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Literature Review

At-home vs In-office Bleaching: A Systematic Review and Meta-analysis

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Clinical Relevance

Although there is a general concept that at-home dental bleaching is more effective and yields less tooth sensitivity than in-office bleaching, this study could not confirm this due to the high variability of protocols in both bleaching techniques.

SUMMARY

Objective: A systematic review and meta-analysis were performed to evaluate the risk and intensity of tooth sensitivity during in-office and at-home bleaching in adult patients. The efficacy of dental bleaching was also evaluated.

Methods: A comprehensive search was performed in the MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database, Brazilian Library in Dentistry, Cochrane Library, and System for Information on Grey Literature in Europe without restrictions. The annual conference of the International Association for Dental Research abstracts (1990-2014) and unpublished and ongoing trials registry were also searched. Dissertations and theses were searched using the ProQuest Dissertations and Periódicos Capes Theses databases. Only randomized clinical trials that compared the prevalence or intensity of tooth sensitivity during in-office and at-home bleaching in adult patients were included and studies that evaluated the efficacy of these dental bleaching techniques, in terms of shade guide units (ΔSGU) and in terms of color difference measured with a spectrophotometer (ΔE*).

Results: After the removal of duplicates, 1139 articles were identified. After title and abstract screening, 29 studies remained. Fifteen studies were further excluded, whereas 12 studies remained for qualitative analyses and 8 for the meta-analysis of the primary and secondary outcomes. No significant difference in the risk/intensity of tooth sensitivity or in bleaching efficacy was observed in the present study.

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Conclusion: In an overall comparison of at-home and in-office bleaching, no differences were detected, either regarding risk/intensity of tooth sensitivity or the effectiveness of the bleaching treatment. This comparison, however, does not take into consideration variations in the protocols (daily usage time, number of bleaching sessions, and product concentration) of the bleaching techniques in the studies included.

INTRODUCTION

Public demand for esthetic dentistry, including dental bleaching, has increased in recent years.[1] In such context, clinicians are acutely aware of the importance of dental bleaching in daily clinical practice.

Nowadays, there are two types of dentist-supervised techniques: at-home or in-office bleaching. Although at-home bleaching has been the most frequent treatment for vital teeth, some patients do not want to use a bleaching tray on a daily basis for several weeks; so they request in-office bleaching, which produces more immediate results.[2,3]

Although several clinical studies have proven the effectiveness of in-office and at-home bleaching,[4-10] tooth sensitivity is a very common side effect[11] for both bleaching approaches. It affects between 37% and 90% of the patients undergoing at-home bleaching[6,9,12-17] and between 16.7% and 100% of the patients using in-office bleaching.[13,18-20] Although tooth sensitivity of at-home bleaching is reported to be mild,[12,13,21] the intensity of tooth sensitivity after in-office bleaching is usually moderate[7,22-24] and in some cases so severe that patients eventually abandon the procedure.[25] Some authors speculate that such an adverse effect may be due to the release of inflammatory mediators such as cyclooxygenase and lipoxygenases on the dental pulp.[26]

The high number of bleaching gels and protocols evaluated in randomized clinical trials[4-7,9,13] inhibits clinicians from reaching a clear conclusion about which protocol presents increased risk and intensity of tooth sensitivity. Some studies report higher tooth sensitivity of in-office bleaching than at-home bleaching,[5,13] whereas others report similar tooth sensitivity[27,28] or higher tooth sensitivity of the at-home protocol than the in-office bleaching.[7] Similar controversy exists in terms of bleaching efficacy. There are some authors that believe that at-home bleaching provide better and more stable whitening than the in-office protocol.[29] Others showed similar immediate and long-term results for both techniques.[30,31]

In face of conflicting results published in the literature, the aim of this systematic review of the literature was to determine whether there are evidence-based differences in sensitivity and efficacy between in-office and at-home bleaching techniques. For this, the following PICO question (Population, Intervention, Comparison and Outcome) was answered: is the risk and intensity of tooth sensitivity, as well as bleaching efficacy, in adults that underwent in-office bleaching different from those that underwent at-home bleaching?

METHODS

Protocol and Registration

This study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO - CRD42015015564) and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for report.[32]

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:

1. Population (P): adult patients that underwent vital tooth bleaching.
2. Intervention (I): in-office bleaching.
3. Comparison (C): dentist-supervised at-home bleaching.
4. The outcome (O): risk and intensity of tooth sensitivity during dental bleaching; color change in shade guide units (ΔSGU) and in in terms of color difference measured with a spectrophotometer (ΔE*) will be the secondary outcomes.
5. Study design (S): randomized clinical trials (RCTs).

To identify trials to be included for this review, the electronic databases such as MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO), and Cochrane Library (Table 1) were searched. The reference lists of all primary studies were hand searched for additional relevant publications and the related articles link of each primary study in the PubMed database without restrictions to publication date or languages.

Other sources were also used to identify more articles. The abstracts of the annual conference of the International Association for Dental Research and their regional divisions (1990-2014) were searched. The grey literature using the database System for Information on Grey Literature in Europe and dissertations and theses using the ProQuest Dissertations and Theses Full text database, as well as the Periódicos Capes Theses database, were explored.

To locate unpublished and ongoing trials related to the review question, the following clinical trials registries were searched: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Eligibility Criteria

Parallel and split-mouth RCTs that compared in-office vs at-home bleaching in adult patients of any age group were included. No controlled clinical trials, editorial letters, pilot studies, historical reviews, *in vitro* studies, cohort, and observational and descriptive studies, such as case reports and case series, were excluded.

Additionally, RCT studies were excluded if 1) studies compared only in-office or only at-home bleaching treatments; 2) studies whose participants took analgesics or anti-inflammatory drugs before or during bleaching treatment; 3) studies that always used desensitizers before and after bleaching; and 4) studies in which the at-home protocol was performed with over-the-counter products.

Study Selection and Data Collection Process

Initially, the articles were selected by title and abstracts according to the previously described search strategy. Articles that appeared in more than one database were considered only once. Full-text articles were also obtained when the title and abstract presented insufficient information to make a clear decision. Subsequently two reviewers classified those that met the inclusion criteria. To handle such a large number of studies, a study ID for each eligible study was used, combining first author and year of publication. Relevant information about the study design, participants, interventions, and outcomes were extracted using customized extraction forms by three authors.

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, 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 for each bleaching protocol was obtained. When more than one bleaching agent from the same bleaching protocol was included in the study, their values were merged to make a single entry. Concerning color change, the data that represented the immediate result (up to three months after bleaching) were used.

Risk of Bias in Individual Studies

Quality assessments of the selected trials were carried out by two independent reviewers, using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[33] The assessment criteria contain six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. During data selection and quality assessment, any disagreements between the reviewers were solved through discussion, and if needed, by consulting a third reviewer.

For each aspect of the quality assessment, the risk of bias was scored following recommendations as described in the Cochrane Handbook for Systematic reviews of Interventions 5.1.0 (http://handbook.cochrane.org). At domain level, the judgment for each entry involved recording "yes," indicating low risk of bias, "no," indicating high risk of bias, and "unclear," indicating either lack of information or uncertainty over the potential for bias. At the study level, the study was considered to be at "low" risk of bias if all key domains for each outcome were at low risk of bias. If one or more key domains (see below) were judged as "unclear" or at "high" risk of bias, the study as a whole was considered at high risk of bias. When the study was judged as unclear in its key domains, authors were contacted to obtain more information and to allow a definitive yes or no judgment.

For the patient-centered outcomes (risk and intensity of tooth sensitivity) and for color change in ΔE^*, studies were considered to be at low risk of bias if there were adequate sequence generation and allocation concealment (key domains). Patient blinding was not considered a key domain as patients could easily identify the different bleaching protocols. Examiner blinding was not essential for evaluation of color in ΔE^* as the previous knowledge

Table 1: *Electronic Database and Search Strategy*

Pubmed (23/December/2014)	
#1 (tooth discoloration[MeSH Terms]) OR"tooth staining"[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])	**#2** (peroxides[MeSH Terms]) OR tooth bleaching[MeSH Terms]) OR bleaching agents[MeSH Terms]) OR tooth bleaching agents[MeSH Terms]) OR hydrogen peroxide[MeSH Terms]) OR carbamide peroxide[Supplementary Concept]) OR"tooth bleaching"[Title/Abstract]) OR"tooth whitening"[Title/Abstract]) OR"dental bleaching"[Title/Abstract]) OR"dental whitening"[Title/Abstract]) OR whitening[Title/Abstract]) OR bleaching[Title/Abstract]) OR"bleaching agents"[Title/Abstract]) OR"bleaching systems"[Title/Abstract]) OR"whitening agents"[Title/Abstract]) OR"whitening systems"[Title/Abstract]) OR"bleaching techniques"[Title/Abstract]) OR"whitening techniques"[Title/Abstract]) OR"hydrogen peroxide"[Title/Abstract]) OR"carbamide peroxide"[Title/Abstract]) OR"power bleaching"[Title/Abstract]) OR"in-office bleaching"[Title/Abstract]) OR"in-office vital bleaching"[Title/Abstract]) OR"vital bleaching"[Title/Abstract]) OR"vital whitening"[Title/Abstract]) OR"professional bleaching"[Title/Abstract]) OR"professional whitening"[Title/Abstract]) OR"home-use"[Title/Abstract]) OR"home bleaching"[Title/Abstract]) OR"home whitening"[Title/Abstract]) OR"at-home bleaching"[Title/Abstract]) OR"at-home whitening"[Title/Abstract]) OR"home-care bleaching"[Title/Abstract]) OR"home-applied bleaching"[Title/Abstract]) OR"nightguard vital bleaching"[Title/Abstract]) OR"night-guard vital bleaching"[Title/Abstract])
#1 AND #2	
Scopus (23/December/2014)	
#1 (TITLE-ABS-KEY ("tooth discoloration") OR TITLE-ABS-KEY ("tooth staining") OR TITLE-ABS-KEY ("discolored tooth") OR TITLE-ABS-KEY ("stained tooth")	**#2** (TITLE-ABS-KEY (peroxides) OR TITLE-ABS-KEY ("hydrogen peroxide") OR TITLE-ABS-KEY ("carbamide peroxide") OR TITLE-ABS-KEY ("tooth bleaching agent") OR TITLE-ABS-KEY ("dental bleaching") OR TITLE-ABS-KEY ("tooth whitening") OR TITLE-ABS-KEY ("bleaching system") OR TITLE-ABS-KEY ("whitening system") OR TITLE-ABS-KEY ("power bleaching") OR TITLE-ABS-KEY ("in-office bleaching") OR TITLE-ABS-KEY ("vital bleaching") OR TITLE-ABS-KEY ("vital whitening") OR TITLE-ABS-KEY ("professional bleaching") OR TITLE-ABS-KEY ("professional whitening") OR TITLE-ABS-KEY ("home-use") OR TITLE-ABS-KEY ("at-home bleaching") OR TITLE-ABS-KEY ("at-home whitening") OR TITLE-ABS-KEY ("home-care bleaching") OR TITLE-ABS-KEY ("home-applied bleaching") OR TITLE-ABS-KEY ("nightguard vital bleaching")
#1 AND #2	
Web of Science (27/December/2014)	
#1 Topic: ("tooth discolo*ration") OR Topic: ("discolo*red teeth") OR Topic: ("discolo*red tooth") OR Topic: ("tooth staining") OR Topic: ("stained teeth") OR Topic: ("stained tooth")	**#2** Topic: (peroxides) OR Topic: ("tooth bleaching") OR Topic: ("bleaching agents") OR Topic: ("tooth bleaching agents") OR Topic: ("hydrogen peroxide") OR Topic: ("carbamide peroxide") OR Topic: ("dental bleaching") OR Topic: ("tooth whitening") OR Topic: ("dental whitening") OR Topic: ("vital bleaching") OR Topic: ("vital whitening") OR Topic: (whitening) OR Topic: (bleaching) OR Topic: ("bleaching techniques") OR Topic: ("bleaching systems") OR Topic: ("whitening systems") OR Topic: ("professional whitening") OR Topic: ("professional bleaching") OR Topic: ("power bleaching") OR Topic: ("in office bleaching") OR Topic: ("in office vital bleaching") OR Topic: ("home use") OR Topic: ("at home bleaching") OR Topic: ("at home whitening") OR Topic: ("home applied bleaching") OR ("home whitening") OR Topic: ("home bleaching") OR Topic: ("night guard vital bleaching") OR Topic: ("home care bleaching")

Table 1: Continued.

Pubmed (23/December/2014)	
#1 AND #2	
LILACS and BBO (27/December/2014)	
#1 (MH:"tooth discoloration"OR"tooth staining"OR"dicolored tooth"OR"discolored teeth"OR"tooth discolouration"OR"discoloured teeth"OR"discoloured tooth"OR"stained tooth"OR"stained teeth"OR"descoloração dental"OR"manchamento dental"OR"dentes escuros"OR"escurecimento dental"OR"dientes oscuros"OR"manchas en los dientes"OR"oscurecimiento dental")	**#2** (MH: peroxides OR MH:"tooth bleaching agents"OR MH:"tooth bleaching"OR MH:"bleaching agents"OR MH:"hydrogen peroxide"OR"carbamide peroxide"OR"peróxido de carbamida"OR"dental bleaching"OR"clareamento dental"OR"blanqueamiento dental"OR"in office bleaching"OR"clareamento de consultório"OR"blanqueamiento en oficina"OR"blanqueamiento dental de oficina"OR"tooth whitening"OR"power bleaching"OR"dental whitening"OR"bleaching systems"OR"whitening systems"OR"sistemas clareadores"OR"vital bleaching"OR"clareamento em dentes vitais"OR"blanqueamiento en dientes vitales"OR"in office vital bleaching"OR"professional bleaching"OR"professional whitening"OR"clareamento professional"OR"blanqueamiento professional"OR"vital whitening"OR"home-use"OR"at home bleaching"OR"at home whitening"OR"clareamento caseiro"OR"blanqueamiento en casa"OR"home-applied bleaching"OR"home whitening"OR"home bleaching"OR"nigthguard vital bleaching"OR"night guard vital bleaching"OR"home care bleaching")
#1 AND #2	
Cochrane Library (15/December/2014)	
#1 MeSH descriptor: [Tooth Discoloration] explode all trees #2"tooth staining":ti,ab,kw or"discolored tooth":ti,ab,kw or"tooth discoloration":ti,ab,kw or"discolored teeth":ti,ab,kw or"tooth discolouration":ti,ab,kw (Word variations have been searched) #3"discoloured tooth":ti,ab,kw or"discoloured teeth":ti,ab,kw or"stained tooth":ti,ab,kw or"stained teeth":ti,ab,kw (Word variations have been searched) #4 #1 or #2 or #3 #5 MeSH descriptor: [Peroxides] explode all trees #6 MeSH descriptor: [Tooth Bleaching Agents] explode all trees #7 MeSH descriptor: [Bleaching Agents] explode all trees #8 MeSH descriptor: [Hydrogen Peroxide] explode all trees #9"carbamide peroxide":ti,ab,kw or"dental bleaching":ti,ab,kw or"in-office bleaching":ti,ab,kw or"tooth whitening":ti,ab,kw or"power bleaching":ti,ab,kw (Word variations have been searched) #10"bleaching techniques":ti,ab,kw or whitening:ti,ab,kw or bleaching:ti,ab,kw or"dental whitening":ti,ab,kw or"bleaching systems":ti,ab,kw (Word variations have been searched) #11"whitening systems":ti,ab,kw or"vital bleaching":ti,ab,kw or"in-office vital bleaching":ti,ab,kw or"professional bleaching":ti,ab,kw or"professional whitening":ti,ab,kw (Word variations have been searched) #12"vital whitening":ti,ab,kw or"home-use":ti,ab,kw or"at-home whitening":ti,ab,kw or"at-home bleaching":ti,ab,kw or"home-applied bleaching":ti,ab,kw (Word variations have been searched) #13"home whitening":ti,ab,kw or"home bleaching":ti,ab,kw or"nightguard vital bleaching":ti,ab,kw or"night-guard vital bleaching":ti,ab,kw or"home-care bleaching":ti,ab,kw (Word variations have been searched) #14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 #15 #4 and #14	

of the treatment would not affect the results produced by the instrument. However, examiner blinding was considered to be essential in the subjective color assessment performed with shade guide units. Therefore, for color change in ΔSGU, three items of the Cochrane tool as key domains were considered: adequate sequence generation, allocation concealment, and examiner blinding.

Summary Measures and Synthesis of 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 tooth sensitivity) or continuous (intensity of tooth sensitivity, ΔSGU, and ΔE*).

Only studies classified at low risk of bias in the key domains were used in the meta-analysis. The outcomes were summarized by calculating the Hedge's g standardized mean difference for the continuous data and the odds ratio along with the 95% confidence interval for the dichotomous data.

When matched data were available (split-mouth and crossover designs), an external correlation of 0.5

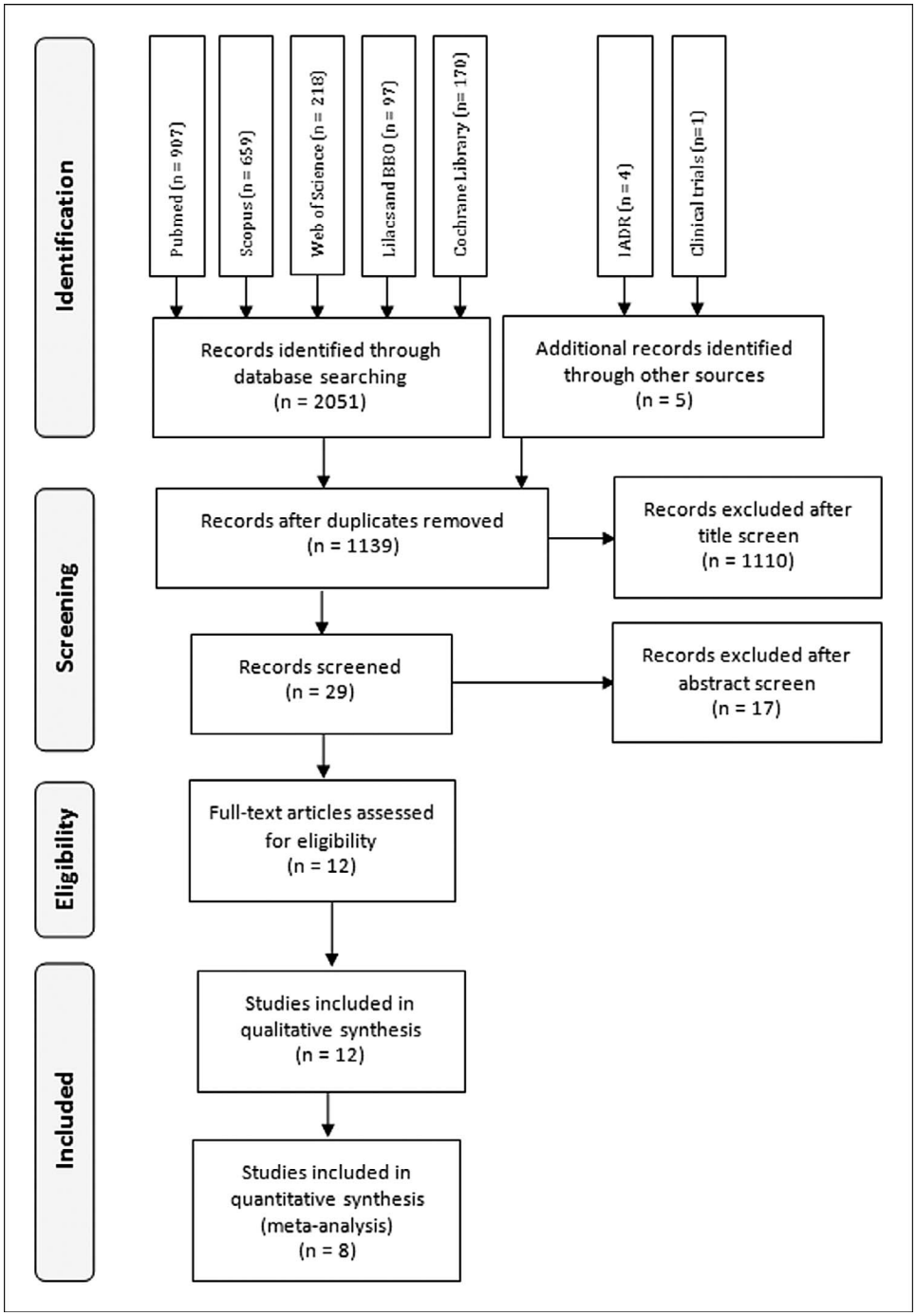

Figure 1. *Flow diagram of study identification.*

was imputed among data from both groups, as this information was not available in any of the studies. Sensitivity analyses using lower (0.1) and higher (0.9) external correlations were performed to check the impact of such imputation in all meta-analysis.

The random-effects models were used. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. All analyses were conducted using CMA software (version 3, Biostat, Englewood, New Jersey, USA). No subgroup analysis was performed. Sensitivity analyses were also conducted to investigate the reasons for high heterogeneity whenever detected.

RESULTS

Study Selection

After the database screening and removal of duplicates, 1139 studies were identified (Figure 1). After

title screening, 29 studies remained, and this number was reduced to 12 after careful examination of the abstracts.

Characteristics of Included Articles

The characteristics of the 12 studies selected are listed in Table 2. The parallel study design was predominantly used in these studies.[7,13,27,30,34-36] Some of the studies used the split-mouth design.[4,5,28,31,37]

Six of the 12 studies used a 0-10 visual analog scale for pain evaluation,[4,5,13,28,34,35] and 3 studies used a 0-4 numeric rating scale.[7,27,30] One study just evaluated the risk of tooth sensitivity.[37] Two studies did not evaluate tooth sensitivity.[31,36]

For color evaluation, ten studies used a shade guide.[4,5,7,27,28,30,31,34,36,37] Six of these 12 studies added an objective instrument (spectrophotometer or colorimeter) for color assessment.[4,5,27,28,31,36] Color slide photography was used in one study[34] and photography in two others.[27,37] Two studies did not evaluate the color.[13,35]

The number of patients per group included in these studies ranged from 10 to 30. In 2 of the 12 articles, most participants were male[5,31]; in 3 articles, females predominated.[7,28,30] Seven studies did not report this information.

Regarding the bleaching protocol (Table 2), nine studies used 10% carbamide peroxide for at-home bleaching.[4,5,7,13,27,30,31,34,37] Carbamide peroxide with different concentrations, such as 15%,[28] 16%,[35] 20%,[7] and 32%,[36] was also used for at-home bleaching. For in-office bleaching, the majority of studies used 35% hydrogen peroxide.[4,7,13,27,30,34,35,37] Only three studies used 38% hydrogen peroxide for this bleaching modality.[7,28,31] Two studies used 25% hydrogen peroxide for this technique.[5,36]

The daily time use of the at-home bleaching gel varied from 3 to 10 minutes, and the number of days varied from 6 to 28 days. The application protocol of the in-office bleaching was quite variable. Most of the studies applied the product for 20-45 minutes in each clinical session.[4,7,13,27,28,30,31,35,37] However, variations in this protocol were observed, with applications lasting 15[34] or 60 minutes[5,36] in each session (Table 2). Half of the studies performed two to three bleaching sessions,[4,7,13,27,30,37] with some exceptions. Some studies performed only one in-office bleaching session,[5,28,31,35,36]and another study performed a variable number of clinical sessions to reach the patient's satisfaction[34] (Table 2).

Assessment of the Risk of Bias

The selected studies risk of bias is presented in Figure 2. Few full-text studies reported the method of randomization, allocation concealment, and whether or not the examiner was blinded during color assessment in shade guide units.

E-mails were sent to authors of nine studies[4,5,7,13,27,34-37] to request further information. Responses were obtained from the authors of eight studies.[4,5,7,13,27,34-36]

In summary, from the 12 studies, 3[13,36,37] were considered to be at high/unclear risk of bias in the key domains of the Cochrane risk of bias tool, yielding 9 studies[4,5,7,27,28,30,31,34,35] that met the best requirement features (randomization and allocation concealment) for meta-analysis of risk and intensity of tooth sensitivity and color change in ΔE^*.

From the 12 studies, 4[13,35-37] were considered to be at high/unclear risk of bias in the key domains of the Cochrane risk of bias tool, yielding 8 studies[4,5,7,27,28,30,31,34] that met the best requirement features (randomization, allocation concealment, and blinding) for meta-analysis of ΔSGU. Although the study of Giachetti and others[31] was classified at low risk of bias, the authors did not evaluate color change in shade guide units or ΔE^*, which is the reason why the study was not included in the meta-analyses of color change. Additionally, this study did not evaluate bleaching-induced tooth sensitivity; therefore, it was not included in the meta-analyses of tooth sensitivity.

Meta-analysis

All meta-analysis was performed on studies classified as low risk of bias in the key domains and from which the information about the outcome could be extracted.

Risk of Tooth Sensitivity—This analysis was based on five studies.[4,5,7,28,30] The odds ratio was 2.186, with a 95% confidence interval of 0.63-7.53 (p=0.215). Based on these studies, a significant statistical difference between the groups could not be identified (Figure 3). Data were heterogeneous (χ^2 test, $p<0.001$; $I^2=87.8\%$; Figure 3), which means that all studies included in the analysis did not share a common effect size. Through a sensitivity analysis, the high heterogeneity of this outcome was caused by the study of Basting and others.[7] By removing this study from the present meta-analysis, the heterogeneity was seen not to be significant, and the overall odds ratio was shown as significant, with a lower

Table 2: *Summary of the Studies Selected for This Systematic Review*

Study ID	Study design [setting]	Method of color assessment	Subjects' age in mean ± SD [range] (yr)	No. of subjects (male [%])	No. patients [drop-outs]
Acosta 1999[37]	Split mouth [n.r.]	Shade guide unit (Vitapan classical) and photography	n.r. ± n.r. [15-20]	n.r.	20 [n.r.]
Auschill 2005[34]	Parallel [University]	Shade guide unit (Vitapan classical) and color slide photography	29.8 ± n.r. [n.r.]	n.r.	39 [0]
Basting 2012[7]	Parallel [n.r.]	Shade guide unit (Vitapan classical)	n.r. ± n.r. [18-42]	18 [19]	94 [13]
Bernardon 2010[4]	Split mouth [n.r.]	Shade guide unit (Vitapan classical) and spectrophotometer (Easyshade)	n.r. ± n.r. [n.r.]	n.r.	90 [n.r.]
da Costa 2010[5]	Split mouth [n.r.]	Shade guide unit (Vita Bleachedguide) and spectrophotometer (Easyshade)	n.r. [23-57]	12 [60]	20 [0]
de Almeida 2012[13]	Parallel [n.r.]	n.r.	n.r.± n.r. [18-28]	n.r.	40 [0]
Giachetti 2010[31]	Split mouth [University]	Spectrophotometer (Easyshade)	22 ± 1.4 [20-25]	10 [59]	17 [1]
Kim-Pusateri 2009[36]	Parallel [n.r.]	Shade guide unit (Trubyte Bioform) and colorimeter (ShadeVision)	n.r. ± n.r. [n.r.]	n.r.	24 [n.r.]
Moghadam 2013[28]	Split mouth [n.r.]	Shade guide unit (Vitapan classical and Vitapan 3D Master) and spectrophotometer (Easyshade)	n.r. ± n.r. [18-55]	8 [40]	20 [n.r.]
Pintado-Palomino 2015[35]	Parallel [University]	n.r.	n.r. ± n.r. [18-40]	n.r.	113 [n.r.]
Tay 2012[30]	Parallel [University]	Shade guide unit (Vitapan classical)	AH: 21 ± 3.8 IO: 21 ± 3.2	AH: 14 [47] IO: 8 [27]	60 [0]
Zekonis 2003[27]	Parallel [university]	Shade guide unit (Trubyte Bioform), clinical photographs and colorimeter (Chroma meter)	n.r. ± n.r. [n.r.}	n.r.	20 [1]

Table 2: Extended.

Study ID	Bleaching tray	Groups/materials	Bleaching protocol	Outcomes evaluated		
				Color change	Tooth sensitivity	Gingival irritation
Acosta 1999[37]	n.r.	AH: 10% CP[a] IO: 35% HP[b]	AH: during night [10 days] IO: 20-30 min [3 sessions]	ΔSGU	Absolute risk	n.r.
Auschill 2005[34]	With reservoirs	AH: 10% CP[c] IO: 38% HP[d]	AH: 8h daily (number of cycles needed for therapy success) IO: 15-min; 1 cycle per appointment (number of cycles needed for therapy success)	ΔSGU	VAS 0-10	Absolute risk
Basting 2012[7]	Without reservoirs	AH_1: 10% CP[c] AH_2: 20% CP[e] IO_1: 38% HP[d] IO_2: 35% HP[f]	AH: 2 h daily [21 days] IO_1: 3 × 15 min [3 sessions] IO_2: 30 min [3 sessions]	ΔSGU	Absolute risk and NRS 0-3	n.r.
Bernardon 2010[4]	Without reservoirs	AH: 10% CP[g] vs. IOL: 35% HP[h] IO vs IOL AH vs AH + IO	AH: 8 h daily [21 days] IO: 3 × 15 min [2 sessions]	ΔSGU and ΔE*	VAS 0-10	n.r.
da Costa 2010[5]	n.r.	AH: 3% CP[i] IO: 25% HP[j]	AH: 8 h daily [6 days] IO: 4 × 15 min [1 session]	ΔSGU and ΔE*	Absolute risk and VAS 0-10	VAS 0-10
de Almeida 2012[13]	With reservoirs	AH: 10% CP[g] IO: 35% HP[k] IOL_1: 35% HP[k] IOL_2: 35% HP[k]	AH: 4 h daily [21 days] IO: 3 × 10 min [3 sessions]	n.r.	Absolute risk and VAS 0-10	n.r.
Giachetti 2010[31]	n.r.	AH: 10% CP[c] IO: 38% HP[d]	AH: 6-8 h daily [14 days] IO: 2 × 10 min [1 session]	Whitening index	n.r.	n.r.
Kim-Pusateri 2009[36]	n.r.	AH_1: 32% CP[l] AH_2: 32% CP[l] IO: 25% HP[m] IOL: 25% HP[m]	AH_1: 3 min daily [28 days] AH_2: 15 min daily [28 days] IO: 2 × 30 min [1 session]	ΔSGU and ΔE*	n.r.	n.r.
Moghadam 2013[28]	With reservoirs	AH: 15% CP[n] IO: 38% HP[d]	AH: 4 h daily [14 days] IO: 3 × 15 min [1 session]	ΔE*	Absolute risk and VAS 0-10	n.r.
Pintado-Palomino 2015[35]	n.r.	AH: 16% CP[o] IO: 35% HP[k]	AH: 4 h daily [14 days] IO: 3 × 15 min [1 session]	n.r.	VAS 0-10	n.r.
Tay 2012[30]	Without reservoirs	AH: 10% CP[g] IO: 35% HP[k]	AH: 6 h daily [28 days] IO: 3 × 15 min [2 sessions]	ΔSGU	Absolute risk and NRS 0-4	n.r.
Zekonis 2003[27]	With reservoirs	AH: 10% CP[c] IO: 35% HP[p]	AH: 8 – 10 h or during night [14 days] IO: 3 × 10 min [2 sessions]	ΔSGU and ΔE*	Absolute risk and NRS 0-4 scale	NRS 0-4 scale

Table 2: Continued.

Abbreviations: AH, at-home bleaching; CP, carbamide peroxide; HP, hydrogen peroxide; IO, in-office bleaching; n.r., not reported; SD, standard deviation; VAS, Visual Analog Scale: a 10-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end; VRS, Visual Rating Scale: none, mild, moderate, considerate, severe; ΔSGU, shade guide units; ΔE* (color difference measured with a spectrophotometer).
[a] *NightWhite Excel 10%, Discus DentaL, Culver City, CA, USA;*
[b] *Superoxol 35%, Moyco Union Broach-Thompson, Montgomeryville, Penn, USA;*
[c] *Opalescence 10%, Ultradent, South Jordan, UT, USA;*
[d] *Opalescence XtraBoost 38%, Ultradent, South Jordan, UT, USA;*
[e] *Opalescence 20%, Ultradent, South Jordan, UT, USA;*
[f] *Pola Office 35%, SDI, Bayswater, Victoria, Australia;*
[g] *Whineness Perfect 10%, FGM, Joinville, SC, Brazil;*
[h] *Whiteness HPMaxx 35%, FGM, Joinville, SC, Brazil;*
[i] *NightWhite Excel 3%, Discus DentaL, Culver City, CA, USA;*
[j] *Zoom AP 25%, Discus Dental, Culver City, CA, USA;*
[k] *Whineness HP 35%, FGM, Joinville, SC, Brazil;*
[l] *Sapphire take-home 32%, DenMat, Lompoc, CA, USA;*
[m] *Sapphire Chairside 25%, DenMat, Lompoc, CA, USA;*
[n] *Opalescence 15%, Ultradent, South Jordan, UT, USA;*
[o] *Whineness Perfect 16%, FGM, Joinville, SC, Brasil;*
[p] *StarBrite 35%, Interdent, Los Angeles, CA.*

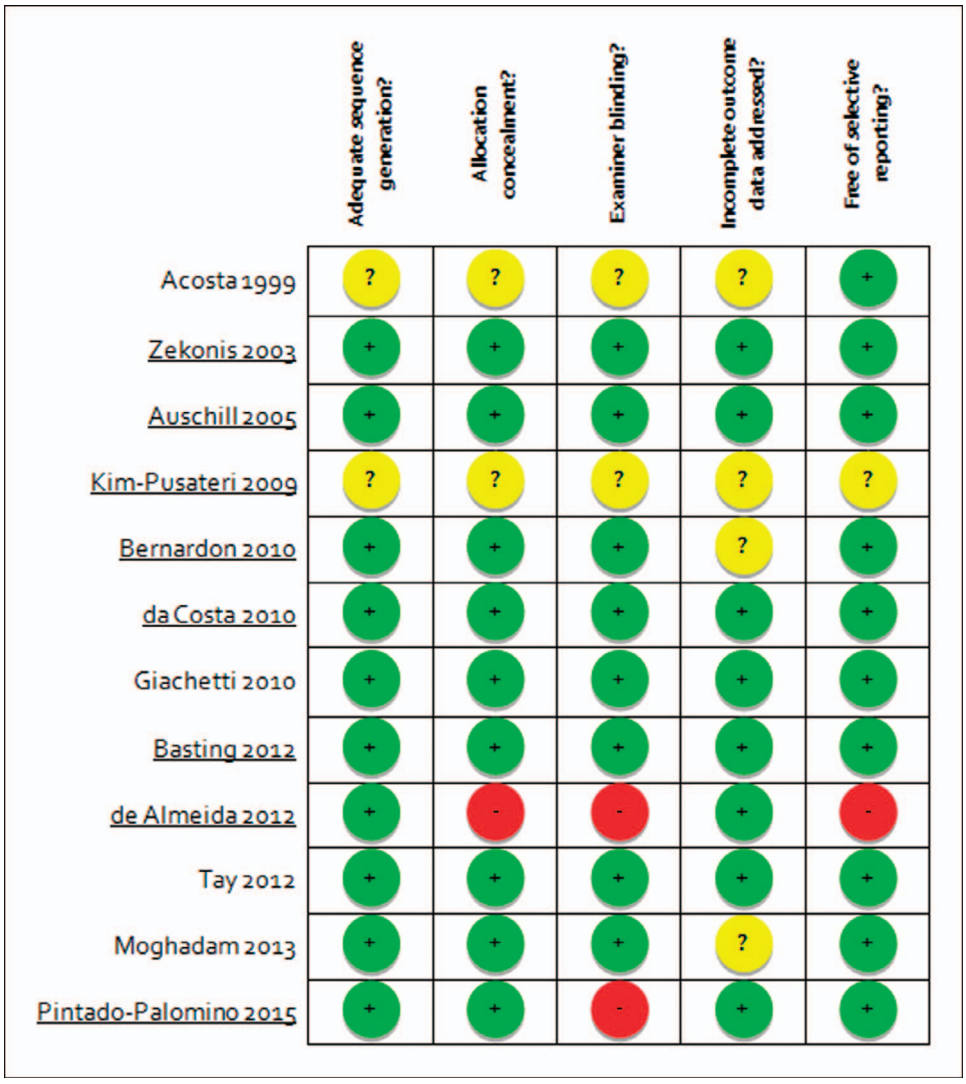

Figure 2. *Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Underlined authors provided extra information by e-mail to allow assessment of the risk of bias.*

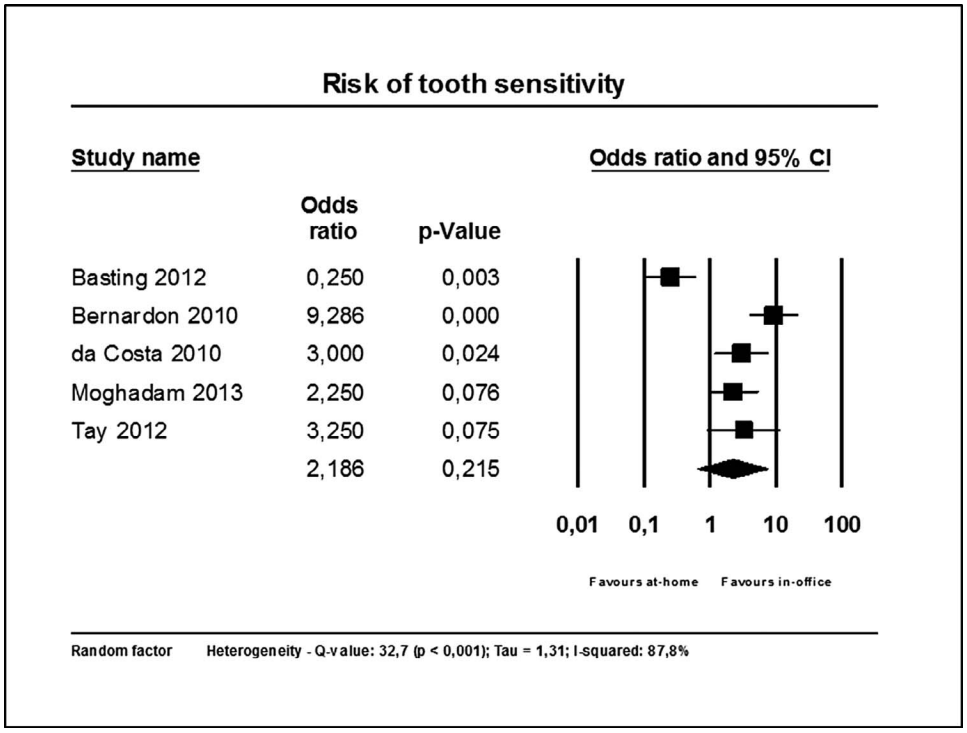

Figure 3. *Forest plot of the risk of tooth sensitivity for in-office vs at-home bleaching.*

chance of tooth sensitivity for the at-home bleaching protocol (data not shown).

Intensity of Tooth Sensitivity—This analysis was based on five studies.[4,7,30,34,35] The Hedge's g standardized difference in means was 0.823, with a confidence interval varying from −0.42 to 2.09 (p=0.193). This provides evidence that there is no difference in the intensity of tooth sensitivity between the two bleaching protocols (Figure 4). Data were heterogeneous (χ^2 test, p<0.001; I^2=95.6%; Figure 4), which means that all studies included in

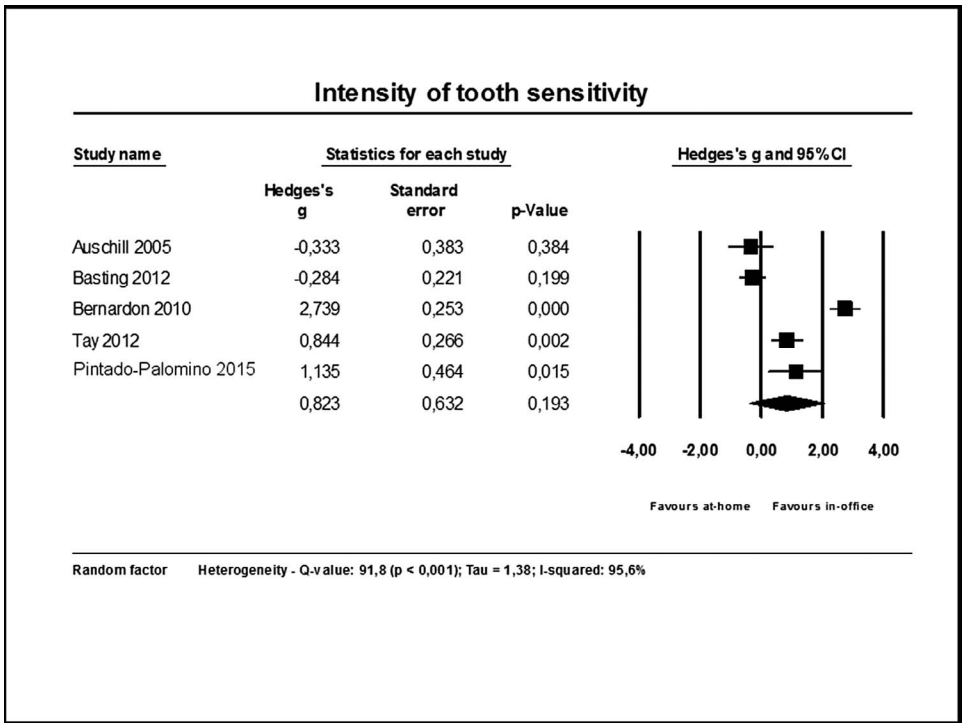

Figure 4. *Forest plot of the intensity of tooth sensitivity for in-office vs at-home bleaching.*

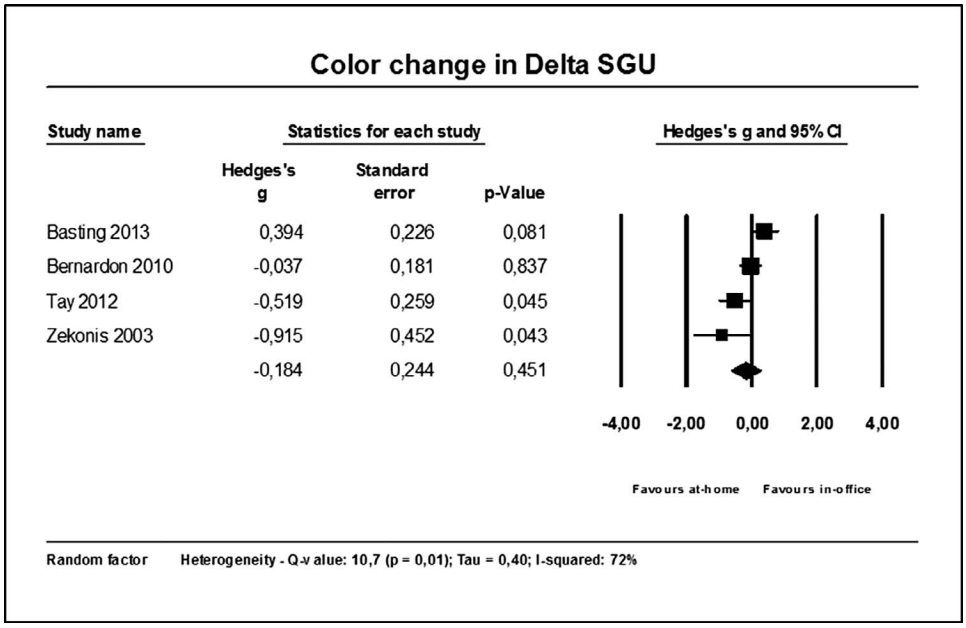

Figure 5. *Forest plot of the color change in shade guide units for in-office vs at-home bleaching.*

the analysis did not share a common effect size. Through a sensitivity analysis, no study that was responsible for such high heterogeneity was identified, and the reduced number of studies prevented us from performing meta-regression or subgroup analysis.

Color Change in ΔSGU—This analysis was based on four studies.[4,7,27,30] The Hedge's g standardized difference in means was −0.184, with a confidence interval varying from −0.66 to 0.29 (p=0.451). This showed that there was no difference in the color change measured in shade guide units (Figure 5). Data were heterogeneous (χ^2 test, p=0.01; I^2=72%; Figure 5), which means that all studies included in the analysis did not share a common effect size. Through a sensitivity analysis, no study that was responsible for such high heterogeneity could be identified.

*Color Change in ΔE**—This analysis was based on four studies.[4,5,27,28] The Hedge's g standardized difference in means was −0.260, with a confidence interval varying from −0.77 to 0.22 (p=0.292). This showed that there was no difference in the color change measured with a spectrophotometer (Figure 6). Data were heterogeneous (χ^2 test, p=0.05;

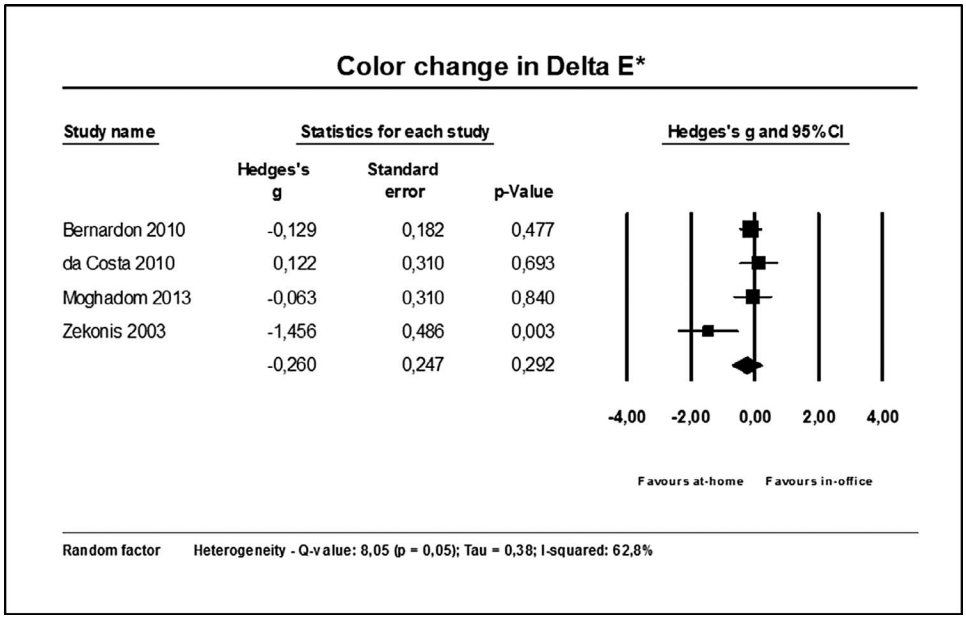

Figure 6. *Forest plot of the color change in ΔE* for in-office vs at-home bleaching.*

I^2=62.8%; Figure 6), which means that all studies included in the analysis did not share a common effect size.

Sensitivity Analysis for Imputations—For the matched data (split-mouth designs), the change of the external correlation for extreme conditions (0.1 and 0.9) did not affect the results of any of the meta-analysis run for this study. The low number of studies included in all meta-analyses prevented us from evaluating the impact of some predictors on the estimates.

A high heterogeneity of the risk of tooth sensitivity and color change in shade guide units was caused by the study of Basting and others.[7] By removing this study from the present meta-analysis, no heterogeneity was detected, and the I^2 was reduced by half, with no change in the overall Hedge's g effect size (data not shown).

DISCUSSION

The most important advantage of proper randomization is that it balances both known and unknown prognostic factors in the assignment of treatments. Besides randomization, allocation concealment is equally important as it protects the randomization process, so that the treatment to be allocated is not known before the patient is enrolled into the study. The adequate management of these two domains minimizes selection bias.[38]

This is the reason why only studies classified as low risk of bias of these domains were included in the meta-analyses. There is abundant evidence that the proper conduction of these steps in RCTs reduces the possibility of systematic errors[39,40]; studies with low methodologic quality tend to overestimate the results, favoring the intervention under testing.[41,42]

In the present study, no significant difference between techniques in any of the comparisons was found. An increased risk and intensity of tooth sensitivity for the in-office bleaching were expected, due to the use of bleaching agents in concentrations much higher than that used in the at-home protocol.[1,43,44] However, due to the large variation of bleaching protocols and concentrations of the bleaching products, this association was not observed.

This similarity in risk and intensity of tooth sensitivity could be partially explained by the fact that most of the studies used at-home and in-office bleaching agents with potassium nitrate and sodium fluoride[4,7,27,28,30,34,35] or at least sodium fluoride[5,7] in their composition. Potassium nitrate and sodium fluoride were already associated with reduced risk and intensity of tooth sensitivity in earlier clinical trials comprising in-office and at-home bleaching.[22,45-48]

The similar results in terms of color change were somehow expected, as bleaching is a time- and concentration-dependent procedure.[49,50] The use of low concentration products can reach similar whitening degree as high concentration products as long as they are used for longer periods. Cardoso and others[51] showed that different application times of the at-home bleaching gel may reach equally satisfactory results in relation to efficacy of bleaching treatment as long as the shorter application times are compensated for by prolonging the number of treatment days. In agreement with such findings are the studies that compared both techniques and assessed the patient's satisfaction. These studies reported similar overall satisfaction in terms of comfort and whitening results,[4,5,31] demonstrating that both techniques can yield satisfactory bleaching efficacy.

Nonetheless, the similarity in outcomes between techniques should be interpreted with caution due to two reasons: 1) a low number of studies included in the meta-analyses and 2) the high heterogeneity of the studies detected by the χ^2 statistics. When facing meta-analyses with high heterogeneity, more important than the discussion of the summary outcomes and the overall results is the identification of factors responsible for such heterogeneity.[52]

The low number of studies identified in the literature search and included in the meta-analysis prevented us from evaluating the impact of such variants (different protocols, concentration of the bleaching agents, product brand and composition, etc) on the outcomes through a meta-regression. It is generally assumed that there should be 10 studies for every predictor to be included in a meta-regression.[52]

The high heterogeneity observed in this study is probably due to the different in-office and at-home bleaching protocols, varied number of clinical sessions, and different concentrations of bleaching gels among the RCTs. For instance, the use of a single bleaching session[5,28,31] or even shorter application times of 10-20 minutes[31,34] were reported in many clinical studies of in-office bleaching. Such degree of variation was also detected for at-home bleaching. The daily use time ranged from 2^7 to 10 hours[4,27] for 6,[5] 14,[27,28,31] and 21-28 days.[4,7,30]

Additionally, in some studies, a fair comparison between in-office bleaching and at-home bleaching was not performed. One week of at-home bleaching

with 10% or 16% carbamide peroxide gel usually results in a change of two to four shade guide units,[4,5,12,27,37] which is approximately equivalent to the change reported after a single in-office bleaching session with 35% hydrogen peroxide gel.[4,27,53,54] Therefore, comparing a single in-office bleaching session with a 14-day at-home protocol[28,31,35] will certainly favor the at-home bleaching in terms of color change and may even minimize the tooth sensitivity of in-office bleaching. In the same line, there were studies comparing two in-office bleaching sessions with three-week at-home bleaching[4] and also two in-office bleaching sessions with a four-week at-home bleaching.[30]

In regard to the heterogeneity of the studies, it is worth mentioning that in two of the four meta-analyses, the high heterogeneity was mainly determined by the study of Basting and others.[7] Most in-office bleaching gels are delivered at low pH because they are more stable as acid solutions than as base solutions.[55,56] However, in the specific study of Basting and others,[7] the authors used two in-office bleaching gels: one with an alkaline pH and the other with an acidic pH. The gel with an alkaline pH showed a very low risk of tooth sensitivity. Although this is an unusual finding, it may be explained by differences in the decomposition kinetics of the hydrogen peroxide at different pHs.

While it is in an acidic solution, oxygen free radicals and hydroxyl anions are produced, but an alkaline solution has a higher concentration of perhydroxyl ions.[57] In an alkaline media, the dissociation of hydrogen peroxide (HP) into free radicals is the greatest, as the dissociation constant (pKa) of the HP is around 11.5. HP in a pH of 9 dissociated 2.7 times more than it did in a pH of 4.4.[55] Thus, if more HP dissociates into free radicals within the dental structure, less surplus of HP is available to travel within dentin and reach the pulp chamber. This low diffusion of HP into the pulp chamber when using an alkaline in-office gel was demonstrated in an in vitro study.[58] This may explain the very low risk of tooth sensitivity of one of the in-office bleaching gels used in the study of Basting and others[7] and in another clinical study.[22]

Further randomized clinical trials comparing both techniques should be performed to allow a more comprehensive evaluation of the variants of the bleaching techniques through meta-analyses. Studies are encouraged to present their data of color change weekly for at-home and also one week after each in-office bleaching session in shade guide units and in ΔE*. Although alternative methods to evaluate color change can also be reported, as well as changes in L*, a*, and b*, this should be accompanied by reports of the changes in shade guide units and in ΔE* so that the study becomes comparable with other clinical studies. This is the reason why the study of Giachetti and others,[31] even after being classified at low risk of bias, was not included in any of the meta-analysis of color change.

CONCLUSIONS

Neither the risk/intensity of tooth sensitivity nor the effectiveness of the bleaching treatment was influenced by the choice of bleaching technique. However, this should be interpreted with caution as it represents an overall comparison without taking into consideration variations in the protocols (daily use time, number of bleaching sessions, and product concentration) of the bleaching techniques in the studies included.

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Regulatory Statement

This study protocol was registered at the PROSPERO (CRD42015015564), and followed the recommendations of the PRISMA statement for report.

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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