desensitizing agents acted significantly reducing tooth sensitivity and the *odds-ratio* of patients submitted to in-office tooth whitening.

KEYWORDS: Dental whitening, Dentin desensitizing agents, Dentin sensitivity, Randomized controlled trial, Clinical trial; Trial.

1 INTRODUCTION

Among the aesthetic procedures in dentistry, tooth whitening is the most sought-after and conservative [1]. It can be performed through the home technique, in which the patient uses a tray, or the office technique, performed by the professional in an outpatient setting [2]

Whichever technique is selected, tooth whitening occurs through the chemical degradation of chromogen pigments present in the tooth structure. These pigments are characterized by high molecular weight and low mobility. When light falls upon these molecules, partial absorption occurs, resulting in the perception of darkened teeth. Hydrogen peroxide, when in contact with organic compounds of the tooth structure, releases free radicals, such as nascent oxygen. The oxygen, in contact with the chromogen pigments, promotes a cleavage reaction, making them smaller and more reflective, resulting in the perception of lighter teeth. The basic whitening process involves the oxidation of organic compounds, with carbon dioxide and water as byproducts [3].

Using lower concentrations of peroxide reduces the risk of sensitivity [4]. Post-whitening tooth sensitivity is characterized by acute, sudden, short-lasting pain. Increasing the concentration of hydrogen peroxide (30 to 35%) to accelerate the whitening process is related to a higher saturation of hydrogen ions, resulting in increased expression of inflammatory mediators such as prostaglandins and cyclooxygenases. Both play a role in triggering nociceptive impulses and pain perception [4].

To decrease dentin sensitivity after office bleaching, different topical and systemic protocols have been introduced. The use of desensitizing agents before whitening has proven to be an excellent alternative, reducing the prevalence and intensity of sensitivity [5]. Moreover, the prescription of analgesics, desensitizing gels, laser therapy, ozone therapy, fluorides, the reduction of the concentration of the bleaching gel, and the reduction of the treatment time can contribute to the reduction of sensitivity [6]. The association of protocols, such as the use of topical desensitizing agents with corticosteroids or potassium salts, can act synergistically in reducing pain [7].

Despite the existence of few clinical trials that prove the efficacy of systemic medications in reducing dentin sensitivity during and after tooth whitening, the apparent ineffectiveness can be explained by the fact that the systemic analgesic effect does not reach the pulp tissue, which is involved by mineralized tissue. In addition, the immune system, lymphatic drainage, and the dentin substrate itself can alter the characteristics of the medication. Some analgesics can relieve pain temporarily by inhibiting certain prostaglandins, but other inflammatory mediators are not affected [8, 9].

Topical desensitizing agents can be classified as neural, obliterating or mixed agents. Neural agents, such as potassium, act on nerve impulse transmission, depolarizing the extracellular concentration of ions in the neural membranes and reducing the symptoms of dentin hypersensitivity. Obliterating agents, such as glutaraldehyde, oxalates, strontium, varnishes and fluorides, seal the dentinal tubules by precipitating proteins, remineralizing the structure and reducing the flow of fluid inside the tubule. The mixed agents, such as potassium oxalate, act in depolarizing nerve fibers due to the action of potassium present in its composition, and obliterate the dentinal tubules exposed by the reaction of oxalate with dentin, forming calcium oxalate crystals [10, 11]

Given the above, it can be seen that there is still no desensitizer that adequately controls tooth sensitivity during and after whitening. This can be attributed to flaws in the sample calculation, the concentration of the whitening agent used, and the patient's perception of pain [4, 12]. Therefore, the aim of this systematic literature review is to answer the following PICO question (problem/patient/population, intervention/indicator, comparison, and outcome): What is the effect of desensitizing agents in controlling tooth sensitivity in office whitening? The purpose of this systematic review and meta-analysis is to summarize the available evidence on the effectiveness of desensitizing agents in reducing tooth sensitivity following tooth whitening.

2 MATERIALS AND METHODS

2.1 Protocol and Registration

This study protocol was based on the Main Items for Reporting Systematic Reviews and Meta-Analyses - PRISMA, and registered in the International Prospective Register of

Systematic Reviews (PROSPERO - CRD42021235207). In addition, the report of this study is based on the PRISMA checklist (PAGE et al., 2021).

2.1 Focus question

Are desensitizing agents effective in controlling tooth sensitivity in-office bleaching?

2.2 PICO Question

Participants (P): patients with whitened teeth submitted to in-office tooth whitening;

-Intervention (I): desensitizing agents;

-Comparisons (C): placebo or negative control;

-Outcome (O): endpoints of tooth sensitivity assessment: pain measured within 24 hours and odds ratio.

2.3 Eligibility Criteria

Only blinded, split-mouth, or paraplegic randomized clinical trials were included in this meta-analysis, and they had to respond to the PICO format mentioned above. For the exclusion criteria, we excluded non-randomized clinical trials, observational studies, laboratory studies, case reports, reports of treatment protocols, clinical trials that did not have a placebo or negative control group, studies that did not use the same bleaching gel for the experimental groups, personal opinions, letters, abstracts, posters, texts not available in full and duplicate studies.

2.4 Research Strategy

Search strategies tailored to each of the following selected databases were adopted: EMBASE, Latin American and Caribbean Health Sciences (LILACS), LIVIVO, PubMed, SCOPUS, Web of Science, and The Cochrane Library. In addition, a literature search was performed partially in Google Scholar. All searches of the electronic databases were performed in the period September 2021 to August 2022.

The keywords for the search of the RCTs (randomized clinical trials) included: Tooth bleaching; dentin desensitizing agents; dentin sensitivity; randomized controlled clinical trial; clinical trial; trial.

2.5 Study Selection and data collection

A two-stage selection process was performed. In the first phase, three reviewers independently reviewed the titles and abstracts to identify eligible studies using online software (Rayyan, Qatar Computing Research Institute). After that, in the second phase, the reading of the eligible studies in full was performed by the same reviewers as in the first phase. Any discrepancies between studies were resolved by discussion and consensus, and a fourth reviewer was included to make the final decision when necessary (see flow chart in Figure 1). For the qualitative analysis, only those studies that met the minimum eligibility criteria were included.

2.6 Qualitative evaluation

Only studies that provided the following data were considered for qualitative analysis: name of authors, year of publication, number of participants, country, type of study, bleaching agent, desensitizing agent, bleaching approach, description of a control group, description of treatment group, outcomes assessed, sensitivity scale, interval and duration of analysis, power calculation, sample size calculations, description of statistical tests.

The risk of bias of the included RCTs was independently assessed by three reviewers using the Cochrane Collaboration Tool and ROBIS (Risk of Bias for Systematic Reviews).

2.7 Statistical methodology

This meta-analysis of RCTs was conducted to estimate the efficacy of desensitizing agents for tooth sensitivity. The type of data for outcome measurement included dichotomous data and continuous data. Dichotomous data were summarized by odds ratio (OR) with 95% confidence interval (CI). Continuous data for tooth sensitivity (TS), were summarized by mean difference (MD) with a 95% CI. The analysis of

OR was performed using the log odds ratio as the outcome measure. TS analysis was performed using the standardized mean difference as the outcome measure. A random effects model was fitted to all data. The amount of heterogeneity was estimated using the restricted maximum likelihood estimator (VIECHTBAUER et al., 2005). In addition to tau² estimation, the Q-test for heterogeneity (Cochran 1954) and the I^2 statistic were performed. Student residuals and Cook's distances were calculated to evaluate discrepant and/or influential studies in the context of the adopted model. The rank correlation test and the regression test, use the standard error of the observed results as pra edictor. The data collected in the study were analyzed using JAMOVI software (The Jamovi Project (2020), Jamovi (Version 1.2) [14].

3 RESULTS

3.1 Study Selection

The search strategy started on September 04, 2021, and closed on August 11, 2022. After searching the databases, 932 articles were found in the databases and additionall, 54 records were found in the grey literature, for a total of 986 records found. After eliminating 433 duplicate records, 553 papers remained for analysis. After reading titles and abstracts, 73 articles remained, of which, along the way, 60 papers were excluded for not meeting the eligibility criteria for qualitative analysis. Finally, 13 articles were selected for this systematic review and meta-analysis, of which 10 articles were used for the OD analysis and 11 papers for the TS analysis.

3.2 Qualitative Analysis of the Studies

According to the ROBIS *risk of bias* analysis (Table 1), most studies showed low risk and two studies showed uncertain risk. This uncertain risk is explained by an inefficient or low sample size calculation, sometimes an inefficient blinding of either patients or research collaborators.

Most of the studies were conducted with the Split Mouth type design in 54% of the included studies, while 46 % of the studies were parallel type. The average number of participants in each study was 60 for Split Mouth 67 for parallel type. Regarding the sample calculation, of the evaluated articles that were published, only 15.4% did not present a sample calculation, and these were those published before 2013.

Regarding the number of groups, most studies had 2 groups (92%). All studies included in this review presented the inclusion of negative control or placebo groups. The studies included in this review were mostly developed in Brazil (84.6%), followed by Spain and Jordan (7.7% each).

The endpoints used by the studies included in this work were TS and OD. The tooth sensitivity (TS) in up to 24 hours was studied by 85% of the analyzed articles, while the odds ratio (OD) was analyzed by 77% of the included studies. In relation to the evaluation methods of dentin sensitivity, the most used, 85%, was VAS (visual analog scale) with measurement in millimeters (mm) of pain, while 61.5% of the studies used two simultaneous scales for pain evaluation: VAS scale measured at the millimeter level and NRS scale with scores from 0 to 4.

The most commonly used desensitizing agents were potassium nitrate with 46.1% and gluteraldehyde with 15.4%. The use of gluteraldehyde, medication, and ozone accounted for 7.7% each. Other remaining desensitizers accounted for 15.4%. As for the bleaching approach, it was possible to verify that hydrogen peroxide between 35% and 40% was the most used, being the concentration range more indicated for in-office bleaching analyzed in this study. As for the number of bleaching sessions performed, 38.5% were done in a single session, and most of the studies did it in two sessions (61.5%) separated by a one-week interval.

3.3 Meta-Analysis

Figure 2 presents the forest plot of the main results of the meta-analysis performed with 11 randomized clinical trial studies regarding the ST outcome. Most of the mean differences obtained, based on the random effects model used in this study, were negative (69%). The standardized mean difference obtained for the ST outcome was:

- 0.1409. The overall analysis estimated a statistically significant difference in the impact of desensitizing agent use in obtaining lower dental sensitivity scores when compared to placebo treatment (p = 0.036, 95% CI: -0.273; -0.009).

The heterogeneity analysis that for the TS analysis revealed that the studies showed low heterogeneity: Tau = 0.08, Tau2: 0.006, Q: 20.765, i2: 10.99%. The analysis of the studentized residual revealed that none of the studies evaluated demonstrated a value greater than ± 2.8905 and, therefore, there was no indication of outliers in the context of the model studied. According to Cook's test distances, none of the studies could be considered as overly influential. Both the rank correlation and the regression test indicated no asymmetry in the funnel plot (p = 0.4354 and p = 0.1084, respectively).

For the OR analysis, 10 randomized clinical trial studies were included, as shown in figure 3, which presents the forest plot of the main results of this meta-analysis. Most of the mean differences obtained, based on the random effects model used in this study, were negative (70%). The estimated mean log of OR was performed based on the random effect was -0.554. The overall analysis estimated a statistically significant difference in the impact of desensitizing agent use on OR when comparing the treatment group with the placebo group, so that the use of desensitizing agent provided statistically lower OR results for the treatment group (p = 0.013, 95% CI: -0.994; -0.115).

The analysis of heterogeneity that for the OR analysis revealed that the studies showed low heterogeneity: Tau = 0.416, Tau2: 0.1735, Q: 15.629, i2: 36.16%. The analysis of the studentized residual revealed that none of the studies evaluated demonstrated a value greater than ± 2.807 and, therefore, there was no indication of outliers in the context of the model studied. According to Cook's test distances, none of the studies could be considered as overly influential. Both the rank correlation and the regression test indicated no asymmetry in the funnel plot (p = 0.4843 and p = 0.5536, respectively).

DISCUSSION

Desensitizing products are used in order to reduce painful symptoms when the exposed dentin surface is subjected to tactile or chemical stimuli. Several substances are proposed to provide the desensitizing effect, such as ozone, potassium nitrate, sodium fluoride, ascorbic acid, low-intensity laser, glutaraldehyde, intraoral medications, oxalates, and dentifrices. According to Pintado-Palomino et al. [7], the action of these desensitizing agents can occur by reducing the excitability of dental nerve endings or by obliterating dentinal tubules. In order to investigate the effectiveness of these desensitizing substances after tooth whitening, this systematic review followed by meta-analysis was proposed.

The results found in this review showed that, in 54% of the included studies, the design of the studies was of the Split Mouth type. These studies are performed by applying different products in the same dental hemi-arch of an individual, while in the other hemi-arch, a second product is applied, usually a control (positive or negative), to evaluate its efficacy. This type of study has greater accuracy, since the degree of sensitivity, being a factor obtained by individual perception, can influence the result of the study. Therefore, there is greater credibility in the production of scientific evidence [15, 16, 17].

In turn, 46% of the studies were of the parallel type, in which each group of participants is exposed to only one of the interventions studied. This type of study involves the formation of at least two groups characterized as parallel studies, in which individuals remain in the group to which they were allocated until the end of the research. This type of study requires a large sample size but has the disadvantage of having a highly selected and unrepresentative investigated group, and are more expensive experiments to conduct [15, 18, 19].

The studies that approached the *Split Mouth* methodology presented a smaller sample size than the parallel type since the same participant receives both products instead of just one, this is another advantage of the *Split Mouth studies*. Based on the above, the most suitable type of study for pain studies is those with the Split *Mouth* design.

Regarding the calculation of the sample, it is clear that there has been a change in complexity since 2013, and 100% of the studies included in this review included a description of this calculation. Probably with the popularization of the clinical trials databases and the CONSORT (*Consolidated Standards of Reporting Trials*) norms, the randomized clinical trial studies elected the degree of organization and planning seeking to reduce the risk of bias, bringing more predictability and confidence in the results.

Tooth sensitivity, the focus of the study, was assessed by 100% of the included studies. For its evaluation, the most used method was the VAS (Visual Analog Scale) in 75.9% of the studies, which comprises a horizontal line of 100 mm in length, labeled on one side as no pain and on the opposite side as pain or discomfort, and may also be indicated numerically from zero to 10 [20].

Some studies (69.2%) used two simultaneous scales for pain assessment, such as the Numerical Analog Scale (ANS or NRS), which ranges from zero (no pain) to 4 (severe/severe pain) according to the sensitivity of each patient. However, the correlation between the scales was not performed, which is an interesting suggestion, in order to evaluate if there is a difference in the effectiveness of using the two (scores) and measuring on a millimeter scale.

This meta-analysis was performed in order to evaluate the real desensitizing effect of desensitizing agents, because when only a systematic review on the subject is performed, one finds some flaws in some of the data provided and in the bias analysis.

In the present meta-analysis 13 studies were selected, in which the sensitivity perceived by patients was lower in the desensitizing groups, in which a low heterogeneityand a low i^2 is really observed. This attests to the real efficacy of desensitizing agents when associated with tooth whitening. Efficacy is reaffirmed even in an odds ratio analysis, with i^2 a little higher, but a slightly moderate heterogeneity.

Additional evaluations, such as color change after bleaching, were also performed. However, all papers found no changes or were not significant for the study.

Regarding the period of pain experience, the most evaluated was up to 48 hours after whitening. This corroborates the fact that the sensitivity caused occurs mostly until 24 hours after the procedure because the perception of minimum pain to be recorded occurs at most 48 hours after bleaching and rare are the records after this period [21, 22].

The most commonly used desensitizing agent in the review was potassium nitrate (46.1%), one of the best known and studied. Potassium nitrate increases the concentration of potassium ions around nerve fibers, preventing repolarization and reducing the transmission of the pain stimulus [23, 5]. According to Tay et al [21], potassium nitrate crosses enamel and dentin towards the pulp, making a "calming" effect, affecting the transmission of nerve impulses.

In some studies, in the review, the use of potassium nitrate did not produce a significant desensitizing action or even none statistically compared to a placebo. According to Loguercio et al [24] the union of calcium phosphate, fluoride, and potassium nitrate can

generate a negative interaction in which the (slightly acidic) bleaching gel can solubilize the phosphate salt that has a basic pH. These phosphate ions react with the available phosphate itself, thus reducing its soothing effect on the pulp. Another explanation for the lower efficiency of potassium nitrate is due to the particle size of the peroxide which is so small that itcan enter the interstitial spaces in the dentinal tubules [21].

However, it was found in the studies that when the desensitizing agent remained on the tooth surface for a certain time, followed by the agitation of the product with a rubber cup, better desensitizing results were observed.

Another desensitizer tested, glutaraldehyde (15.4%), was present in the studies by Diniz et al [25] and Parreiras et al [26]. This substance causes a cross-linking with the enamel matrix proteins and with the proteins present in the dentin tubular fluid, thus reducing the passage of peroxides [26]. The action of gluteraldehyde can also beexplained by the reaction produced by the contact of enamel proteins with the desensitizer, hindering the penetration of peroxides through the enamel [20].

The application of gluteraldehyde on dentin for at least 1 minute reduces the intensity of sensitivity [20, 26]. Also, its association with potassium nitrate 5% aids in reducing sensitivity after bleaching [26]. This corroborates the reduction in sensitivity presented by the studies.

New desensitizing agents have been studied, such as ozone. It was cited by Al-Omiri et al [27]. Its mode of action is that in contact with the dental tissue, it generates oxidative processes that can degrade endotoxins that are responsible for the inflammation process after whitening [10, 28]. It also clogs the dentinal tubules, contributing to the reduction of sensitivity. However, it is important to perform the application of ozone after bleaching. This is due to the fact that it can potentiate the deeper penetration of hydrogen peroxide, resulting in more advanced oxidative processes, leading to more radicals reacting with the pulp tissue and generating pain [27].

Pintado-Palomino et al [8] studied dentifrices with desensitizing compounds such as potassium nitrate, arginine, and vitroceramic and bioactive compounds. They act by reducing the excitability of nerve stimuli and/or by obliterating dentinal tubules [29]. However, their use can prevent a more aggressive sensitivity after tooth whitening, but it makes more studies on their mechanisms of action necessary. Even so,it is a viable option as an adjunct in the treatment of desensitization after whitening.

Nano-bioactive materials were used by Burey et al [30] when their deposition on enamel was not sufficient for penetration of the bleaching gel and did not generate a reduction in sensitivity. This is because these nano-bioactive materials facilitate the

deposition of calcium and phosphate that reacts with hydroxyls, carbonates, and fluorides, and forms a new protective layeron the tooth [31, 32].

The use of eugenol, known for its anti-inflammatory and analgesic activity, as a desensitizing agent, by Vilela et al [33], however, did not show significant results in reducing the sensitivity resulting from tooth whitening. This occurred because eugenol could not overcome the enamel barrier to penetrate into the dentin and reach the pulp tissue, reducing sensitivity [13].

The use of a dipyrone gel by Rezende et al [13] demonstrated ineffectiveness against desensitization. One of the hypotheses is that dipyrone did not penetrate into enamel and dentin to produce the desensitizing effect due to some factors such as high molecular weight, pH of the substances, tissue permeability, charge, and nature of the vehicle [34, 35].

The concentration of hydrogen peroxide present in bleaching can influence the patient's sensitivity. Studies have shown that peroxide can induce cellular alterations in pulpal enzymes, causing sensitivity [36]. In the study, hydrogen peroxide between 35 and 40% experienced in-office bleaching was the most commonly used. The office bleaching method is more used because of the greater clinical control. However, they are the ones that have more sensitivity after bleaching, even if in some cases some desensitizing agents already present in the formula of these bleaching agents are used [37].

Most of the studies that evaluated sensitivity also evaluated color change. What we realize is that no matter the concentration of the bleaching agent or method that is performed bleaching, the final effect on the color will be very similar. Everything will depend on the convenience of the professional, the patient, and the individualization that each case demands [38, 39, 40, 37].

The effect of most desensitizing agents on tooth sensitivity after in-office tooth whitening was negative with a mean difference of -0.14. Considering that the scale used was the VAS, with values fixed between 0 and 10, a small effect of the desensitizing agent on TS was perceived when compared to the negative control/placebo group. This is because when analyzing the forest graph of outcome analysis of TS, the "diamond" does not touch the non-difference line, which is even more noticeable in the OR outcome forest graph.

The desensitizing agents evaluated in the studies included in this work decreased pain sensation. However, some methodological flaws can be found, in which some studies did not present adequate sample size calculation, therefore, the analysis of the external validity of the studies in these cases was compromised. Another fact is the presence of many young patients in the samples, many students of the undergraduate dental courses

themselves, which probably occurs because of the convenience of patient selection. However, the pain threshold of these patients is probably lower, and they have thicker enamel layers than patients in older age groups. Possibly, non-young adult patients, having thicker dentin tissue, could present different results from the action of desensitizing agents than young patients.

CONCLUSION

Based on the findings of this study, it was possible to verify that the desensitizing agents were effective in controlling tooth sensitivity in office bleaching, since they significantly decreased tooth sensitivity and the *odds ratio of* patients submitted to this type of bleaching.

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APPENDICE S

Appendix 1 - Data search strategy.

Database	Search query 04/09/2021 (new consultation held on 11/08/2022)
EMBASE	tooth bleaching agent' AND 'desensitizing agent' AND 'dentin sensitivity' AND 'randomized controlled trial' AND 'clinical trial
LILACS	("tooth whitening") or "tooth whitening agents" [Words] and ("dentin desensitizing agents") or "dentin desensitizing agents" [Words]
LIVIVE (Articles)	((("tooth bleaching") AND "dentin desensitizing agents") OR "dentin sensitivity") AND TI=("randomized controlled trial" OR "clinical trial" OR "trial")
PubMed	(("Tooth bleaching"[MeSH Terms] OR "Tooth bleaching") AND ("Dentin Desensitizing Agents"[MeSH Terms] OR "Dentin Desensitizing Agents" AND "Dentin Sensitivity"[MeSH Terms] OR "Dentin Sensitivity")) AND ("randomized controlled trial"[Title/Abstract] OR "CLINICAL TRIAL" or "TRIAL"))

SCOPUS	(TITLE-ABS-KEY (tooth AND bleaching) AND TITLE-ABS-KEY (dentin AND desensitizing AND agents) OR TITLE-ABS-KEY (dentin AND sensitivity) AND TITLE-ABS-KEY (randomized AND controlled AND trial) OR TITLE-ABS-KEY (clinical AND trial) OR TITLE-ABS- KEY (trial)
Web of Science (Articles)	TS=("tooth bleaching") AND TS=("dentin sensitivity") AND TS=("trial")
	Grey Literature
Google Scholar	tooth bleaching" AND "dentin desensitizing sensitivity" OR "dentin sensitivity" AND "randomized controlled trial" OR "clinical trial"

ANNEXES

Figure 1- Flow diagram of the study identification

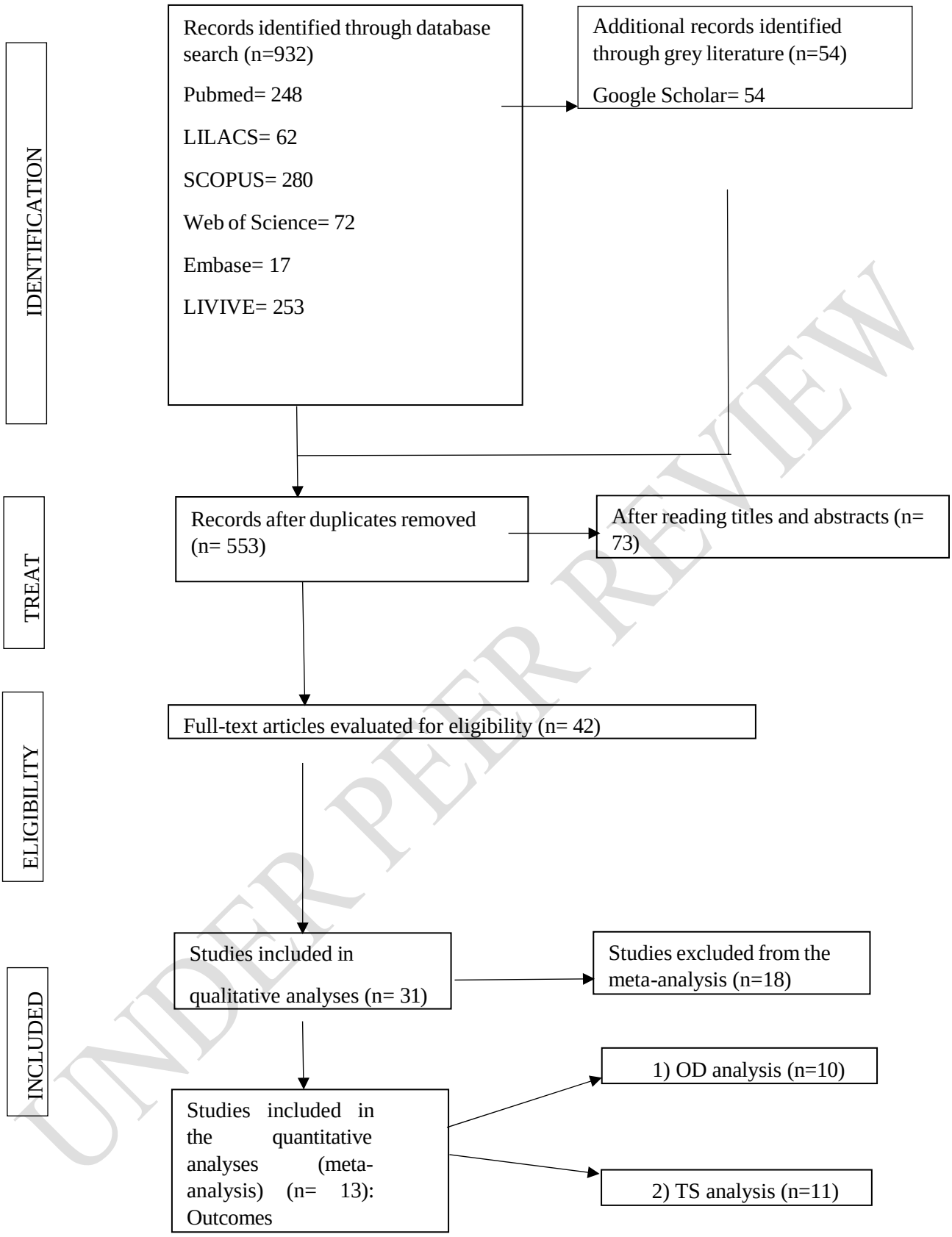

Table 1- ROBIS of risk of bias

	Random sequence generation	Allocation concealment	Blinding of patients	Evaluator Blinding	Incomplete results data	Selective Reporting
Palé, 2013 [38]	+	+	+	+	?	+
Pintado-Palomino, 2015 [8]	+	+	+	?	+	+
Al-Omiri, 2018 [27]	+	+	+	+	+	+
Diniz, 2018 [25]	+	+	+	+	+	+
Loguercio, 2015 [24]	+	+	+	+	+	+
Parreiras, 2018 [26]	+	+	+	+	+	+
Rezende, 2018 [13]	+	+	+	+	+	+
Silva Junior, 2019 [39]	+	+	+	+	+	+
Maran, 2020 [22]	+	+	+	+	+	+
Rezende, 2020 [2]	+	+	+	+	+	+
Tay, 2009 [21]	+	+	+	+	+	+
Vilela, 2021 [40]	+	+	+	+	+	+

Burey, 2021 [30]	+	+	+	+	+	+

Table 2- Data from the articles

Studys	Ano	Country	Type of study	Total number of participants	Whitening Agent	Desensitizing	Lightening Approach	Nr of bleaching sessions	Description of the control group	Study Group Description	Evaluated Endings	Sensitivity Scale	Follow-up	Power of study	Sample Calculation	Description statistical tests
Tay	2009	Brazil	parallel	30	35% PH	Desensitize KF 2%		1	Placebo	Whitening + Desensitizing Ag	OD	NRS 0-4	48 TIMES	NC	NC	Fisher's exact test
Palé	2013	Spain	parallel	32	28% PH	Potassium nitrate 5%.	Consulting	1	Placebo	Potassium nitrate 5% applied to the tooth 30 minutes before	TS	VAS 0-10	15 days	NC	NC	INC
Painted-Palomino	2015	Brazil	parallel	140	35% PH	Nanohydroxypatita paste	Consulting	1	Cont Negative	Bioactive crystalline ceramic particles, Nanohydroxyap atite paste and bioactive bioglass particles	TS	VAS 0-10	72 hours	calculates the	calculates the	Anova and Tukey test
Loguercio	2015	Brazil	parallel	40	35% PH	Nano Calcium Phosphate Paste	Consulting	1	Placebo	Nano Calcium Phosphate Paste	OD	NRS	48 hours	calculates the	calculates the	Fisher's exact test
Al-Omiri	2018	Jordan	parallel	45	38% PH	Ozone	Consulting	1	Placebo	Ozone therapy	TS	VAS 0-10	0	calculates the	calculates the	post hoc test

Diniz	2018	Brazil	split moth	33	35% PH	Gluteraldehyde	Office	2	Placebo	Apply gluteraldehyde before for 60s	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test
											TS					ANOVA and Tukey test
Parreiras	2018	Brazil	split mouth	42	35% PH	Gluteraldehyde 5%; Nitrate of potassium 5%.	Office	2		Desensitizing gel 5% Glutaraldehyde and 5% Potassium Nitrate	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test
											TS					Wilcoxon
Rezende and	2018	Brazil	split mouth	120	35% PH	Dipyrone gel 500 mg/ml	Consulting	2	Placebo	Dipyrone gel 500 mg/ml applied to the tooth face left for 10 min and shaken 20 sc with micro-applicator.	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test
											TS					Wilcoxon and Friedman

Silva Junior	2019	Brazil	parallelo	115	35% PH	Potassium nitrate 5%; Sodium fluoride 0.2%.	Consulting	2	Placebo	Potassium nitrate and 2% sodium fluoride gel used for 10 days before whitening, with daily use of 10 min on a soft plate.	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	Thu 2
											TS					Mann-Whtiney and Fridman
Maran	2020	Brazil	split mouth	60	35% PH	Potassium nitrate 5%.	Consulting	2	Negative control	Lightening gel containing 5% potassium nitrate	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test
											TS					Wilcoxon and Student - Newman-Keuls

Rezend and	2020	Brazil	split mouth	43	35% PH	Potassium nitrate 10% potassium nitrate	Consulting	2	Placebo	Potassium nitrate 10% applied to the tooth for 10 min and activated for 20 s with a micro-applicator	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test
											TS					Wilcoxon and Friedman
Vilela	2021	Brazil	split mouth	56	35% PH	Eugenol nanoencapsulado (EM) 1%.	Consulting	2	PLacebo	Nanoencapsulated eugenol gel of the 1% applied on the tooth, agitated for 20 s with a micro-applicator and kept for 10 min.	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test
											TS					Wilcoxon, Tukey and Friedman
Burey	2021	Brazil	split mouth	66	40% PH	Nanoparticles bioactive material (n-Bm) 5%.	Consulting	2	Placebo	Hydrogen Peroxide 40% with 5% bioactive nanoparticles	OD	NRS 0-4 and VAS 0-10	48 hours	calculates the	calculates the	McNemar's test

											TS					Wilcoxon - t and orANOVA test - Tukey

Legend: PH: hydrogen peroxide; VAS: visual analog scale; NRS: numerical analog scale.

Table 3

STUDIES	NUMBER OF PARTICIPANTS	BLEACHING AGENT	DESENSITIZER	WHITENING APPROACH	DESCRIPTION OF THE STUDY GROUP
Palé, 2013	32	28% PH	Potassium nitrate 5%.	Office	Potassium nitrate 5% applied to the tooth 30 minutes before
Pintado-Palomino, 2015 (1)	140	35% PH	Active ceramic particles	Office	Active ceramic particles applied 30 s before
Pintado-Palomino, 2015 (2)	140	35%PH	Bioactive bi-glass particles	Office	Bioactive bio-glass particles applied 30 s before
Pintado-Palomino, 2015 (3)	140	35% PH	Nanohydroxyapatite paste	Office	Nanohydroxyapatite paste agitated by felt disk for 10s
Al-Omiri, 2018	45	38% PH	Ozone	Office	G1 = using first ozone and then 38% PH. G2 = first with 38% PH and then ozone.
Diniz, 2018	33	35% PH	Gluteraldehyde	Office	Apply gluteraldehyde before for 60s
Parreiras, 2018	42	35% PH	Gluteraldehyde 5%; Potassium nitrate 5%.	Office	Desensitizing gel applied to the tooth (half arch of the maxilla) for 10 minutes and agitated with a rubber cup for 10 s
Rezende, 2018	120	35% PH	Dipyrone gel 500 mg/ml	Office	Dipyrone gel 500 mg/ml applied to the face of the teeth left on for 10 min and shaken 20 s with micro-applicator.
Silva Junior, 2019	115	35% PH	Potassium nitrate 5%; Sodium fluoride 0.2%.	Office	Potassium nitrate and 2% sodium fluoride gel used for 10 days before whitening, with daily use for 10 min on a soft plate.
Maran, 2020	60	35% PH	Potassium nitrate 5%.	Office	Lightening gel containing 5% potassium nitrate
Rezende, 2020	43	35% PH	Potassium nitrate 10% potassium nitrate	Office	Potassium nitrate 10% applied to the tooth for 10 min and activated for 20 s with a micro-applicator
Vilela, 2021	56	35% PH	Nanoencapsulated Eugenol (EM) 1%.	Office	Nanoencapsulated eugenol gel 1% applied on the tooth, agitated for 20 s with a micro-applicator and held for 10 min.
Burey, 2021	66	40% PH	Bioactive nanoparticles (n-Bm) 5%.	Office	Hydrogen Peroxide 40% with 5% bioactive nanoparticles

Figure 2 - Forest plot of the main results of the meta-analysis performed with 11 studies of randomized clinical trials regarding the outcome TS

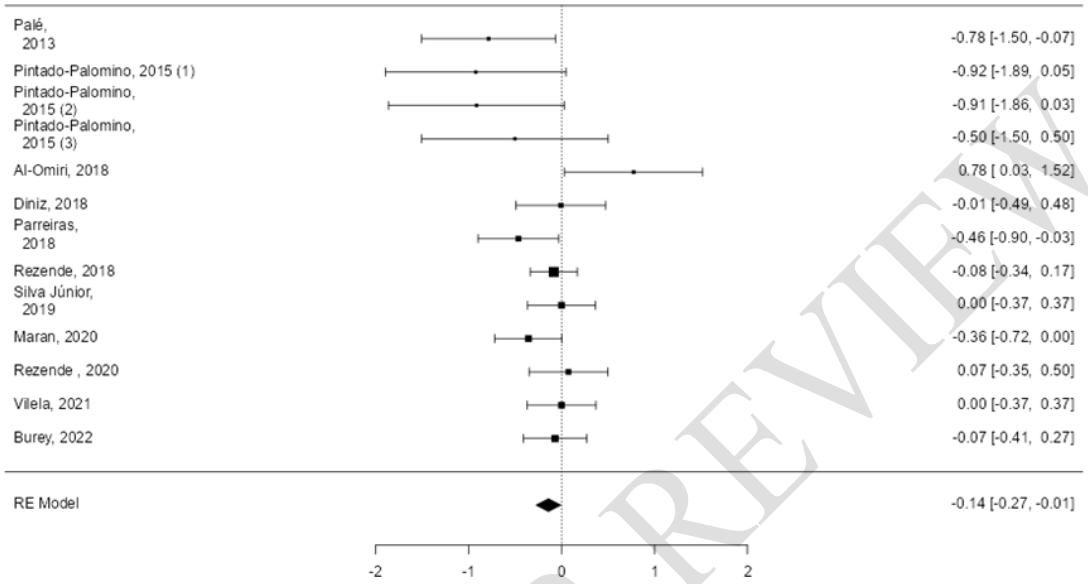

Figure 3 - Forest plot of the main results of the meta-analysis performed with 10 studies of randomized clinical trials regarding the OR outcome