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Tooth Sensitivity After Dental Bleaching With a Desensitizer-containing and a Desensitizer-free Bleaching Gel: A Systematic Review and Meta-analysis

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Clinical Relevance

The use of bleaching gel with desensitizer does not reduce the risk and intensity of sensitivity after tooth whitening.

SUMMARY

Objectives: A systematic review and meta-analysis were performed to evaluate the risk and intensity of tooth sensitivity (TS) after dental bleaching with a desensitizer-containing and a desensitizer-free bleaching gel in adult patients. Color change and risk of gingival sensitivity was also evaluated.

Methods: A comprehensive search was performed MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO), EMBASE and Cochrane Library, and System for Information on Grey Literature in Europe (SIGLE) without restrictions to identify randomized clinical trials. Abstracts from the annual conference of the International Association for Dental Research (1990–2016), unpublished and ongoing trials registries, dissertations, and theses were also searched. The quality of the evidence was rated using the Grading of Rec-

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ommendations: Assessment, Development and Evaluation (GRADE) approach.

Data: After duplicates were removed, 1352 articles were identified. After title and abstract screening, only 47 studies remained for qualitative evaluation. Most of the studies had unclear risk of bias. No difference between groups were observed for the risk ratio of TS (risk ratio = 0.99; 95% confidence interval [CI] = 0.74–1.33); intensity of TS (standardized difference in means [SMD] = 0.04; 95% CI = 0.79–0.70); color change in shade guide units (SMD – 0.04; 95% CI = 0.50–0.42); color change in ΔE* (SMD = 0.41 (95% CI = 0.07–0.89); and risk ratio of gingival irritation (SMD = 1.05; 95% CI = 0.81–1.36). Except for the risk of TS, graded as moderate quality of evidence, all other outcomes were rated as low and very low quality.

Conclusions: 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 was similar between groups, but the quality of the evidence for these outcomes was graded as low or very low, thus reducing the level of confidence in these outcomes.

INTRODUCTION

An increased demand for esthetic dentistry has been observed in the dental field over the past 10 years. Some popular magazines suggest that whiter teeth make the smile more attractive and improve people's self-esteem.[1] This explains why a recent study showed that approximately 89% of the participants wished to have their teeth whitened.[2]

Currently, two dentist-supervised techniques are available for dental bleaching: at-home whitening[3-5] and in-office bleaching.[6-8] Although studies show the safety and effectiveness of both techniques.[7,9-11] clinicians still face the undesirable side effect of tooth sensitivity (TS) when performing whitening procedures.

Unfortunately, this side effect is very frequent. Studies have reported that bleaching-induced TS affects 67% to 100% of the participants who received in-office bleaching,[6,7,12-14] and 37% to 90% of the participants who performed at-home bleaching.[3-5,10,15-18]

More precise estimates were recently reported.[19] By evaluating the individual patient data of 11 clinical trials involving bleaching, those authors reported that the risk of TS for in-office bleaching when using 35% hydrogen peroxide (HP) (62.9%; 95% confidence interval [CI] 56.0–67.3) and for at-home bleaching with 10% to 16% carbamide peroxide (CP) (51%; 95% CI 41.4.–60.6)[19] were quite similar. On the other hand, the intensity of TS was very different between the bleaching protocols. On a 0 (no pain) to 4 (very intense pain) pain scale, the overall mean intensity of bleaching-induced TS for in-office bleaching was 2.8 ± 2.9, whereas at-home bleaching patients reported sensitivity of 0.5 ± 0.9.[19] This makes the at-home procedure the most recommended bleaching protocol.[20-22]

The presence of TS has led some researchers to evaluate techniques for minimizing or even eliminating bleaching-induced TS. Recently evaluated techniques include reducing the concentration and usage time of the bleaching product,[9,23-25] applying topical desensitizing agents while bleaching,[25-27] and administering systemic medicines.[12,28,29]

Topical application of desensitizing agents appears to be an effective strategy for reducing TS for both at-home bleaching[16,26,30] and in-office bleaching.[31-34] To reduce the application time, some manufacturers have incorporated some desensitizing agents, such as potassium nitrate and sodium fluoride, into the formulation of bleaching gels[35-37] so that the extra step of applying a desensitizing gel could be eliminated.

Few studies have addressed the effectiveness of desensitizer-containing bleaching gels in reducing bleaching-induced TS, while the available studies report conflicting results. Some authors reported a reduction of bleaching-induced TS when desensitizer-containing gels were used,[5,7,9,14,38,39] whereas others reported no significant difference between desensitizer-containing and desensitizer-free bleaching gels.[22,35]

In light of this, the aim of this systematic review of the literature was to answer the following PICO (problem/patient/population, intervention/indicator, comparison, and outcome) question: Are the risk and intensity of TS in adult patients who have submitted to dental bleaching lower when desensitizer-containing products are compared with desensitizer-free bleaching products?

METHODS AND MATERIALS

Protocol and Registration

This study was registered at the PROSPERO under protocol number CRD 42016036411. For this report,

we followed the recommendations of the PRISMA statement for systematic reviews.[40]

Information Sources and Search Strategy

The controlled vocabulary (MeSH terms) and free keywords in the search strategy were defined based on the PICO question described earlier. For the primary outcomes, we evaluated the risk and intensity of TS during dental bleaching as measured using the visual analog scale (VAS) and numerical rating scale (NRS), during and up to 24 hours after dental bleaching (ie. the period during which patients are more prone to experiencing TS). Color change in the shade guide units (SGUs) and in ΔE (CIEL*a*b* system), as well as the risk of gingival sensitivity, were also evaluated as secondary outcomes.

The following electronic databases were used to identify eligible studies: Cochrane Library, MEDLINE via PubMed, EMBASE, Latin American and Caribbean Health Sciences Literature database (LILACS), and Brazilian Library in Dentistry (BBO). The authors also searched the following citation databases: Scopus and Web of Science (Table 1). The reference lists of all primary studies were searched for additional relevant publications and the related articles link of each primary study in the PubMed database. No restrictions on publication date or languages were imposed.

Grey literature, which is not available through the usual bibliographic sources like databases or indexes, was also investigated (eg, unpublished observations, dissertations, conference proceedings)[41-43] The abstracts of the annual conference of the International Association for Dental Research and its regional divisions (1990–2016) were explored. The System for Information on Grey Literature in Europe (SIGLE), ProQuest Dissertations and Theses full-text database, and Periodicos CAPES theses were also included in the search strategy.

To locate unpublished and ongoing trials related to the review question, the following clinical trial registries were searched: Current Controlled Trials, International Clinical Trials Registry Platform, ClinicalTrials.gov, Registro Brasileiro de Ensaios Clinicos (ReBec), and EU Clinical Trials Register.

Eligibility Criteria

Parallel and split-mouth randomized clinical trials that compared the risk and intensity of TS during in-office and at-home dental bleaching in adult patients of any age group were included. Randomized clinical trials were excluded if: 1) the studies evaluated the effect of topical desensitizing agents containing potassium nitrate and/or sodium fluoride; 2) the studies did not have both groups under investigation; or 3) the studies included both groups but did not compare bleaching gels with equivalent concentrations.

Initially, the articles were selected based on their titles and abstracts according to the previously described search strategy, with duplicates removed. Full-text articles were also obtained, and subsequently, three reviewers (MR, FMC, and KC) classified those that met the inclusion criteria. To handle many studies, a study identification was given to each eligible study, combining the first author and the year of publication.

Data were extracted using customized extraction forms that included details about study methods, designs and settings, age and sex of the participants, details regarding the bleaching protocol, bleaching agents, and type of desensitizing gel added in the included studies.

If there were multiple reports of the same study (ie, reports with different follow-ups), data from all reports were extracted directly into a single data collection form to avoid overlapping data. When data were not reported in the studies, the authors were contacted by email at least twice to request the missing information.

When data from multiple bleaching sessions were provided, an average of the figures was calculated for each bleaching protocol. When evaluating color change, the data that represented the most immediate result (up to 3 months' after bleaching) was used. When more than one bleaching agent from the same group was included in the study, their values were combined to make a single entry.

Risk of Bias in Individual Studies

Three independent reviewers (MR, FMC, and KC) performed quality assessments using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[44] The assessment criteria contained six domains: sequence generation, allocation concealment, the blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias.

For each aspect of the quality assessment, the risk of bias was scored following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions 5.1.0* (http://handbook.cochrane.org). At the study level, studies were at a low risk of

bias if there was adequate sequence generation, allocation concealment, and patient blinding (key domains). The study was considered unclear if any of the aforementioned key domains was unclear. If at least one of the aforementioned domains was at a high risk of bias, the study was considered to have a high risk of bias. When the study was judged as unclear in its key domains, the authors were contacted to obtain more information and to allow a definitive "yes" or "no" judgment.

During data selection and quality assessment, any disagreements among the reviewers were solved through discussion and, if needed, by consulting a fourth reviewer (AR).

Summary Measures and Synthesis of the Results

Data were analyzed using Revman 5 (Review Manager Version 5, The Cochrane Collaboration, Copenhagen, Denmark). Data from eligible studies were either dichotomous (absolute risk of TS and gingival irritation) or continuous (intensity of TS, ΔSGUs, and ΔE). The outcomes were summarized by calculating the standardized mean difference for the continuous data and the risk ratio with a 95% confidence interval (CI).

Random-effects models were employed. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. All analyses were conducted using Revman 5 (Review Manager Version 5, The Cochrane Collaboration, Copenhagen, Denmark). No subgroup analysis was performed. Sensitivity analyses were also conducted to investigate the reasons for high heterogeneity whenever detected.

Assessment of the Quality of Evidence Using GRADE

We graded the quality of the evidence for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) to determine the overall strength of the evidence for each meta-analysis.[45] The GRADE approach is used to contextualize or justify intervention recommendations with four levels of evidence quality, ranging from high to very low.

The GRADE approach begins with the study design (randomized clinical trials or observational studies) and then addresses five reasons for possibly decreasing the rating of the quality of the evidence by one or two levels (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) and three reasons for possibly increasing the rating of the quality (large effect, management of confounding factors, dose-response gradient).[45] Each one of these topics was assessed as no limitations, serious limitations, and very serious limitations to allow for the categorization of the quality of the evidence for each outcome as: high, moderate, low, and very low. The high quality rank suggests very high confidence that the true effect lies close to the estimate of the effect. On the other extreme, "very low quality" suggests that there is very little confidence in the effect estimate and that the estimate reported can be substantially different from what was measured.

The GRADEpro Guideline Development Tool, available online (www.gradepro.org), was used to create a summary of findings table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*.[41]

RESULTS

Study Selection

After the database screening and the removal of duplicates, 1352 studies were identified (Figure 1). After title screening, 142 studies remained, which were reduced to 47 after a careful examination of the abstracts. Eight studies remained after reading the full text, with the others excluded for the following reasons:

1) Studies without a control[7,17,46-52];
2) Inadequate control group[37,53-56];
3) Studies that used desensitizer-containing and desensitizer-free bleaching gels without equivalent HP/CP concentrations[5,10,22,57-62];
4) Studies that did not have a desensitizer-containing bleaching agent[8,63-69];
5) Studies that involved application of topical desensitizers instead of desensitizer-containing bleaching gels.[70-77]

Characteristics of Included Articles

The characteristics of the eight selected studies are listed in Table 2. The parallel study design was used in five studies[14,35,36,38,78] and the split-mouth design in three studies.[22,39,79]

Four of the eight studies used only a VAS for pain evaluation,[22,36,39,78] two studies used only the NRS pain scale,[14,79] and one study used both the VAS and NRS scales.[38] The study of Browning and others[35] did not evaluate pain intensity.

Table 1: *Electronic Database and Search Strategy*

Pubmed (31/May/2016)		
#1 (Tooth discoloration[MeSH Terms]) OR Dentition, Permanent[MeSH Terms]) OR "tooth staining"[Title/Abstract]) OR "tooth stain"[Title/Abstract]) OR "stained tooth"[Title/Abstract]) OR "stained teeth"[Title/Abstract]) OR "tooth discoloration"[Title/Abstract]) OR "tooth discolouration"[Title/Abstract]) OR "discolored tooth"[Title/Abstract]) OR "discoloured tooth"[Title/Abstract]) OR "discolored teeth"[Title/Abstract]) OR "discoloured teeth"[Title/Abstract]) OR "teeth discoloration"[Title/Abstract]) OR "teeth discolouration"[Title/Abstract]) OR "dental discoloration"[Title/Abstract]) OR "dental discolouration"[Title/Abstract]) OR "tooth discolorations"[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 Peroxides[MeSH Terms]) OR Carbamide peroxide[Supplementary Concept]) OR Hydrogen peroxide[MeSH Terms]) OR dentin desensitizing agents[MeSH Terms]) OR dentin sensitivity[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 "tooth sensitivity"[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 "dentin sensitivity"[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 controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))
#1 AND #2 AND #3		
Scopus (31/May/2016)		
#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 (SUBJAREA , "DENT"))
#1 AND #2 AND #3		
Web of Science (31/May/2016)		
#1 TOPIC: ("tooth stain$") OR TOPIC: ("stained t??th") OR TOPIC: ("tooth discoloration$") OR TOPIC: ("tooth discolouration") OR TOPIC: ("discolored t??th") OR TOPIC: ("discoloured t??th") OR TOPIC: ("teeth discoloration") OR TOPIC: ("teeth discolouration") OR TOPIC: ("dental discoloration") OR TOPIC: ("dental discolouration") OR TOPIC: ("t??th color") OR TOPIC: ("t??th colour")	**#2** TOPIC: (bleaching) OR TOPIC: (whitening) OR TOPIC: ("tooth sensitivity") OR TOPIC: ("potassium oxalate") OR TOPIC: ("GLUMA Desensitizer") OR TOPIC: (desensitization) OR TOPIC: (glutaraldehyde) OR TOPIC: ("potassium nitrate") OR TOPIC: ("dentin sensitivity") OR TOPIC: ("hydrogen peroxide") OR TOPIC: ("carbamide peroxide") OR TOPIC: ("sodium fluoride") OR TOPIC: ("calcium phosphate$") OR TOPIC: ("desensitizing agents") OR TOPIC: ("CPP-ACP")	

Table 1: *Electronic Database and Search Strategy (cont.)*

#1 AND #2		
Lilacs and BBO (31/May/2016)		
#1 tw:((mh:(Tooth discoloration)) OR (mh:(Dentition, Permanent)) OR (tw:("tooth color")) OR (tw:("tooth colour")) OR (tw:("teeth 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:("descoloraçõ̃es dos Dentes")	**#2** mh:(Tooth Bleaching)) OR (mh:(Tooth Bleaching agents)) OR (mh:(Peroxides)) OR (mh:(Hydrogen peroxide)) OR (mh:(dentin desensitizing 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")	**#3** db: ("LILACS" OR "BBO")
#1 AND #2		
Cochrane Library (31/May/2016)		
#1"tooth staining":ti,ab,kw or "tooth stain":ti,ab,kw or "stained tooth":ti,ab,kw or "stained teeth":ti,ab,kw or "tooth discoloration":ti,ab,kw (Word variations have been searched) #2"tooth discolouration":ti,ab,kw or "discolored tooth":ti,ab,kw or "discoloured tooth":ti,ab,kw or "discolored teeth":ti,ab,kw or "discoloured teeth":ti,ab,kw (Word variations have been searched) #3"teeth discoloration":ti,ab,kw or "teeth discolouration":ti,ab,kw or "dental discoloration":ti,ab,kw or "dental discolouration":ti,ab,kw or "tooth discolorations":ti,ab,kw (Word variations have been searched) #4"tooth color":ti,ab,kw or "tooth colour":ti,ab,kw or "teeth color":ti,ab,kw or "teeth color":ti,ab,kw (Word variations have been searched)	#5Dentition, Permanent #6Tooth discoloration #7#1 or #2 or #3 or #4 or #5 or #6 #9Tooth Bleaching agents #10Peroxides #11Hydrogen peroxide #12dentin desensitizing agents #13dentin sensitivity #14nitrates #15Glutaral #16Sodium Fluoride	#17bleaching:ti,ab,kw or whitening:ti,ab,kw or "tooth sensitivity":ti,ab,kw or "potassium oxalate":ti,ab,kw or "GLUMA Desensitizer":ti,ab,kw (Word variations have been searched)#18desensitization:ti,ab,kw or glutaraldehyde:ti,ab,kw or "potassium nitrate":ti,ab,kw or "dentin sensitivity":ti,ab,kw or "hydrogen peroxide":ti,ab,kw (Word variations have been searched) #19"carbamide peroxide":ti,ab,kw or "sodium fluoride":ti,ab,kw or "calcium phosphates":ti,ab,kw or "calcium phosphate":ti,ab,kw or "desensitizing agents":ti,ab,kw (Word variations have been searched) #20"CPP-ACP":ti,ab,kw (Word variations have been searched) #21#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 #22#7 and #21
Embase (31/May/2016)		
#1 'tooth discoloration'/exp OR 'secondary dentition'/exp OR 'tooth color':ab,ti OR 'tooth colour':ab,ti OR 'teeth color':ab,ti OR 'teeth colour':ab,ti OR 'tooth staining':ab,ti OR 'tooth stain':ab,ti OR 'stained tooth':ab,ti OR 'stained teeth':ab,ti OR 'tooth discoloration':ab,ti OR 'tooth discolouration':ab,ti OR 'discolored tooth':ab,ti OR 'discoloured tooth':ab,ti OR 'discolored teeth':ab,ti OR 'discoloured teeth':ab,ti OR 'teeth discoloration':ab,ti OR 'teeth discolouration':ab,ti OR 'dental discoloration':ab,ti OR 'dental discolouration':ab,ti OR 'tooth discolorations':ab,ti AND [embase]/lim	**#2** 'tooth bleaching agent'/exp OR 'peroxide'/exp OR 'urea'/exp OR 'hydrogen peroxide'/exp OR 'desensitizing agent'/exp OR 'dentin sensitivity'/exp OR 'potassium nitrate'/exp OR 'glutaraldehyde'/exp OR 'sodium fluoride'/exp OR bleaching:ab,ti OR whitening:ab,ti OR 'tooth sensitivity':ab,ti OR 'potassium oxalate':ab,ti OR 'gluma desensitizer':ab,ti OR desensitization:ab,ti OR glutaraldehyde:ab,ti OR 'potassium nitrate':ab,ti OR 'dentin sensitivity':ab,ti OR 'hydrogen peroxide':ab,ti OR 'carbamide peroxide':ab,ti OR 'sodium fluoride':ab,ti OR 'calcium phosphates':ab,ti OR 'calcium phosphate':ab,ti OR 'desensitizing agents':ab,ti OR 'cpp-acp':ab,ti AND [embase]/lim	**#3** [randomized controlled trial]/lim AND [embase]/lim
#1 AND #2 AND #3		

Table 2: *Characteristics of the Included Studies*

Study ID	Study Design [Setting]	Method of Color Assessment	Subjects' Age, Mean ± SD [Range] (y)	No. of Subjects Male [%]	Groups/Materials
Browning and others (2008)[35]	Parallel [NR]	Vita Classical[a]	NR	NR	AHD1: 10% CP[b] AHD2: 10% CP[b] + 3% potassium nitrate[c] AHD3: 10% CP[b] + 0.5% potassium nitrate[c] AHD4: 10% CP[d] + 0.5% potassium nitrate + 0.25 sodium fluoride [c] AH5: placebo (without peroxide and desensitizing)[c]
Da Costa and others (2012)[22]	Split-mouth [NR]	Vita Bleached guide[e] and Spectrophotometer Vita Easyshade[f]	NR [21–75]	12 [50%]	AHD: 35% CP in a tray with potassium nitrate and sodium fluoride[g] AH: 14% HP without desensitizer[h]
Alonso de la Peña (2006)[79]	Split mouth [NR]	Vita Lummin Vacuum[i]	31.8 ± 4.5 [18–50]	5 [32%]	AHD: 3.5% HP with a 5% potassium nitrate [j] AH: 10% CP without desensitizer[b]
Gallo and others (2009)[36]	Parallel [NR]	Trubyte Bioform Color Ordered Shade Guide System[k]	NR	NR	AHD: 30% CP with 5% potassium nitrate[c] AH: 30% CP without desensitizer[c]
Giniger and others (2005)[38,92]	Parallel [NR]	Vita Classical[a]	AHD: 44.8 ± 19.0 [NR] AH: 43.6 ± 19.2 [NR] AHD: 43.6 ± NR [NR] AH: 49.2 ± NR [NR]	AHD: 12 [48%] AH: 13 [52%] AHD: 9 [64%] AH: 6 [46%]	AHD: 16% CP with 0.5% soluble calcium phosphate derived in part from calcium nitrate and potassium[l] AH: 16% CP without desensitizer[m]
Navarra and others (2014)[14]	Parallel [university]	Spectrophotometer Vita Easyshade[f]	25.3 ± NR [20–50]	NR [NR]	AHD: 10% CP with potassium nitrate and sodium fluoride[c] AH: 10% CP[c]
Tam (2001)[39]	Split mouth [university]	Vita Lummin Vacuum[i] and photography	31 ± 1 [20–53]	7 [41%]	AHD: 10%CP + with 3% potassium nitrate and 0.11% sodium fluoride[n] AH: 10% CP°
Ziebolz and others (2007)[78]	Parallel [NR]	Adobe Photoshop (L*a*b* values)[p] colorimeter[q]	AHD: 26.6 ± 4.5 [20–48] AH: 26.9 ± 5.3 [20–47]	AHD: 10 [33%] AH: 12 [40%]	AHD: 20% CP with 5% potassium nitrate and sodium fluoride[r] AH: 7.5% HP without desensitizing[s]

Color change was evaluated in five studies using shade guides[22,35,36,38,79] and two studies using objective color measure instruments (spectrophotometer or colorimeter).[14,22] Adobe Photoshop (L*a*b* values) was used in one study[78] and photography in another one.[39]

The number of patients per group in these studies ranged from 16 to 60. The mean age of all participants in the clinical trials was approximately 32.1 years.[14,38,39,78,79] In three of the eight articles, most of the participants were female.[39,78,79] Two studies had a similar sex distribution,[22,38] and in three studies, this information was not reported.[14,35,36]

When considering the bleaching protocol, all studies performed at-home bleaching. In five of seven studies, only CP was used,[14,35,36,38,39] and the remaining used CP and HP in corresponding concentrations,[22,78,79] Concentrations of the bleaching products varied from 10% to 35% for CP and 3.5% to 14% for HP. The time of usage also varied. CP products were used from 30 min to overnight, whereas HP was used from 30 minutes to 3 hours, once or twice daily. The total number of days the patients used the gel varied from 12 days to 4 weeks.

Assessment of the Risk of Bias

A few full-text studies reported the method of randomization and allocation concealment. Blinding was reported in six studies.[14,22,35,36,38,39] At the study level, all eight studies were judged as having an unclear risk of bias, as at least one key domain had an unclear risk (Figure 2).

Meta-Analysis

Meta-analysis was performed on all studies from which the information was reported and could be extracted. This resulted in a different number of studies included in each meta-analysis as described below.

Table 2: *Characteristics of the Included Studies (ext.)*

Study ID	Bleaching Protocol	Bleaching Tray	Mechanism of Action of the Desensitizer	Outcomes Evaluated		
				Color Change	Tooth Sensitivity	Gingival Irritation
Browning and others (2008)[35]	Overnight, Minimum 6 h per 2 wk	With reservoirs	Potassium nitrate: nerve desensitization Sodium fluoride: remineralizing	ΔSGU	Risk of TS without stimulus Total number of days with TS	GI, tongue and throat sensitivity
Da Costa and others (2012)[22]	30 min per 15 d	With reservoirs	Potassium nitrate: nerve desensitization Sodium fluoride: remineralizing	ΔSGU and ΔE	VAS 1–10 without stimulus	NR
Alonso de la Peña (2006)[79]	Once daily for 3 h/d for 4 wk	NR	Potassium nitrate: nerve desensitization	ΔSGU	NRS 0–4 without stimulus	Risk of GI
Gallo and others (2009)[36]	1 h/d for 10 d for a total of 10 h of treatment.	Without reservoirs	Potassium nitrate: nerve desensitization	Final SGU	VAS 1–10 with stimulus.	Löe and Silness Gingival Index
Giniger and others (2005)[38,92]	Once daily for a minimum of 3 h (or overnight) over the course of 14 d	Without reservoirs	Potassium nitrate: nerve desensitization CP: remineralizing	ΔSGU	VAS 0–10 and NRS 0–3 with stimulus	Löe and Silness Gingival Index
Navarra and others (2014)[14]	14 nights at last 6 h	NR	Potassium nitrate: nerve desensitization Sodium fluoride: remineralizing	ΔE	NRS 0–3 without stimulus	NR
Tam (2001)[39]	Overnight for 14 consecutive nights	NR	Potassium nitrate: nerve desensitization Sodium fluoride: remineralizing	VAS color	VAS 0–10 without stimulus	NR
Ziebolz and others (2007)[78]	AHD: Once daily, 3–4 h for 12 d AH: Twice a day, 30 min, for 12 d	With reservoirs	Potassium nitrate: nerve desensitization Sodium fluoride: remineralizing	L*a*b* values	VAS 0–10 with and without stimulus	Oral examination

*Abbreviations: AH: at-home dental bleaching without desensitizer; AHD, at-home dental bleaching with desensitizing; CP, carbamide peroxide; ΔE, color difference measured with a spectrophotometer; GI, gingival irritation (on a 0–3 scale: 0 = healthy tissue and 3 = the most severe gingivitis, including tissues that spontaneously bleed; HP, hydrogen peroxide; ID, identification; L*a*b* values, L*: brightness—dark to light, a*: green to red and b*: blue to yellow; NR , not reported; NRS, numeric rating scale; SD, standard deviation; SGU, shade guide unit; ΔSGU, color change in shade guide units; VAS, visual analog scale; VAS color, visual analog score for tooth color.*

[a] *Vitapan Classical, Vita Zahnfabrik,Bad Säckingen, Germany.*
[b] *10% CP Opalescence, Ultradent Products, South Jordan, UT, USA.*
[c] *Uninformed, brand was not identified.*
[d] *10% CP Opalescence PF, Ultradent Products, South Jordan, UT, USA.*
[e] *Vita Bleachedguide 3D-Master, Vita Zahnfabrik, Bad Sackingen, Germany.*
[f] *Spectrophotometer Vita Easyshade, Vita Easyshade, Vident, Brea, CA, USA.*
[g] *35% CP Opalescence PF, Ultradent Products, South Jordan, UT, USA.*
[h] *14% HP Crest, Whitestrips, Procter & Gamble, Manson, OH, USA;*
[i] *Vita Lummin Vacuum, Vita Zahnfabrik, Bad Säckingen, Germany.*
[j] *3.5% HP with 5% potassium nitrate, FKD, Kin Lab, Barcelona, Spain.*
[k] *Trubyte Bioform Color Ordered Shadeguide system, Dentsply Trubyte, York, PA, USA.*
[l] *The 16% CP gel (NiteWhite Excel 3 Regular) was incorporate the calcium ion (as CaNO3) and the phosphate ion (as K4P2O7) produced exclusively for this study by Discus Dental, Culver City, CA, USA.*
[m] *NiteWhite Excel 3 Regular 16% CP, Discus Dental, Culver City, CA, USA.*
[n] *The 10% CP gel with 3% potassium nitrate + 0.11 fluoride was produced exclusively for this study by Ultradent Products, South Jordan, UT, USA;*
[°] *The 10% CP gel was produced exclusively for this study by Ultradent Products, South Jordan, UT, USA.*
[p] *Adobe Photoshop®, Adobe Systems Inc, San Jose, CA, USA.*
[q] *Dental colourimeter Shade Eye—Shofu Dental Corporation, San Marcos, CA, USA.*
[r] *20% CP Opalescence PF, Ultradent Products, South Jordan, UT, USA.*
[s] *7.5% HP Visalys Whitening, Kettenbach, Eschenburg, Germany.*

Risk of Tooth Sensitivity—This outcome was reported in four studies.[22,35,78,79] The risk ratio was 0.99 with a 95% CI of 0.74 to 1.33 (p=0.95). Data were not heterogeneous (χ^2 test: p=0.74; I^2=0%; Figure 3), which means all studies included in the analysis shared a common effect size.

Intensity of Tooth Sensitivity—This analysis was based on three studies that reported this outcome

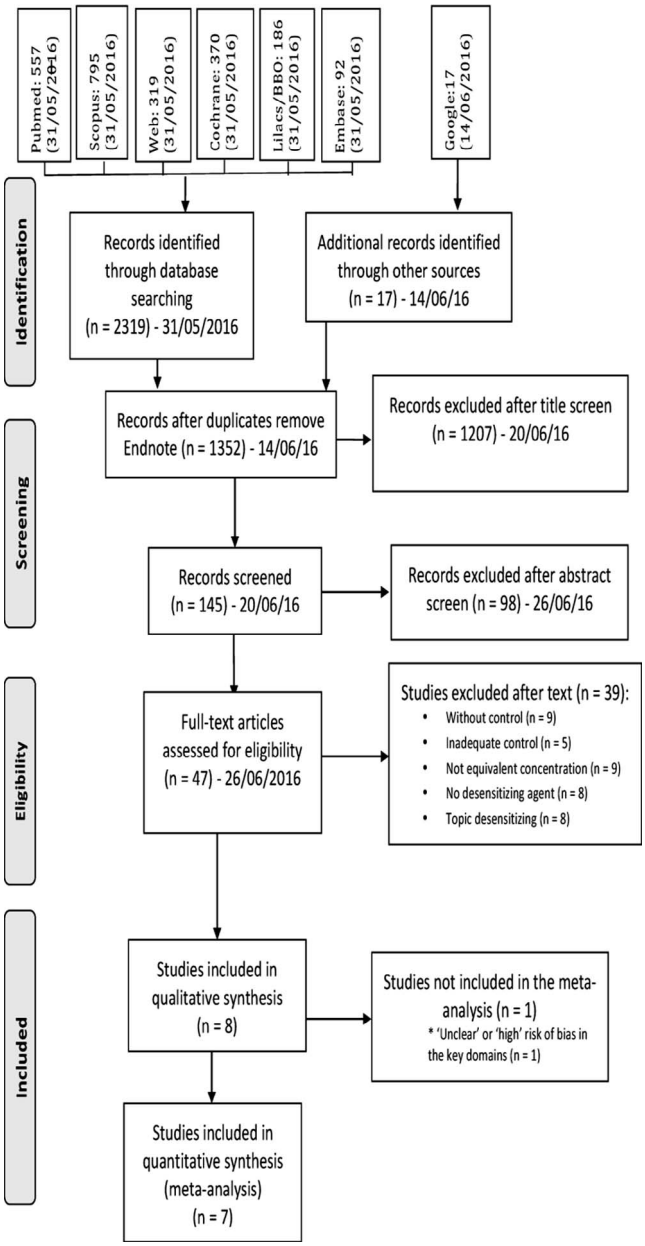

Figure 1. *Flow diagram of study identification.*

with a stimulus.[36,38,78] Although Navarra and others[14] reported the data of TS intensity, their values were not combined with the other studies in the meta-analysis because it was the only study that did not collect data with a stimulus. The standardized difference in means was –0.04 (95% CI=–0.79 to 0.70), with no significant difference in the intensity of TS between the products (p=0.91; Figure 4). Data were heterogeneous (χ^2 test: p=0.006; I^2=81%; Figure 4).

Color Change in ΔSGU—This analysis was based on four studies that reported this information.[22,35,36,38] The standardized difference in means was –0.04 (95% CI=–0.50 to 0.42), which demonstrated no difference in color change between groups (p=0.87; Figure 5). Data were heterogeneous (χ^2 test: p=0.05; I^2=61%; Figure 5).

*Color Change in ΔE**—This analysis was based on only two studies that reported relevant data.[14,22] The standardized difference in means was 0.41 (95% CI=–0.07 to 0.89), showing no difference between the groups (p=0.10; Figure 6). Data were heterogeneous (χ^2 test: p=0.60; I^2=0%; Figure 6).

Risk of Gingival Irritation—This analysis was based on four studies that reported this information.[22,35,78,79] The risk ratio was 1.05 (95% CI=0.81 to 1.36), showing no significant difference between the groups (p=0.95; Figure 7). Data were not heterogeneous (χ^2 test: p=0.74; I^2=0%; Figure 7).

Sensitivity Analysis—The study of Browning and others[35] did not report the standard deviation (SD) of the mean for the ΔSGU, and therefore an SD that corresponded to 1/3 of the mean was arbitrarily used. This decision was based on the analysis of the coefficient of variation of the other studies. Sensitivity analysis indicated that changing the SD for extreme values and removing the study from the meta-analysis would not alter the conclusions.

A sensitivity analysis was performed to identify any study that was responsible for the high heterogeneity in the meta-analysis of the intensity of TS and color change for both instruments. No study was found to be responsible for such heterogeneity.

Assessment of the Quality of Evidence

In the summary of findings (Table 3), the outcomes, other than the risk of TS, graded as moderate in the quality of evidence, were assessed as low and very low quality using GRADE. The reasons for downgrading the evidence were due to the unclear risk of bias of most studies, imprecision due to low sample sizes and high confidence intervals, and inconsistency with an unexplained heterogeneity (Table 3).

DISCUSSION

All studies from the present investigation were judged as having an unclear risk of bias, as most of the authors did not adequately report the sequence generation, allocation concealment, or blinding. This is not a new problem; a study by Devereaux and others[80] reported that 55% of the full-text studies failed to report the presence or absence of the concealment of randomization. In another study,

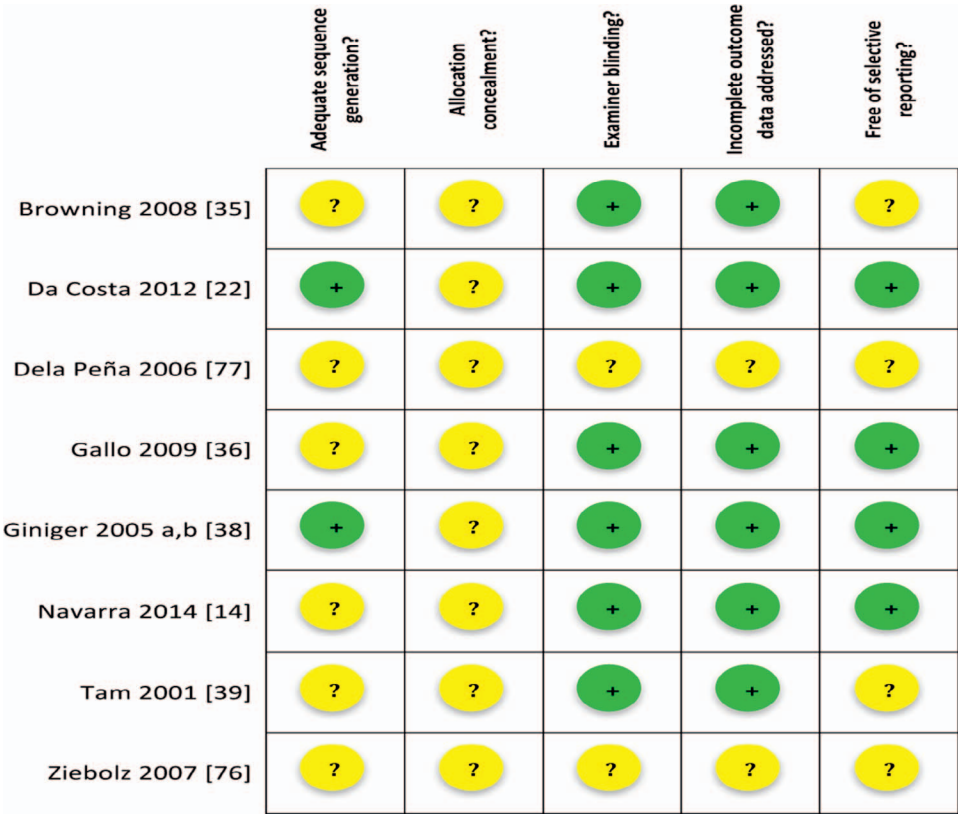

Figure 2. *Summary of the risk of bias assessment according to the Cochrane Collaboration tool.*

the authors reported that the odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials after adjustment for other variables.[81] The absence of adequate allocation concealment can lead to selection bias, one of the most important problems that randomization is supposed to eliminate.[82] As a result, one may expect an overestimation of the results in benefit of the experimental group being tested for studies with this issue.[81,83]

There is abundant evidence to support that adequate sequence generation, allocation concealment, and blinding are essential for gathering reliable results in clinical trials.[81] A meta-analysis will never produce more trustworthy findings than those of the primary articles. Studies in this field should be more rigorous during study design and the reporting of findings.

When considering the meta-analysis of the risk and intensity of TS, no significant difference between the groups was observed. Few studies were used in this meta-analysis, which restricts the precision of the effect estimate of TS intensity (risk ratio). This lack of difference was attributed to several factors; for example, it is expected that lower TS intensity in the control group makes it difficult to find differences between groups. In the present study it is possible to show that, on a 0–10 pain scale, the intensity of bleaching-induced TS for at-home bleaching was low and ranged for 1.1 to 3.6.[36,38,78] However, the most important factor is the great variability in bleaching protocols reported in the results section. Observe that, while Giniger and others[38] showed favorable results in the desensitizer group, on the other side, Ziebolz and others[78] showed the opposite. Therefore, more RCTs need to be done comparing at-home bleaching techniques using gels with and without desensitizers.

It is worth mentioning that the different types of desensitizing agents incorporated in the bleaching gels could have contributed to the lack of differences. The primary studies used bleaching gels containing only potassium nitrate,[36,79] a combination of potassium nitrate and calcium,[38] or potassium nitrate and sodium fluoride.[14,22,35,39,78]

Note that the action mechanism of the different types of desensitizing agents incorporated in the bleaching gels are not the same. While potassium salts have a presumptive effect on reducing activation of the sensory nerve by preventing the depolarization of the nerve fiber,[84,85]; fluoride and calcium remineralize exposed dentin tubules and, conse-

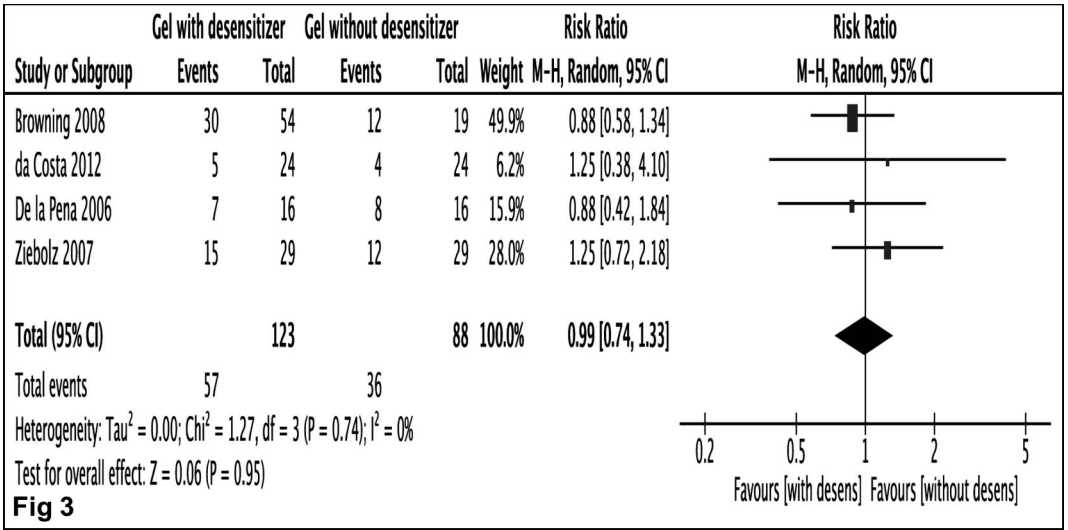

Fig 3

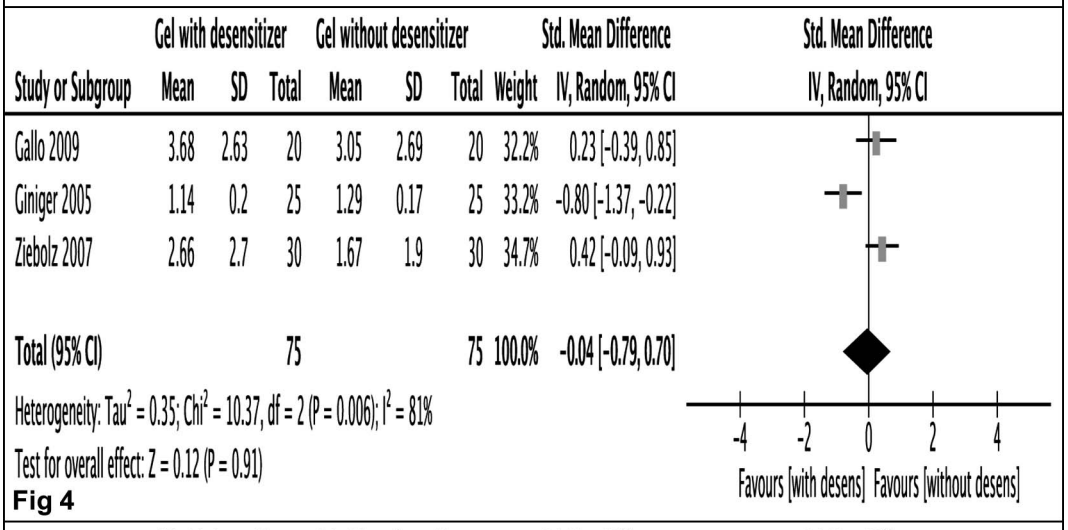

Fig 4

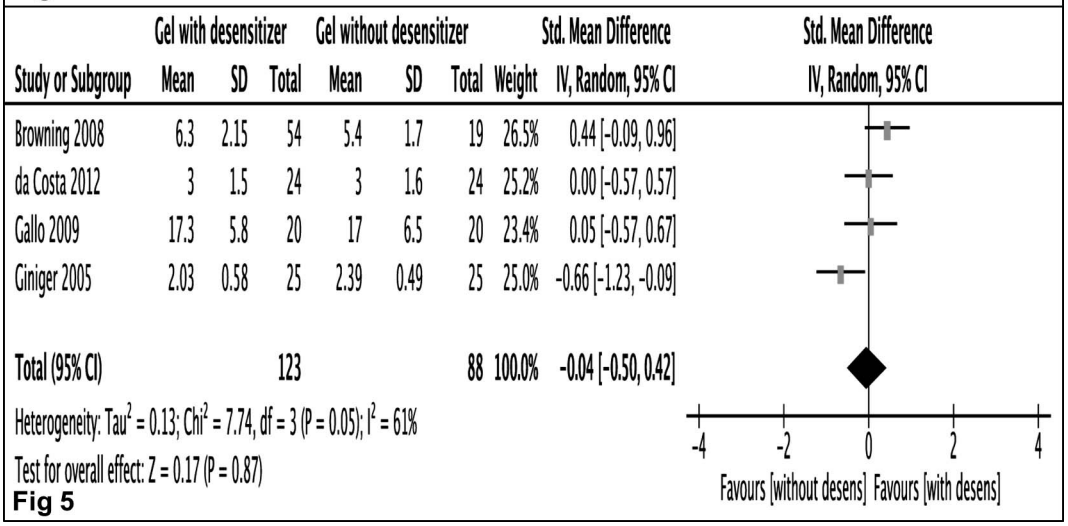

Fig 5

Figure 3. *Forest plot of the risk of tooth sensitivity for dental bleaching with desensitizer vs without desensitizer.*

Figure 4. *Forest plot of the intensity of tooth sensitivity (with stimulus) for dental bleaching with desensitizer vs without desensitizer.*

Figure 5. *Forest plot of the color change in shade guide units for dental bleaching with desensitizing vs without desensitizing.*

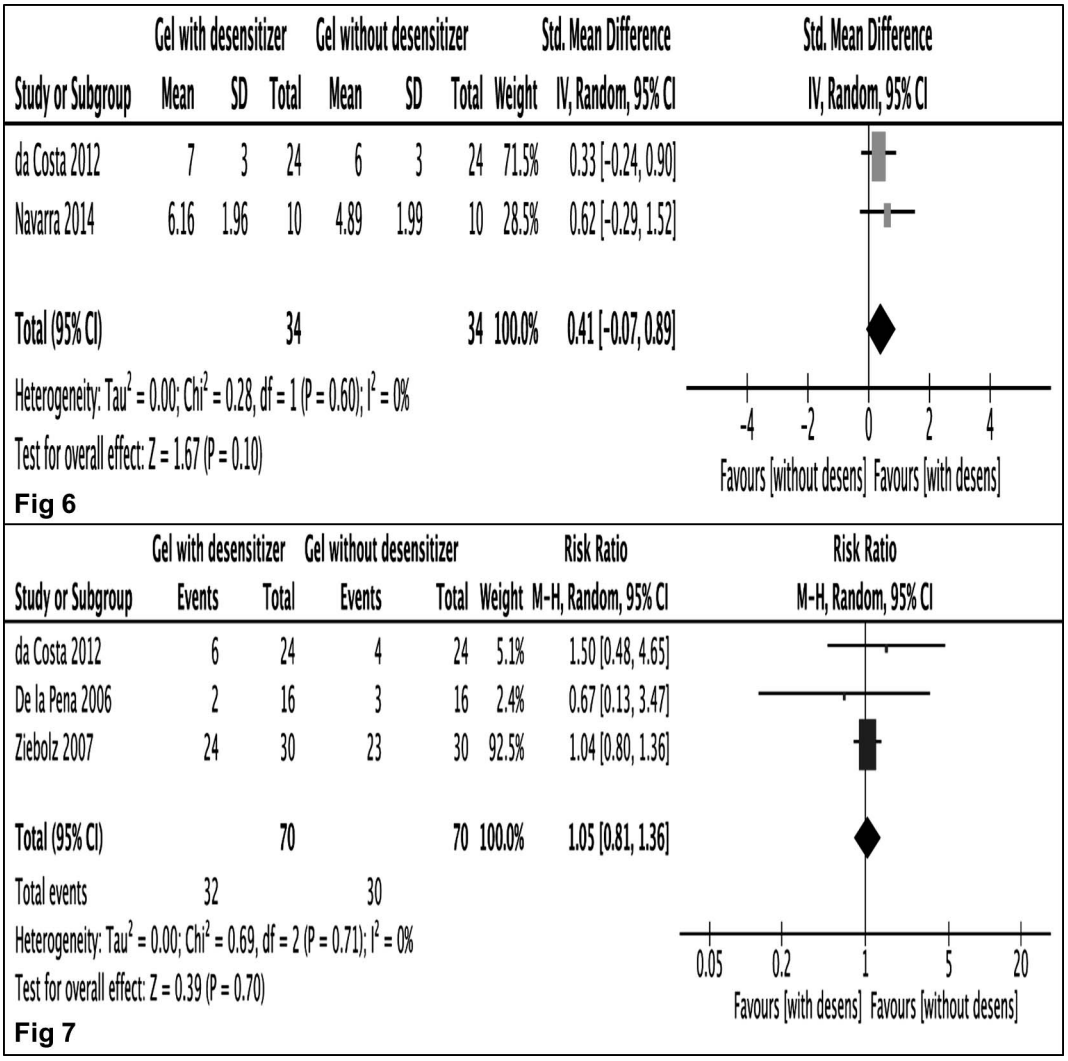

Figure 6. *Forest plot of the color change in ΔE* dental bleaching with desensitizer vs without desensitizer.*

Figure 7. *Forest plot of the risk of gingival irritation for dental bleaching with desensitizer vs without desensitizer.*

quently, reduce dentin permeability.[85,86] Unfortunately, based on the studies included in this systematic review, we cannot affirm the superiority of either treatment approach because in these studies the desensitizing agents were usually mixed in the same product as reported in Table 2. Future RCTs need to be done comparing at-home bleaching gels with and without each specific desensitizer.

Although these desensitizing components are effective, they may need some time to reach the pulp and exert their effectiveness before the application of HP.[27,31,39] The topical application of desensitizing agents appears to be an effective strategy for reducing TS with at-home bleaching[16,26,30] and in-office bleaching.[31-34] As both components are applied simultaneously, HP can reach the pulp tissue faster due to its lower molecular mass.[87] Therefore, by the time potassium nitrate reaches the pulp, reducing transmission of nerve impulses by potassium nitrate[31,79] is no longer possible, as HP may have caused cell damage or even directly activated the neuronal receptors (TRPA1 ion channel) of the dental pulp complex[88] that ultimately triggers the transmission of pain impulses.

All of the included studies used the at-home bleaching technique and reported a color change of three to eight units on the Vita shade scale, which is in agreement with earlier reports in the literature.[4,5,7,10,89] This variation in the number of whitening units can be the result of the different contact periods of the bleaching agent. The effec-

Table 3: *Summary of Findings Table*

Desensitizing-containing compared to desensitizing-free products for adults submitted to dental bleaching						
Patient or population: adults submitted to dental bleaching						
Setting: cosmetic care in university						
Intervention: desensitizing-containing products						
Comparison: desensitizing-free products						
Outcomes	**Anticipated Absolute Effects[a] (95% CI)**		**Relative Effect (95% CI)**	**No of Participants (Studies)**	**Quality of the Evidence (GRADE)[b]**	**Comments**
	Risk With Desensitizer-Free Products	**Risk With Desensitizer-Containing Products**				
Risk of tooth sensitivity assessed with pain scales	409 per 1000	405 per 1000 (303–544)	RR 0.99 (0.74–1.33)	211 (4 RCTs)	⊕⊕⊕○ Moderate[c]	From a total of seven included studies only four reported this outcome.
Intensity of tooth sensitivity assessed with pain scales after stimulation	-	SMD 0.04 SD lower (0.79 lower to 0.7 higher)	-	150 (3 RCTs)	⊕○○○ Very low[c,d,e]	From a total of eight included studies, only three reported this outcome in a similar manner, that is, pain. Measurement was performed after application of stimulus. Only one study (not included) measured pain intensity without stimulation
Color change in shade guide units assessed with shade guides	-	SMD 0.04 SD lower (0.50 lower to 0.52 higher)	-	211 (4 RCTs)	⊕○○○ Very low[c,d,e]	From a total of eight included studies, only four reported this outcome.
Color change in ΔE* assessed with spectrophotometer	-	SMD 0.41 SD lower (0.07 lower to 0.89 higher)	-	68 (2 RCTs)	⊕⊕○○ Low[c,f]	From a total of right included studies only two reported this outcome.
Risk of gingival irritation assessed with pain scales	429 per 1000	450 per 1000 (347–583)	RR 0.99 (0.74–1.33)	211 (4 RCTs)	⊕⊕○○ Low[c,e]	From a total of eight included studies only three reported this outcome.

Abbreviations: CI, confidence interval; RCT, randomized clinical trial; RR, risk ratio; SD, standard deviation; SMD, standardized mean difference; RCT, randomized clinical trial;.
[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] GRADE (Grading of Recommendations: Assessment, Development and Evaluation) uses the following levels of evidence: ⊕⊕⊕⊕ = high quality means researchers are very confident that the true effect lies close to that of the estimate of the effect; ⊕⊕⊕○ = moderate quality means the researchers are moderately confident in the effect estimate (ie, 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 quality means researchers' confidence in the effect estimate is limited (ie, the true effect may be substantially different from the estimate of the effect); and ⊕○○○ = very low quality means researchers have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c] The great majority of the studies were at unclear risk in sequence generation and allocation concealment domains.
[d] Inconsistency of the data with unexplained heterogeneity.
[e] High 95% CI, which does not exclude important harm or benefit.
[f] Very low sample size, excluding the optimal information size, with a very high 95% CI.

tiveness of bleaching is not only related to the concentration but also to usage time.[9,23-25,58,90,91] Indeed, by looking at the findings of the primary studies, this difference in the bleaching protocol can be detected. The studies of Costa and others[22] and Gallo and others[36] reported a color change of only three units on the Vita shade guide, whereas the studies of Browning and others[35] and Giniger and others[38] found a variation of approximately eight shade guide units. Although da Costa and others[22] and Gallo and others[36] kept the product in contact with the teeth for 30 minutes to 1 hour, Browning and others[35] and Giniger and others[38] left the gel on the dental surfaces for a minimum of 3 hours.

No difference was found between gels with and without desensitizers when considering gingival sensitivity, which was already expected because no component in the bleaching gel is able to neutralize the action of peroxides in the soft tissues.

In summary, the hypothesis of equality between materials in relation to TS cannot be rejected. This is the only outcome for which the quality of the evidence was considered moderate. However, one

should keep in mind that the quality of the evidence of the outcomes for color change, intensity of TS, and risk of gingival irritation was graded as low and very low. This downgrade in the level of evidence for these outcomes was the result of the low number of studies due to the lack of information in primary studies. For instance, Table 3 explains that only three of eight studies reported the intensity of TS in a similar manner, and only two of eight studies reported color change in delta E. This reduced the total number of participants in the meta-analysis, generating high confidence intervals, with the estimates already coming from studies with an unclear risk of bias.

In light of this, more RCTs should be conducted using a rigorous methodology for at-home bleaching techniques using gels with and without desensitizers. Although the current research strategy included at-home and in-office bleaching, only at-home bleaching studies were found and included in the present systematic review of the literature, indicating that future RCTs need to be performed comparing in-office bleaching techniques using gels with and without desensitizers.

CONCLUSION

Incorporating desensitizers in at-home bleaching gels did not reduce the risk of TS; the quality of the evidence for this outcome was considered moderate. No difference between the groups was observed for the other outcomes (intensity of TS, color change, and risk of gingival irritation), although the quality of the evidence of these outcomes was low or very low. This indicates that more RCTs with large sample sizes and a rigorous methodology are required to confirm these results.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of approval of the State University of Ponta Grossa. This study was registered at the PROSPERO under protocol number CRD 42016036411.

Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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