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REVIEW

Are combined bleaching techniques better than their sole application? A systematic review and meta-analysis

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Abstract

Objectives A systematic review and meta-analysis were performed to answer this research question: "Does combined in-office (IO) and at-home (AH) bleaching produce improved color change and lower tooth sensitivity (TS) better than solely AH or IO bleaching in adults?"

Material and methods Randomized controlled trials in adults that compared combined versus sole application bleaching were included. The risk of bias (RoB) was evaluated using the Cochrane Collaboration tool. Meta-analyses were conducted for color change in shade guide units (ΔSGU) and with a spectrophotometer (ΔE*), risk, and intensity of TS, using the random effects model. Heterogeneity was assessed with Cochran's Q test and I^2 statistics. GRADE assessed the quality of the evidence. PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library, SIGLE, IADR abstracts, unpublished, ongoing trial registries, dissertations, and theses were searched on August 28, 2017 (updated on January 29, 2019).

Results Twelve studies remained. Two were considered to have low RoB. For combined vs. IO bleaching, no significant difference for ΔE*, ΔSGU, and risk of TS were observed; data were not available to analyze the intensity of TS. For combined vs. AH bleaching, no significant difference for ΔE*, ΔSGU, but lower TS to risk (RR 1.40, 95% 1.10 to 1.80) and intensity (MD 1.40, 95% CI 0.18 to 2.63) were detected for AH bleaching. Quality of evidence was graded as low or very low in all meta-analyses.

Conclusion Lower risk and intensity of TS was observed for the solely AH group without jeopardizing color change. However, more studies are still encouraged due to the low quality of evidence for most of the outcomes.

Clinical relevance If clinicians are to choose between combined or sole AH bleaching, the solely AH may be preferable; combined bleaching may potentiate the risk of TS without benefits in color change. For combined or sole IO bleaching, no important clinical difference in color change and risk of TS were detected; however, intensity of TS could not be compared due to lack of data. Further studies should be conducted due to the low/very low quality of the evidence.

Keywords Tooth bleaching agents · Tooth discolorations · Dentin sensitivity · Systematic review · Meta-analysis

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Introduction

Dental bleaching is the most popular cosmetic procedure because it is a conservative method for treating dental discoloration [1, 2] and it meets the needs of an increasing number of patients who request treatment for esthetic discoloration [3–5]. Furthermore, dental bleaching is technically easier and lower-cost than any other type of cosmetic treatment, such as veneers.

Dentist-supervised dental bleaching can be performed in-office by the dentist, using high-concentrate hydrogen peroxide (HP), or it can be done at-home by the patient, using low-concentrate carbamide peroxide (CP) or low-concentrate HP [6]. Although at-home bleaching is frequently used, some patients do not adapt to the daily use of a tray for several weeks, so they request a tray-free and faster bleaching option [7, 8]. In-office bleaching is a good alternative for such patients. It can be performed in one to four clinical appointments, with applications lasting from 15 to 60 min [9–11]. This technique, however, has the disadvantage of producing a higher intensity of tooth sensitivity (TS) during and after bleaching due to the inflammatory reaction produced by HP and free radicals when they contact the dental pulp [12–15].

A common clinical practice is to combine at-home and in-office bleaching techniques [16–18] to obtain faster bleaching effects [18], improved color stability [17, 19], and reduced levels of TS. Within this context, a single in-office bleaching session is usually performed first to start the bleaching effects quickly [20, 21]. Then, the patient continues the protocol at-home with a custom-made bleaching tray, using low-concentrate products until the desired shade is obtained [17, 18, 22].

Some randomized controlled trials (RCTs) have already compared the combined bleaching technique with the sole use of at-home or in-office protocols [17, 20, 23, 24]; however, conflicting results in terms of risk and intensity of tooth sensitivity [25] and color change and stability [17, 18, 20, 22] have been reported.

Perhaps, such differences can be attributed to differences in protocols and deserve a deeper systematic revision to reach more reliable conclusions and allow for clinical recommendations. Therefore, the aim of the present systematic review of the literature was to evaluate whether there are evidence-based differences in color change, risk, and intensity of tooth sensitivity of combined bleaching versus the sole use of at-home or in-office bleaching protocols.

Materials and methods

Protocol and registration

This systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42016036555. The present study was reported, following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [26].

Information sources and search strategy

The controlled vocabulary (MeSH terms) and free keyword in the search strategy were defined based on the following PICOS question (P: participant, I: intervention, C: comparator, O: outcome, and S: study design):

1. Participant (P): adult patients that underwent vital tooth bleaching;
2. Intervention (I): combined in-office and at-home bleaching;
3. Comparison (C): solely in-office or at-home bleaching;
4. Outcome (O): color change in shade guide units (ΔSGU) and with a spectrophotometer (ΔE*); risk and intensity of TS taken after dental bleaching;
5. Study design (S): randomized controlled trials.

The search strategy was first defined for the MEDLINE database by PubMed, based on using controlled vocabulary (MeSH terms) and free keywords for each concept of the PICO question was searched.

The MEDLINE search strategy was adapted to other electronic databases (Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature [LILACS] database) and citation databases (Scopus and Web of Science) (Table 1). In addition, gray literature was investigated by searching the abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (1990–2018), the System for Information on Gray Literature in Europe database, and dissertations and theses, using the ProQuest Dissertations and Theses full-text database as well as the Periódicos Capes Theses database.

Ongoing studies were searched in the following clinical trial registries: Current Controlled Trials (www.controlled-trials.com), International Clinical Trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (http://www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

In addition, the reference lists of all primary and eligible studies of this systematic review for additional relevant publications were hand-searched. The first two pages of the related-articles link of each primary study in the PubMed database were also searched. In the whole search process, no restriction was placed on publication date and/or language.

Table 1 Electronic database and search strategy conducted initially in 28 August 2017 and was updated in 25 April 2018 and 29 January 2019

Pubmed		
#1 ((((((((((((((((((((tooth discoloration[MeSH Terms]) OR dentition, permanent[MeSH Terms]) OR color[MeSH Terms]) OR "tooth discoloration"[Title/Abstract]) OR "tooth discolouration"[Title/Abstract]) OR "teeth discoloration"[Title/Abstract]) OR "teeth discolouration"[Title/Abstract]) OR "permanent dention"[Title/Abstract]) OR color[Title/Abstract]) OR color[Title/Abstract]) OR "discolored tooth"[Title/Abstract]) OR "discolored tooth"[Title/Abstract]) OR "discolored teeth"[Title/Abstract]) OR "discolored teeth"[Title/Abstract]) OR "dental discoloration"[Title/Abstract]) OR "dental discolouration"[Title/Abstract]) OR "tooth staining"[Title/Abstract]) OR "teeth staining"[Title/Abstract]) OR "stained tooth"[Title/Abstract]) OR "stained teeth"[Title/Abstract]) OR "dental staining"[Title/Abstract])	#2((((((((((((((((((tooth bleaching[MeSH Terms]) OR tooth bleaching agents[MeSH Terms]) OR peroxides[MeSH Terms]) OR hydrogen peroxide[MeSH Terms]) OR carbamide peroxide[Supplementary Concept]) OR dental offices[MeSH Terms]) OR bleaching[Title/Abstract]) OR whitening[Title/Abstract]) OR peroxides[Title/Abstract]) OR "hydrogen peroxide"[Title/Abstract]) OR "carbamide peroxide"[Title/Abstract]) OR "dental offices"[Title/Abstract]) OR "dental office"[Title/Abstract]) OR "in-office"[Title/Abstract]) OR "at-home"[Title/Abstract]) OR "home-use"[Title/Abstract]) OR "home-care"[Title/Abstract]) OR "jump-start"[Title/Abstract]	#7 (randomized controlled trial[pt] OR controlled clinicaltrial[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		
Cochrane		
#1 MeSH descriptor: [Tooth Discoloration] explode all trees	#7 MeSH descriptor: [Tooth Bleaching] explode all tres	
#2 MeSH descriptor: [Dentition, Permanent] explode all trees	#8 MeSH descriptor: [Tooth Bleaching Agents] explode all trees	
#3 MeSH descriptor: [Color] explode all trees	#9 MeSH descriptor: [Peroxides] explode all trees	
#4 t*th next discoloration:ti,ab,kw or t*th next staining:ti,ab,kw or stained next t*th:ti,ab,kw or discolored next t*th:ti,ab,kw (Word variations have been searched)	#10 MeSH descriptor: [Hydrogen Peroxide] explode all trees	
	#11 MeSH descriptor: [Dental Offices] explode all trees	
	#12 "carbamide peroxide":ti,ab,kw or bleaching:ti,ab,kw or whitening:ti,ab,kw or peroxides:ti,ab,kw or "hydrogen peroxide":ti,ab,kw (Word variations have been searched)	
#5 "permanent dention":ti,ab,kw or dental next staining:ti,ab,kw or color:ti,ab,kw or dental next discoloration:ti,ab,kw (Word variations have been searched)	#13 "dental office":ti,ab,kw or "in office":ti,ab,kw or "at home":ti,ab,kw or "home use":ti,ab,kw or "home care":ti,ab,kw (Word variations have been searched)	
	#14 "jump start":ti,ab,kwor "dental offices":ti,ab,kw (Word variations have been searched)	
#6 #1 or #2 or #3 or #4 or #5	#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	
#6 AND #15		
Lilacs/BBO		
(MH:"tooth discoloration" OR MH:"permanent dentition" OR MH:color OR "tooth discoloration" OR "permanent dentition" OR "color" OR "tooth discolouration" OR "teeth discoloration" OR "teeth discolouration" OR color OR color OR "discolored tooth" OR "discolored tooth" OR "discolored teeth" OR "discolored teeth" OR "dental discoloration" OR "dental discolouration" OR "tooth staining" OR "teeth staining" OR "stained tooth" OR "stained teeth" OR "dental staining" OR "descoloração de dente" OR "descoloração dos dentes" OR "decoloración de los dientes" OR "dentição permanente" OR "dentición permanente" OR "de color" OR "dente descolorido" OR "diente escurecido" OR "dentes descoloridos" OR "dientes escurecidos" OR "descoloração dental" OR "descoloración dental" OR "manchamento dental" OR "manchado dental" OR "mancha no dente" OR "mancha nos dentes" OR "mancha en los dientes" OR "dente manchado" OR "diente manchado" OR "dentes manchados" OR "dientes manchados")	(MH:"tooth bleaching" OR MH:"tooth bleaching agents" OR MH:peroxides OR MH:"hydrogen peroxide" OR "carbamide peroxide" OR MH:"dental offices" OR bleaching OR whitening OR peroxides OR "hydrogen peroxide" OR "carbamide peroxide" OR "dental offices" OR "dental office" OR "in-office" OR "at-home" OR "home-use" OR "home-care" OR "jump-start" OR "clareamento dental" OR "blanqueamiento dental" OR peróxidos OR peroxidos OR "peróxido de hidrogênio" OR "peroxido de hidrogeno" OR "peróxido de carbamida" OR "consultório dental" OR "consultorio dental" OR "consultóriosdentais" OR "consultorios dentales" OR branqueamento OR blanqueo OR blanqueamiento OR "emconsultório" OR "en el consultorio" OR caseiro OR casero OR "uso doméstico" OR "cuidados domiciliários" OR associado OR asociado)	
#1 AND #2		
Scopus		

Table 1 (continued)

#1 (TITLE-ABS-KEY (“T??th discoloration”) OR TITLE-ABS-KEY (“t??th staining”) OR TITLE-ABS-KEY (“t??thdiscolouration”) OR TITLE-ABS-KEY (“discolored t??th”) OR TITLE-ABS-KEY (colo*r) OR TITLE-ABS-KEY (“dental discolo*ration”) OR TITLE-ABS-KEY (“dental staining”) OR TITLE-ABS-KEY (“permanent dentition”)) #1 AND #2	#2 (TITLE-ABS-KEY (peroxides) OR TITLE-ABS-KEY (“hydrogen peroxide”) OR TITLE-ABS-KEY (“carbamide peroxide”) OR TITLE-ABS-KEY (“dental office*”) OR TITLE-ABS-KEY (bleaching) OR TITLE-ABS-KEY (whitening) OR TITLE-ABS-KEY (“in-office”) OR TITLE-ABS-KEY (“home-use”) OR TITLE-ABS-KEY (“at-home”) OR TITLE-ABS-KEY (“home-care”) OR TITLE-ABS-KEY (“jump-start”)))
Web of Science #1 TS=(“T*th discolo*ration”) OR TS=(colo?r) OR TS=(“permanent dention”) OR TS=(“discolo*red t*th”) OR TS=(“dental discolo*ration”) OR TS=(“t*th staining”) OR TS=(“stained t*th”) OR TS=(“dental staining”) #1 AND #2	#2 TS=(“t*th bleaching agents”) OR TS=(bleaching) OR TS=(peroxides) OR TS=(“hydrogen peroxide”) OR TS=(“carbamide peroxide”) OR TS=(“dental office*”) OR TS=(whitening) OR TS=(“in-office”) OR TS=(“at-home”) OR TS=(“home-use”) OR TS=(“home-care”) OR TS=(“jump-start”)

Eligibility criteria

Parallel and split-mouth randomized controlled trials conducted with adult patients of any age group that answered the PICO question described at the end of the introduction section were included. RCTs were excluded if the studies compared only different combined bleaching treatments.

Study selection and data collection process

The articles retrieved by the literature search were revised in three phases. All studies were initially scanned for relevance by title, and the abstracts of those that were not excluded at this stage were appraised. The next step included the abstract reading, and the full text of the studies that could not be excluded according to our eligibility criteria in the abstract review was retrieved for further evaluation. Three reviewers then read the full texts to see whether they met the inclusion criteria. Finally, the eligible articles received a study identification (ID), combining first author and year of publication.

Two reviewers independently abstracted data from included articles, such as study design, participants, interventions, and outcomes. In cases of disagreement, a decision was reached by consulting a third reviewer. If there were multiple reports of the same study (i.e., reports with different follow-ups), data from all reports were extracted directly into a single data collection form to avoid overlapping data.

Data from color change after the end of the bleaching treatment was collected with periods ranging from immediately to 2-week post-bleaching (Table 2). This variation was due to the differences in the assessment period reported in the studies; from the 7 studies included [11, 16, 21, 27–30], 4 provided data for 1-week post-bleaching [11, 16, 27, 30], the reason of why we selected this time period for meta-analysis. When this period was not reported, we chose the closest period to 1-week post-bleaching, which was between immediately after [21, 28, 29] 2-week post-bleaching [21]. Preference was given for 2-week post-bleaching when the two options were available [21], since the teeth tend to appear whiter immediately after bleaching due to dental dehydration by teeth isolation and demineralization caused by the acidity of the bleaching agent [31]. Regarding TS, the worst mean value of TS reported for the group was collected.

Risk of bias in individual studies

Quality assessments of the selected trials were carried out by three independent reviewers, using the Cochrane Collaboration tool for assessing the risk of bias in RCTs [32]. The assessment criteria contained six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Disagreements

Table 2 Assessment periods reported by the primary study authors and the period used in this systematic review

Study	Time assessment periods reported in the study	Selected period extracted for this meta-analysis
Bernardon [21]	1, 2, 4, 8, and 16 weeks after start of bleaching	2-week post-bleaching
Coban [27]	1-week and 6-month post-bleaching	1-week post-bleaching
Dawson [16]	Immediately and 1-week post-bleaching	1-week post-bleaching
Machado [28]	Immediately after bleaching and 16-days after start of bleaching	Immediately after bleaching
Rezende [11]	Immediately, 1-week, 1 and 6-month post-bleaching	1-week post-bleaching
Rodrigues [29]	Immediately and 6-month post-bleaching	Immediately post-bleaching
Vochikovski [30]	Immediately, 1-week, 1 and 6-month post-bleaching	1-week post-bleaching

among the reviewers were solved through discussion and, if needed, by consulting a fourth reviewer (A.R.).

For each aspect of the quality assessment, the risk of bias was scored, following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.02 (http://handbook.cochrane.org). Each domain level was judged as having low, high, or unclear risk of bias. At the study level, the study was at low risk of bias if all key domains (see below) for each outcome were at low risk of bias. If one or more key domains were judged as having unclear risk, the study was at unclear risk, and if at least one key domain was considered at high risk of bias, the study was considered at high risk of bias.

For the patient-centered outcomes such as the risk and intensity of TS, the key domains were adequate sequence generation and allocation concealment. Patient blinding was not considered a key domain because patients could easily identify the different bleaching protocols. For color change in ΔSGU, three items of the Cochrane Collaboration tool were considered key domains: adequate sequence generation, allocation concealment, and examiner blinding. However, for ΔE*, examiner blinding was not considered a key domain, because the previous knowledge of the treatment would not affect the results produced by an objective tool for color assessment such as spectrophotometers or colorimeters.

Data synthesis and statistical analysis

Data were analyzed using Revman 5.3 (Review Manager, version 5.3, the Cochrane Collaboration, Copenhagen, Denmark). Meta-analyses were performed in studies classified as low or unclear risk of bias. Studies judged to have high risk of bias were not included in the meta-analyses. Data from eligible studies were summarized by calculating the risk ratio (risk of TS) and the mean difference (intensity of TS and ΔE*). For the ΔSGU, mean difference was calculated when studies used the same shade guide or standardized mean difference were employed when at least one study used a different shade guide tool. For all meta-analyses, random effects model was chosen to summarize a mean effect size of the primary studies. Heterogeneity was assessed using Cochran's Q test and I^2 statistics. According to the Cochrane Handbook for Systematic Reviews of Interventions, the heterogeneity was classified as follows: < 40% may be low; 30–60% may be moderate; 50–90% may be substantial; 75–100% may be considerable.

When a study used a split-mouth design, data was merged keeping the same number of patients used in the comparison, and if the study reported two or more groups with the same intervention, we merged the data using the following below where N_1 and N_2 is the number of participants from groups 1 and 2; SD_1 e SD_2 is the standard deviation of groups 1 and 2, and M_1 and M_2 is the mean of groups 1 and 2.

$$\sqrt{\frac{(N_1-1)SD_1^2+(N_2-1)SD_2^2+\frac{N_1N_2}{N_1+N_2}\left(M_1^2+M_2^2-2M_1M_2\right)}{N_1+N_2-1}}$$

Sensitivity analyses were also conducted to investigate the reasons for high heterogeneity, whenever detected, and also to assess the impact of imputations required for meta-analysis. Individual meta-analysis for studies that compared combined bleaching vs. in-office bleaching and those that compared combined bleaching vs. at-home bleaching was performed, because both types of comparison were identified in the systematic review.

Assessment of the quality of the evidence, using GRADE

The quality of the evidence for each outcome across the studies (body of evidence) was graded by using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) system to determine the overall strength of the evidence for each meta-analysis. 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 5.2.0 (http://handbook.cochrane.org).

The GRADE approach for RCTs addresses five possible reasons (risk of bias, imprecision, inconsistency, indirectness

of evidence, and publication bias) to 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 August 28, 2017, and it was updated on April 25, 2018, and January 29, 2019. After database screening and duplicate removal, 2466 studies were identified, after title screening, 331 studies remained, and this number was reduced to 12 after careful examination of the abstracts (Fig. 1).

Characteristics of included articles

Nine studies were published [10, 11, 16, 18, 21, 22, 28, 29, 33], being one of them an IADR abstract [27] and one was in a thesis format not published yet in a peer reviewed journal [30], and the same study is an IADR abstract [34] and a thesis format not published yet in a peer reviewed journal [35].

The characteristics of the 12 eligible studies are listed in Table 3. Nine studies used parallel design [10, 11, 16, 22, 27, 29, 30, 33, 34], and three studies used the split-mouth design [18, 21, 28] (Table 3).

Eight studies used the Vita Classical Shade guide (Vita Zahnfabrik, BadSäckingen, Germany) [11, 16, 18, 21, 22, 28–30], and three studies used the Vita Bleached guide 3D-Mastershade guide (Vita Zahnfabrik, Bad Säckingen, Germany) [29, 30, 34]. Seven studies used an objective instrument for color assessment (spectrophotometer or colorimeter) [10, 18, 21, 27–30]. Photography was used in four studies [18, 21, 22, 34]. One study did not evaluate color change [33] (Table 3).

The intensity of TS was evaluated using the visual analog scale (VAS) [16, 18, 21, 28, 30]. This outcome was not evaluated in three studies [22, 27, 33]. Four studies evaluated the risk of TS [10, 11, 29, 30, 34] (Table 3).

Age of participants in the primary RCTs and gender

The patients ranged from 18 to 78 years of age. The mean age of all participants that reported this information was approximately 29.7 years (Table 3). In the studies that reported the gender of the sample, females were more prevalent [10, 18, 28–30, 34].

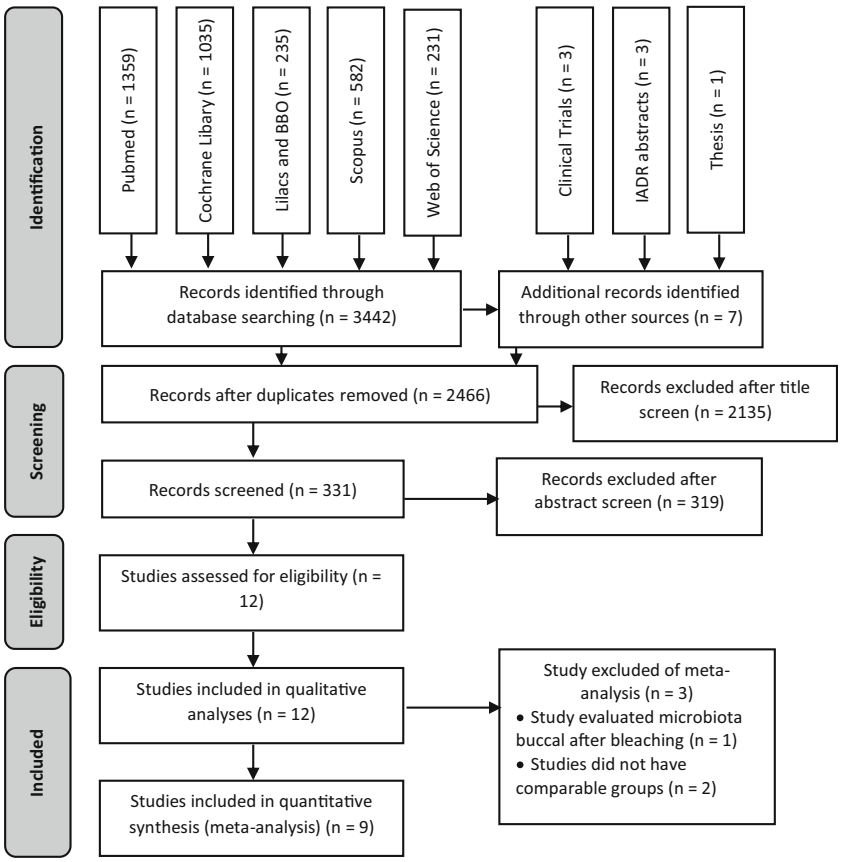

Fig. 1 Flow diagram of study identification

Table 3 Summary of the primary studies included in the systematic review

							Bleaching protocol	Collection of the results	
Study ID	Study design	Number of patients [drop-outs]	Subjects age's mean ± SD [range] (years)	No. of males [%]	Baseline color/ evaluated tooth	Groups/materials	Gel protocol applications × min [sessions] (interval)	Color assessment [outcome]	Tooth sensitivity: scale [outcome]
Bernardon 2010 [21]	Split-mouth	90 [n.r.]	n.r ± n.r. [n.r.–n.r]	n.r. [n.r.]	A2/anterior teeth	Sole$^{AH\ vs.\ IO}$: 10% CP^{a}vs. 35% HP^{b} w/lightSole$^{IO\ vs.\ IO}$: 35% HP^{b} w/light vs. 35% HP^{b}Sole and Combined$^{AH\ vs.\ IO\ +\ AH}$: 10% CP^{a} vs. 35% HP^{b} w/ light [1 session] + 10% CP^{a}	Sole^{AH}: 8 h/daily (14 days)Sole^{IO}: 3 × 15 min [2] (15 days)Combined^{IO+AH}: 3 × 15 min [1] + 8 h/daily (14 days)	Vita Classical^{p}; Spectrophotometer^{q}; Photography[ΔSGU; ΔE*]	VAS 0–10 [intensity of TS]
Coban 2011 [27]	Parallel	45 [n.r]	24.9 ± 4.5 (n.r.–n.r.)	n.r. [n.r.]	A3/anterior teeth	Sole^{IO}: 35% HP^{c}Sole^{AH}: 15% CP^{d}Combined$^{IO\ +\ AH}$: 35% HP^{c} + 6% HP^{e}	Sole^{IO}: 1 × 30 min [3] (7 days)Sole^{AH}: 8 h/daily (14 days)Combined^{IO+AH}: 1 × 30 min [1] + 4 h/daily (14 days)	Spectrophotometer^{q}[ΔE*]	n.r.
Dawson 2011 [16]	Parallel	36 [0]	29.8 ± n.r. [19–58]	n.r. [n.r.]	A3/anterior teeth	Sole^{AH}: AH 16% CP^{f}Combined$^{AH\ +\ IO}$: 16% CP^{f} + 9% HP^{g}Combined$^{AH\ +\ IO}$: 16% CP^{f} + 27% HP^{g}	Sole^{AH}: 7 h/night (14 days)Combined^{AH+IO}:7 h/night (14 days) + 2 × 20 min [1]	Vita Classical^{p}; [ΔSGU]	VAS 0–10 [intensity of TS]
Dias 2011 [34]	Parallel	20 [0]	21.9 ± 2.62 [n.r.–n.r]	1 [5]	0.5 M1/upper incisor	Sole^{AH}: 16% CP^{h}Sole^{IO}: 35% HP^{i}Combined$^{IO\ +\ AH}$: 35% HP^{i} + 16% CP^{h}	Sole^{AH}: 8 h/daily (28 days)Sole^{IO}: 2 × 15 min [4] (7 days)Combined^{IO+AH}: 2 × 15 min [4] + 8 h/daily (28 days)	Vita Bleachedguide^{r}; Photography[ΔSGU]	NRS 0–4 [risk of TS]
Franz-Montan 2009 [33]	Parallel	32 [n.r.]	n.r ± n.r. [18–31]	n.r. [n.r.]	n.r./n.r	Sole^{IO}: 37% HP^{b}Sole^{AH}: 10% HP^{a}Combined$^{IO\ +\ AH}$: 37% HP^{b} + 10% CP^{a}	Sole^{IO}: 1 × 60 min [3] (7 days) Sole^{AH}: 6 h/daily (21 days)Combined^{IO+AH}: 1 × 60 min [3] + 6 h/daily (21 days)	n.r.	n.r.
Kugel 1997 [22]	Parallel	20 [0]	n.r ± n.r. [n.r.–n.r]	n.r. [n.r.]	n.r./n.r	Sole^{IO}: 35% HP^{j}Combined$^{IO\ +\ AH}$: 35% HP^{j} + 15%^{k} CP	Sole^{IO}: 1 × 15 min [2] (6 days)Combined^{IO+AH}: 1 × 15 min [2] + 2 h/daily (5 days)	Vita Classical^{p}; Photography[ΔSGU]	n.r.
Machado 2016 [28]	Split-mouth	21 [0]	23 ± n.r. [18–25]	6 [28.6]	A2/anterior teeth	Combined^{IO+AH}: 38% HP^{l} + 10% CP^{d}Sole^{AH}: 10% CP^{d}	Combined^{IO+AH}: 2 × 15 min [2] (8 days) + 4 h/daily (14 days)Sole^{AH}: 4 h/daily (14 days)	Vita Classical^{p}; Spectrophotometer^{q}[ΔSGU; ΔE*]	VAS 0–10 [intensity of TS]
Matis 2009 [18]	Split-mouth	37 [3]	53.7 ± n.r. [35–78]	14 [37.8]	A3/anterior teeth	Combined$^{IO\ +\ AH}$: 36% HP^{i} + 15% CP^{h}Sole^{IO}: 36% HP^{i}Combined$^{IO\ +\ AH}$: 36% HP^{i} + 15% CP^{h}Sole^{IO}: 36% HP^{i}	Combined^{IO+AH}: 3 × 15 min [1] + Overnight (7 days)Sole^{IO}: 3 × 15 min [1]Combined^{IO+AH}: 1 × 40 min [1] + Overnight (7 days)Sole^{IO}: 1 × 40 min [1]	Vita Classical^{p}; ChromoMeter^{s}; Photography[ΔSGU; ΔE*]	VAS 0–10 [intensity of TS]
Rezende 2014 [11]	Parallel	30 [0]	n.r ± n.r. [n.r.–n.r]	n.r. [n.r.]	A2/anterior teeth	Combined$^{IO\ +\ AH}$: 35% HP^{m} + 6% HP^{n}Sole^{IO}: 35% HP^{m}	Combined^{IO+AH}: 3 × 15 min [2] + 1 h/daily (28 days)Sole^{IO}: 3 × 15 min [2] (7 days)	Vita Classical^{p} [ΔSGU]	NRS 0–4 [risk of TS]
Rodrigues 2018 [29]	Parallel	40 [0]	24.1 ± 5.0 [n.r.–n.r]	12 [30]	A2/anterior teeth	Combined$^{IO\ +\ AH}$: 38% HP^{l} + 10% CP^{d} Sole^{IO}: 35% HP^{d}	Combined^{IO+AH}: 1 × 45 min [1] + 4 h/daily (7 days) Sole^{IO}: 1 × 45 min [2] (7 days)	Vita Classical^{p}; Vita Bleachedguide^{r}; Spectrophotometer^{q}[ΔSGU; ΔE*]	NRS 0–4 [risk of TS]
Vochikovski 2018 [30]	Parallel	80 [0]	23.1 ± 4.8 [18–41]	31 [38.7]	A2/upper incisors	Combined^{IO+AH}: 35% HP^{b} + 4% HP^{o}Sole^{AH}: 4% HP^{o}	Combined^{IO+AH}: 3 × 15 min [1] + 1 h/daily (21 days)Sole^{AH}: 1 h/daily (21 days)	Vita Classical^{p}; Vita Bleachedguide^{r}; Spectrophotometer^{q}[ΔSGU; ΔE*]	NRS 0–4VAS 0–10 [risk and intensity of TS]
	Parallel	90 [2]						Portablespectrometer^{t}[Δchroma]	

Table 3 (continued)

							Bleaching protocol	Collection of the results	
Study ID	Study design	Number of patients [drop-outs]	Subjects age's mean ± SD [range] (years)	No. of males [%]	Baseline color/ evaluated tooth	Groups/materials	Gel protocol applications × min [sessions] (interval)	Color assessment [outcome]	Tooth sensitivity: scale [outcome]
Wetter 2009 [10]			n.r. ± n.r. [18–45]	32 [35.5]	n.r./upper central incisors and canines	Combined^{IO+AH}: 35% HP^{b} w/light +10% CP^{a}Combined^{IO+AH}: 35% HP^{b} w/light +10% CP^{a}Sole^{AH}: 10% CP^{a}	Combined^{IO+AH}: 1 × 20 min [1] + 1 h/daily (7 days)Sole^{AH}: 1 h/daily (14 days)		NRS 0–4 [risk of TS]

ID identification, *SD* standard deviation, *n.r.* not reported in the study, *AH* at-home bleaching, *IO* in-office bleaching, *CP* carbamide peroxide, *HP* hydrogen peroxide, Δ*SGU* shade guide units, Δ*E** color difference measured with a spectrophotometer, *VAS* visual analog scale, *TS* tooth sensitivity, *NRS* numeric rating scale

[a] WhitenessPerfect (FGM, Joinville, Brazil)

[b] Whiteness HP Maxx (FGM, Joinville, Brazil)

[c] Beyond Max (Beyound Technology Corp. NanchangNanchang, Jiangxi, China)

[d] Opalescence PF (Ultradent, South Jordan UT, USA)

[e] Beyond Stay White (Beyond Technology Corp. NanchangNanchang, Jiangxi, China)

[f] Enlighten Home (London, UK)

[g] Enlighten In-Office (London, UK)

[h] Nupro White Gold at-home gel (Dentsply, 38West Clarke Ave., Milford, USA)

[I] Nupro White Gold Office (Dentsply, 38West Clarke Ave., Milford, USA)

[j] Quik Start (DenMat Corp., USA)

[k] Rembrandt Gel Plus (Den-MatCorp, Santa Maria, California)

[l] OpalescenceXtraBoost (Ultradent Inc., South Jordan, UT, USA)

[m] Mix OneSupreme (Villevie, Joinville, SC, Brazil)

[n] Mix Day (Villevie, Joinville, SC, Brazil)

[o] White Class (FGM, Joinville, Brazil)

[p] Vita ClassicalShade (Vita Zahnfabrik, BadSäckingen, Germany)

[q] Spectrophotometer (Vita Easyshade, Vident, Brea, CA, USA)

[r] Vita Bleachedguide 3D-Master (Vita Zahnfabrik, BadSäckingen, Germany)

[s] CR-321 Chromameter (Minolta, Ramsey, N.J.)

[t] Portablespectrometer (PS4, Imbotec, New York, NY)

Patient or population: [dental discoloration in adults]

Intervention: [combined bleaching]

Comparison: [sole at-home or sole in-office bleaching]

Four studies evaluated combined bleaching (in-office plus at-home bleaching) vs. sole in-office bleaching [11, 18, 22, 29], whereas four studies evaluated combined bleaching (in-office plus at-home bleaching) vs. sole at-home bleaching [10, 16, 28, 30]. Three studies included both comparisons [27, 33, 34]. For this reason, individual meta-analyses for each one of these comparisons were performed as it would not be reasonable to merge these data.

In the *sole in-office bleaching*, the product employed was high-concentrate hydrogen peroxide (35% or 38%). In each clinical session, the product remained in contact with the dental structure from 15 to 60 min and, in total, one to four clinical appointments were performed 6 to 15 days apart (Table 3).

In the *sole at-home bleaching*, carbamide peroxide (10% or 16%) or hydrogen peroxide (4%HP) was employed. The bleaching trays were used from 7 to 21 days with a daily use that varied from 1 to 8 h (Table 3).

In the *combined bleaching*, the HP concentration varied from 9 to 38% when used in the in-office protocol. In each clinical session, the product remained in contact with the dental structure from 15 to 60 min. In some studies, the bleaching product was applied only once at the beginning of the treatment, whereas in others, more than one in-office bleaching was applied with an at-home session in between. For the at-home bleaching in the combined protocol, CP (10% or 16%) or HP (4% or 6%) was used in bleaching trays for 5 to 28 days, with daily use of 1 to 8 h (Table 3).

Assessment of the risk of bias

The risk of bias in the eligible studies is presented in Fig. 2. Few full-text studies reported the method of randomization, allocation concealment, and whether the examiner was blinded during color assessment in shade guide units (SGU). In summary, from the 12 studies, only two were considered to have a low risk of bias [29, 30], and the remaining were considered to have an unclear risk of bias.

Meta-analysis

Meta-analyses were performed on all studies from which information about the outcome was reported and could be extracted (Fig. 1). Some studies could not be included in the meta-analysis. One study [33] was not included in none of meta-analyses because the main objective of the study was to evaluate the buccal microbiota after bleaching; therefore, the outcomes of color change and TS were not reported. The study of Wetter [10] was not included in the meta-analysis of color change because they did not report color change in ΔE*, but as change in chroma, lightness, and hue, mainly focusing in interdental difference of color change during different bleaching protocols. The study of Matis [18] and Kugel [22] were not included in the meta-analyses as they did not have comparable groups. Matis [18] performed the in-office bleaching with very shorter application time, i.e., only a single session of 45 min. Kugel performed two clinical sessions, but each one with 15 min contact (total contact time of 30 min). All other studies performed at least two in-office bleaching sessions (30 to 60 min application per session) (at least) 1 week apart resulting in a total contact time of 90 to 120 min. Comparison of these shorter application protocols with a combined technique that associates to it 1 week of at-home bleaching is not a fair comparison.

The study by Dawson [16] had two groups of combined bleaching using two HP concentrations (9% and 27%). Only data from the highest concentration (27%) was used in the meta-analysis to be consistent with the other protocols that compared high-concentrate products in the combined group.

Color change in ΔE*

Combined vs. in-office bleaching A total of two studies were included in this meta-analysis [27, 29]. The mean difference was − 0.63 (95% CI − 3.40 to 2.13) with no significant difference between groups ($p = 0.65$). Data showed considerable heterogeneity ($p = 0.07$; $I^2 = 69\%$) (Fig. 3a). The study by Bernardon [21] was removed from the meta-analysis of color change in Delta E because no direct comparison of the combined groups with the in-office groups was made.

Combined vs. at-home bleaching Four studies were included in this meta-analysis [21, 27, 28, 30]. Imputation of the SD was done in the Machado [28] study based on the coefficient of variation of the other studies. The mean difference was 0.19 (95% CI − 0.57 to 0.95) with no significant difference between groups ($p = 0.62$). Data were not heterogeneous ($p = 0.66$; $I^2 = 0\%$) (Fig. 3b).

Color change in ΔSGU

Combined vs. in-office bleaching The study of Rezende [11] reported the final SGU color, while the other two [29, 34] reported the change from baseline. The comparison of the final measurements in RCT, in theory, estimates the same quantity as the comparison of changes from baseline; in these cases, outcome can only be summarized in the meta-analysis as mean difference. For this reason, the study of Dias [34] had to be removed from the meta-analysis, as the authors employed a different shade guide unit for color assessment (Bleachedguide) and its inclusion could only be done using the standardized mean difference (not possible in this case, as the meta-analysis mixed final SGU measurements with

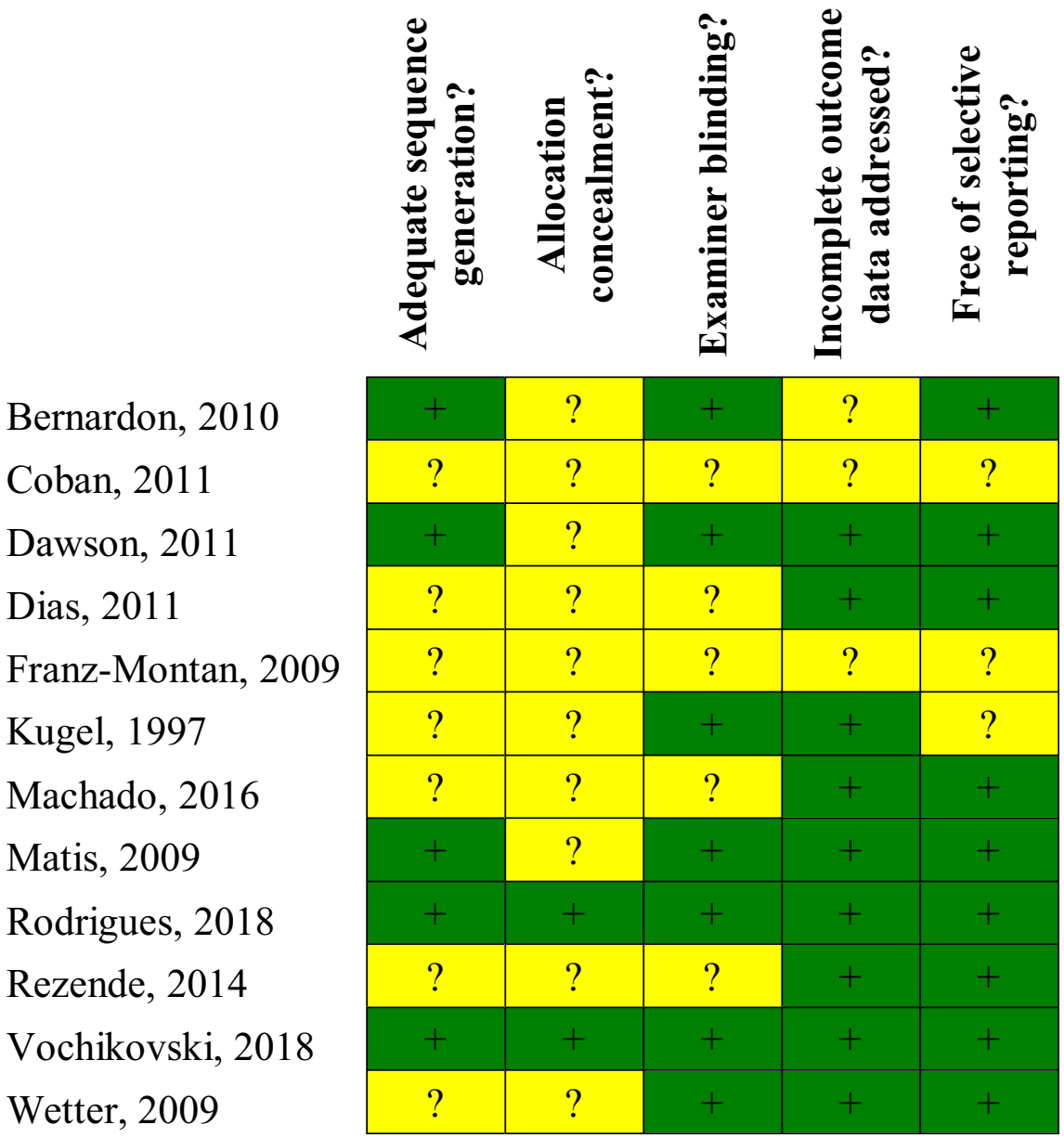

Fig. 2 Summary of the risk of bias assessment according to the Cochrane Collaboration tool

change from baseline values). One study [29] reported the interquartile range; then, an estimate of the standard deviation (SD) was calculated based on these values, being the SD approximately equal to 1.35 times the range of the interquartile range. The study by Bernardon [21] was removed from the meta-analysis of color change in Delta SGU because no direct comparison of the combined groups with the in-office groups was made.

Then, two studies were included in this meta-analysis [11, 29] resulting in a mean difference of − 0.49 (95% CI − 0.87 to − 0.10), with a significant difference between groups (p = 0.01) favoring the in-office protocol. Heterogeneity of the data was not detected (p = 0.77; I^2 = 0%) (Fig. 4a).

Combined vs. at-home bleaching A total of four studies were included in this meta-analysis [16, 21, 28, 30] The studies by Bernardon [21], Dawson [16], and Machado [28] reported the final SGU color, while the study Vochikovski [30] reported the change from baseline. Mean difference was used to summarize data from this meta-analysis and for this reason, the study of Dias [34] had to be removed (as explained above). Imputation of the SD, following the mean coefficient of variation of the other studies that reported final SGU measurements, was done for the study of Machado [28]. A mean difference was − 0.10 (95% CI − 0.54 to 0.33), and it was not statistically different (p = 0.64). A moderate heterogeneity of the data was detected (p = 0.11; I^2 = 51%) (Fig. 4b).

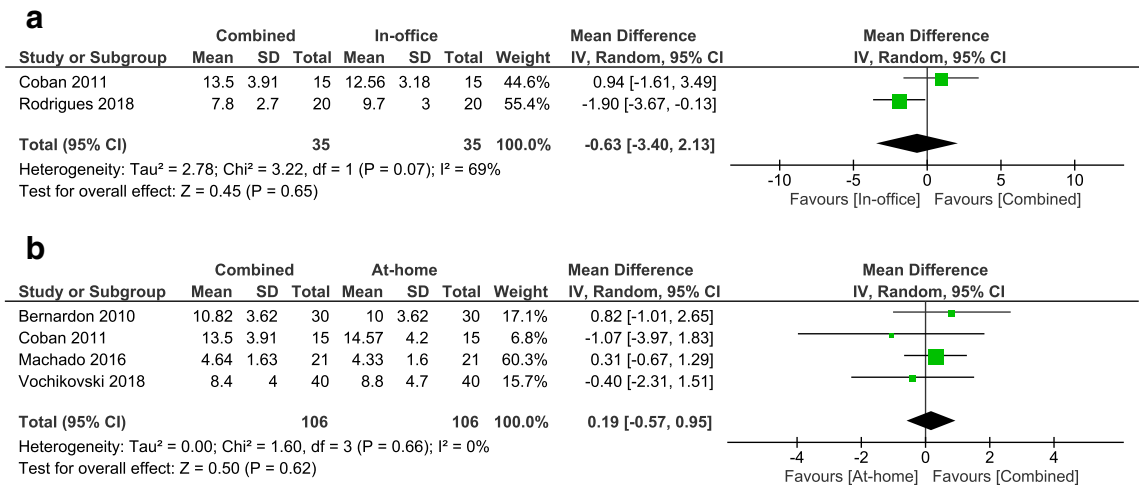

Fig. 3 Forest plot of the color change in ΔE* **a** for combined bleaching vs. in-office bleaching and **b** for combined vs. at-home bleaching

Risk of tooth sensitivity

Combined vs. in-office bleaching Three studies were included in this meta-analysis [11, 29, 34] The risk ratio was 0.98 (95% CI 0.80 to 1.22), showing no significant differences between the groups ($p = 0.89$). No heterogeneity of the data was detected ($p = 0.86$; $I^2 = 0\%$) (Fig. 5a).

Combined vs. at-home bleaching Three studies were included in this meta-analysis [10, 30, 34]. The risk ratio was 1.40 (95% CI 1.10 to 1.80), showing significant differences between the groups ($p = 0.007$). No heterogeneity of the data was detected ($p = 0.80$; $I^2 = 0\%$) (Fig. 5b).

Intensity of tooth sensitivity

Combined vs. in-office bleaching Only one study could be included in this meta-analysis [21]; therefore, this meta-analysis was not run.

Combined vs. at-home bleaching Two studies did not report the SD of TS intensity [21, 28] and was imputed a SD based on the mean coefficient of variation of the two other studies [16, 30]. A total of four studies were included in this meta-analysis [16, 21, 28, 30]. The mean difference was 1.40 (95% CI 0.18 to 2.63), and it was significantly different ($p = 0.02$). Considerable heterogeneity of the data was detected ($p < 0.0001$; $I^2 = 87\%$) (Fig. 6).

Narrative description of studies not included in the meta-analysis

The study of Matis [18] and Kugel [22] reported a significant and clinically important difference between color change in the combined group in comparison with the sole in-office bleaching protocol. A mean difference of 3.15 (95% CI 2.82 to 3.48) and 3.30 (95% CI 1.46 to 5.14) was observed in these studies, respectively, in favor of the combined group. Wetter [10] study mainly focused on interdental differences rather

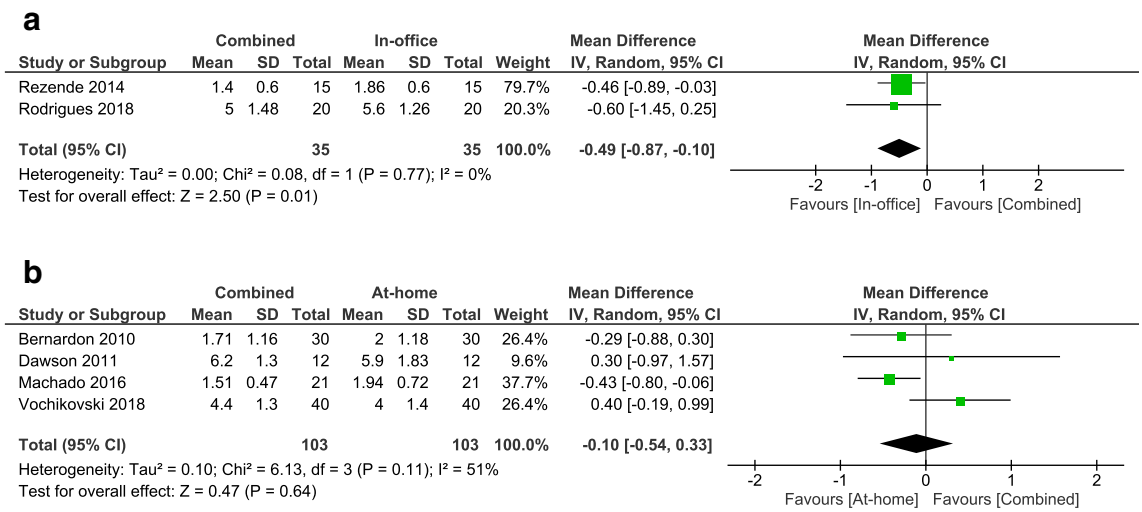

Fig. 4 Forest plot of the color change in ΔSGU **a** for combined bleaching vs. in-office bleaching and **b** for combined vs. at-home bleaching

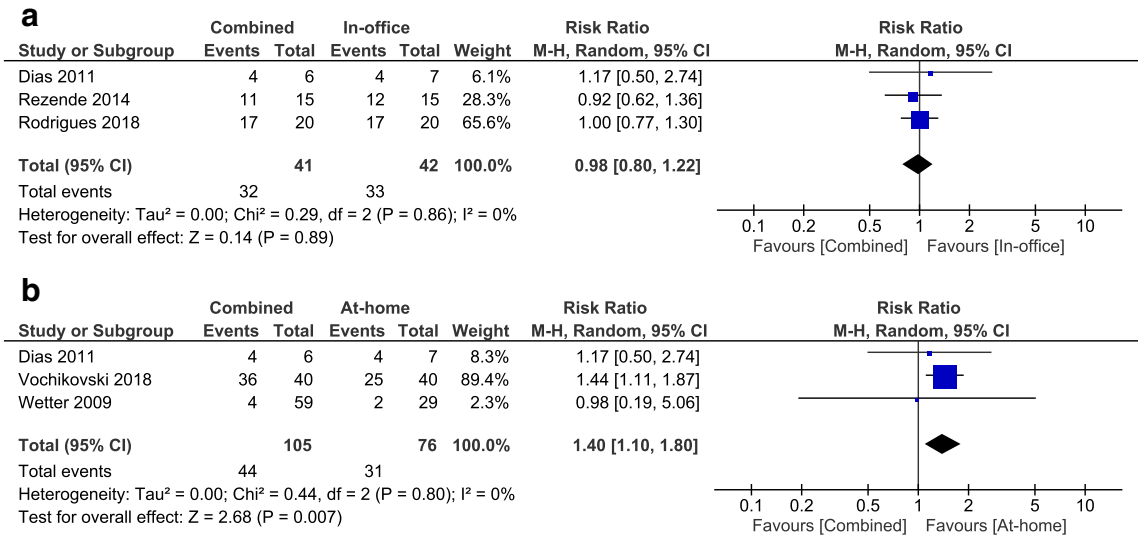

Fig. 5 Forest plot of the risk of TS **a** for combined bleaching vs. in-office bleaching and **b** for combined vs. at-home bleaching

than bleaching protocols. However, by the data described it seems no significant difference was observed between the combined and at-home bleaching protocol. The study of Dias [34] compared in-office vs. combined bleaching (mean difference in ΔSGU of 1.14; 95% CI – 0.49 to 2.77) and at-home vs. combined bleaching (mean difference − 0.57; 95% CI – 2.33 to 1.19), with no difference among the protocols.

Sensitivity analysis

A standard deviation was imputed in the studies that did not report it. The value imputed was based on the average of the coefficient of variation of the other studies that reported the same finding [36]. More extreme imputations, such as a value that corresponded to the lowest coefficient of variation of the primary studies and a value that was as high as the reported mean, was evaluated and no differences in the results therein reported were detected.

Assessment of the quality of evidence

The body of evidence produced by all meta-analyses was very low or low due to unclear risk of bias in most RCTs and the high confidence interval that does not exclude great benefit or great harm. Additionally, three meta-analysis (ΔE combined bleaching vs. in-office; ΔSGU combined bleaching vs. at-home and intensity of TS combined bleaching vs. at-home) also presented inconsistency in the data due to high and non-explained heterogeneity and therefore were graded as very low quality of evidence (Table 4).

Discussion

Systematic reviews and meta-analyses are important in resolving the problem of controversies between clinical trials. In addition, systematic reviews and meta-analyses can provide a critical evaluation of the body of evidence and summarize it for development of recommendations for clinical implementation [37].

The search strategy of any systematic review usually has high sensitivity (number of relevant reports divided by the total number of existing reports). In a search with high sensitivity, the accuracy of the search (number of relevant documents divided by the total number of articles retrieved) is reduced, explaining why a huge number of retrieved articles were obtained and why few articles remained for evaluation [37, 38].

Among the factors that affect the risk of bias in primary studies, correct randomization is essential in an RCT. It

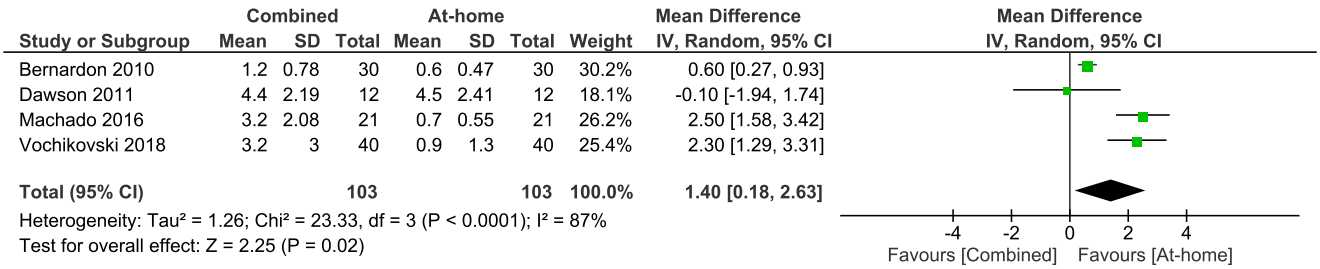

Fig. 6 Forest plot of the intensity of TS for combined bleaching vs. at-home bleaching

Table 4 Summary-of-findings table and quality of the evidence. Only comparisons with meta-analysis were included in the table

Outcome	Relative effect(95% CI)	Anticipated absolute effects (95% CI)			No. of participants (studies)	Certainty
		Risk with (solely at-home or in-office bleaching)	Risk with (combined bleaching)	Difference		
Color change in Delta E (combined vs. IO bleaching) assessed with spectrophotometer/colorimeter	–	–	–	MD 0.63 higher (3.40 lower to 2.13 higher)	70(2 RCTs)	⊕○○○VERY LOW[a,b,c]
Color change in Delta E (combined vs. AH bleaching) assessed with spectrophotometer/colorimeter	–	–	–	MD 0.19 higher(0.57 lower to 0.95 higher)	212(4 RCTs)	⊕⊕○○LOW[a,d]
Color change in Delta SGU (combined vs. IO bleaching) assessed with shade guide	–		–	MD 0.49 lower(0.87 lower to 0.10 higher)	70(2 RCTs)	⊕⊕○○LOW[a,c]
Color change in Delta SGU (combined vs. AH bleaching) assessed with shade guide	–	–	–	MD 0.10 lower(0.54 lower to 0.33 higher)	206(4 RCTs)	⊕⊕○○VERY LOW[a,b,d]
Risk of TS (combined vs. IO bleaching)	RR 0.98 (0.80 to 1.22)	78.6%	77.0%(62.9 to 95.9)	1.6% fewer(15.7 fewer to 17.3 more)	83(3 RCTs)	⊕⊕○○LOW[a,c]
Risk of TS (combined vs. AH bleaching)	RR 1.40 (1.10 to 1.80)	40.8%	57.1%(44.9 to 73.4)	16.3% more(4.1 more to 32.6 more)	181(3 RCTs)	⊕⊕○○LOW[a,d]
Intensity of TS (combined vs. AH bleaching) assessed with VAS pain scale	–	–	–	MD 1.40 higher(0.18 higher to 2.63 higher)	206 (4 RCTs)	⊕○○○VERY LOW[a,b,d]

Follow up to color change: periods ranging from immediately to 2-week post-bleaching

Follow up to TS: the worst mean value reported for the group

*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

[a] Most RCTs are at unclear risk of bias

[b] Inconsistency in the data due to high and non-explained heterogeneity

[c] Estimate based on a reduced number of participants, imprecision

[d] High confidence interval that does not exclude great benefit or great harm, resulting in imprecision

ensures that the chances of a patient being allocated in the test or control group are the same for all participants, which means that known and unknown prognostic factors are balanced among groups [32]. However, the random sequence should be protected until implementation [32] in a process called allocation concealment. Most of the eligible studies from this systematic review were classified as having unclear risk of bias. This judgment was based on the lack of clear description of the randomization and allocation concealment process. This is in accordance with what was recently published by Loguercio et al. 2017 [39], who reported that more than 50% of RCTs about bleaching had a high or unclear risk of bias for randomization and allocation concealment. Unfortunately, effect sizes from studies with inappropriate random sequences and/or allocation concealment favor the experimental group [40], producing biased conclusions.

The combined bleaching technique was suggested to potentiate the bleaching effect and improve color stability [17]. However, neither of the two comparisons performed in this study (combined bleaching vs. solely in-office bleaching and combined bleaching vs. solely at-home bleaching) exhibited a higher degree of color change in 1 to 2 weeks after the end of the bleaching protocol. This belief is probably the result of earlier studies that were used to compare a single in-office bleaching with a 2- or 3-week, at-home protocol [18, 41–44]. A single in-office bleaching session is usually not enough to achieve the same degree of whitening that an extended at-home bleaching protocol would achieve.

This explains the removal of study by Matis [18] in meta-analysis of ΔE* that compared one in-office bleaching session to a combined bleaching that consisted of one in-office bleaching session plus 1 week of an at-home protocol. In such a study, a high effect size was observed in favor of the combined bleaching, a finding not observed in the other studies that performed two [21, 29] or three [27] in-office bleaching sessions. In the same trend, the meta-analysis of color change in ΔSGU for the same comparison (combined vs. in-office bleaching) did not include the study of Matis [18], and the study of Kugel [22] who left the gel in contact with the dental structure for a very short period of only 15 min in two clinical sessions. A previous RCT reported that a single 15-min application per session, even when applied in two clinical sessions, does not produce the same color change as two or three 15-min applications per clinical appointment [45], because it yields a lower whitening degree than two or three-min applications.

While the color change in ΔE for the comparison combined vs. in-office bleaching was not significant, color change in ΔSGU for the same comparison was significant different. While this could be seen as a controversy among the outcomes, one should consider that a statistically significant finding may not report a significant clinical outcome. In this case, the mean difference between groups was approximate half of a color tab unit in the Classical Vita shade guide, not easily detectable by untrained eyes [46].

For the other comparison (combined vs. at-home bleaching), no difference in color change in ΔE* was observed. The at-home protocol of all studies included in this meta-analysis consisted of a 14-day or 21-day regimen, and the combined bleaching consisted of a single 30-min or 45-min application plus a 14-day or 21-day regimen of at-home bleaching. As shown by Kihn [47] the difference of color change was not noticeable until the full 2-week regimen was completed. Thus, a 14-day or 21-day regimen should be performed for an effective tooth bleaching with the at-home protocol without the need of an in-office bleaching session [48–50]. This may justify the heterogeneity of the meta-analysis of color change in ΔE* (combined vs. in-office bleaching) being caused by the study by Rodrigues [29]. These authors only associated a single in-office bleaching with a 7-day at-home protocol in the combined group resulting in an effect size that favored the in-office bleaching. This was not reflected in the meta-analysis of color change in ΔSGU as this scale does not allow detection of subtle differences.

Regarding color change in ΔSGU for this comparison (combined vs. at-home bleaching), heterogeneity was observed to be different from the other primary studies in this comparison; Vochikovski [30] reported higher whitening efficacy for the combined bleaching group. This was the single study that used a low HP concentration (4%) compared to other studies that used 10 to 16% carbamide peroxide. An earlier systematic review of the literature that compared at-home bleaching with carbamide peroxide or low-concentrate HP showed that bleaching with carbamide peroxide yields higher bleaching efficacy in terms of color change [51]. Although both carbamide peroxide and HP are used for whitening, their properties are quite different, and this may play a role in the difference observed. HP-based products are very unstable and release all of their active hydrogen peroxide in 30 to 60 min [52, 53], whereas HP release from carbamide peroxide gels is slower than in HP-based products with a release of about 50% in the first 2 to 4 h and then the remainder over the next 2 to 6 h [52, 54].

The other outcome evaluated in this study was tooth sensitivity, which is the most common side effect after vital tooth bleaching [3, 7]. TS probably arises from the diffusion of HP into the dental structure and then the pulp chamber. In the pulp, HP induces the release of cell-derived factors such as adenosine triphosphate (ATP) and prostaglandins, which can excite or sensitize nociceptors [55, 56]. One of the factors that affect the intensity of TS is the concentration of the bleaching agent. In-office bleaching was associated with a higher intensity of TS than at-home bleaching [57]. This is the reason why a high intensity and risk of TS was observed in the combined bleaching in the comparison combined vs. at-home bleaching.

This was expected due to the use of bleaching agents in concentrations much higher in the combined bleaching than those used in the solely at-home protocol [58–60].

The meta-analysis of intensity of TS was heterogeneous, probably due to the study by Dawson [16]. This was the single study that performed at-home bleaching before the in-office protocol. Perhaps such approach prepared the pulp tissue by the presence or even faster release of catalases to decompose hydrogen peroxide into water and oxygen.

In the meta-analysis of the risk of combined vs. in-office bleaching, no difference in the comparison was found. Indeed, this was observed in an earlier study that merged the results of several RCTs about at-home and in-office bleaching [57]. Unfortunately, the intensity of TS of combined bleaching vs. solely in-office bleaching could not be compared due to the lack of data availability. This should encourage further studies for this comparison.

Some decisions had to be made during data collection and deserve some discussion. The choice to collect the worst TS mean value presented in the study was performed to allow a fair comparison between the protocols. Because TS is lower in the at-home bleaching, if the data was collected only at the end of each treatment (after in-office, or after at-home bleaching or after combined bleaching), the TS of the combined group would be similar to the at-home protocol, because the at-home protocol was usually performed after the initial in-office start. Apart from that, the peak of pain varied among techniques. For in-office bleaching, it was reported to start within 1 h after the beginning of the treatment, with a pain peak within 1 and 6-h post-treatment [61]. For at-home bleaching, most patients usually reported TS in the first days of gel application, and the sensitivity tended to disappear after 4 days for most patients [62].

Another decision was the choice of effect size for color change in ΔSGU. The choice of standardized mean difference would allow the inclusion of one study that employed a different shade guide unit but not data from two studies that only reported final SGU values. The choice of the mean difference makes possible mixing data from final SGU measurements and change from baseline (ΔSGU), but it does not allow inclusion of studies that employed different scales for the outcome measurement. The selected outcome was the one that allowed the inclusion of more studies; however, unfortunately, the summary outcomes were sensitive to these changes.

Finally, the limitations of this study should be reported. EMBASE database was not directly inspected in the search process. However, we believe this limitation is of very low impact in the study results due to the fact that 65% of the journals indexed in EMBASE are also indexed in PUBMED. Additionally, EMBASE content also appears in CENTRAL, Scopus, and Web of Science, being these ones included in the search strategy.

Because few studies remained in this systematic review and the quality of evidence was graded as very low and low, due to unclear risk of bias of most studies, imprecision, and inconsistency (high heterogeneity), more randomized controlled trials with a sound methodology, reporting data in change from baseline, should be conducted to compare both techniques and to allow for a more comprehensive evaluation of protocols. The results reported herein should be interpreted with caution because they represent an overall comparison without taking into consideration variations in the protocols (daily usage time, number of bleaching sessions, product concentration, and days of home use) of the bleaching techniques.

Conclusions

In a comprehensive analysis, without considering other variables but the protocol, we may conclude that there is no benefit in color change was observed when combined bleaching was either compared with sole at-home bleaching or sole in-office bleaching. These findings should be interpreted with caution due to the low quality of evidence of all meta-analysis herein reported.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

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