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At-home Bleaching With 10% vs More Concentrated Carbamide Peroxide Gels: A Systematic Review and Meta-analysis

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Clinical Relevance

Based on the results obtained in this study, similar results are obtained in terms of bleaching effectiveness with different concentrations of carbamide peroxide, but 10% carbamide peroxide produced lower risk and intensity of tooth sensitivity.

SUMMARY

Objective: To perform a systematic review to answer the following research question: Is at-home bleaching in adults with more concentrated carbamide peroxide (CP) gels as effective and safe as bleaching performed with 10% carbamide peroxide gels?

Methods and Materials: A comprehensive search was carried out in the MEDLINE via PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library and SIGLE, without restrictions. IADR abstracts (1990 to 2016) and unpublished and ongoing trial registries, dissertations and theses (ProQuest Dissertations and Periodicos Capes Theses Databases) were also searched. The risk of bias of the included studies was analyzed using the Cochrane Risk of Bias tool from the Cochrane Collaboration. We meta-analyzed the data using the random effects model to compare 10% CP and more concentrated CP gels in terms of color change (ΔSGU or ΔE) and risk and intensity of tooth sensitivity (TS). The quality of the evidence was rated using the GRADE approach.

Results: After the database screening, 182 articles remained, and this number was reduced to 17 after examination of the abstracts and/or full texts. Four articles were follow-ups of earlier studies, and thus we collected 13 studies. Ten studies were at unclear risk of bias, while three were at low risk of bias. Lower risk and intensity of TS was observed

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for 10% CP. The odds ratio for the risk of TS was 0.41 (95% CI 0.20 to 0.84, p=0.01), and the difference in means for TS intensity was 0.44 (95% CI 0.67 to −0.20, p=0.0003). No significant difference was observed in terms of color change in ΔSGU (difference in means 0.29; 95% CI 0.25 to 0.83, p=0.29) and for ΔE (difference in means −0.16; 95% CI 0.38 to 0.06, p=0.16). Except from the ΔSGU, for which the evidence was graded as low quality, the other outcomes were considered at moderate quality.

Conclusions: At-home bleaching with 10% CP showed similar bleaching efficacy with lower risk and intensity of TS in comparison with more concentrated carbamide peroxide gels.

INTRODUCTION

At-home bleaching can be regarded as a popular cosmetic technique for treating dental discoloration since it provides rapid results, employs reduced chair time, and has lower risk of side effects compared to in-office bleaching.[1-3]

The effectiveness of at-home whitening with 10% carbamide peroxide (CP) has been well reported in the literature.[4-7] However, manufacturers have introduced different concentrations of CP (5% to 22%) for at-home bleaching[8,9] and recommended their use for shorter periods of time.

Due to the continuing release of bleaching gels with different concentrations and protocols, choosing the best product for clinical recommendation is a very challenging task since clinicians should choose a product with similar or superior clinical effectiveness while maintaining patients' safety.

For selection of a bleaching agent, two aspects should be taken into consideration: the whitening efficacy and the risk of side effects. In regard to the former, some clinical studies have shown faster color change for bleaching gels with higher concentrations,[10-12] while other studies did not detect significant differences in groups treated with 10% or more concentrated CP agents.[4,13] In the same trend, the risk and intensity of tooth sensitivity (TS), which is the most common side effect of bleaching protocols, are shown to be similar[4,10,13-15] or higher[5,16-18] for more concentrated CP agents.

Therefore, attempts to reach a consensus to make the choice easier are of clinical interest. Consequently, the aim of this systematic review of the literature was to answer the following PICO question: Is 10% CP gel more effective in terms of color change and safer in terms of TS than bleaching gels with higher concentrations of CP for at-home bleaching in adults?

METHODS AND MATERIALS

Protocol and Registration

This study protocol was registered at PROSPERO (CRD42016029360), and we followed the recommendations of the PRISMA statement for the report of a systematic review.[19]

Information Sources and Search Strategy

The controlled vocabulary (mesh terms) and free key word in the search strategy are in Table 1 and defined based on the following PICOS question reported in the end of the introduction section:

1. Population (P): adult patients submitted to dental bleaching
2. Intervention (I): at-home bleaching with 10% CP
3. Comparison (C): at-home bleaching with more concentrated CP agents
4. Outcome (O): risk and intensity of TS during dental bleaching and color change in shade guide units and in ΔE
5. Study design (S): randomized clinical trials

The outcomes were not used in the search strategy to maximize the sensitivity of the search. To identify trials to be included for this review, we searched the electronic databases MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO), and Cochrane Library. An expert librarian guided the whole search strategy. We hand searched the reference lists of all primary studies 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. We searched the abstracts from the annual conference of the International Association for Dental Research (IADR) and the Brazilian regional division (1990–2016). We explored the gray literature using the database System for Information on Grey literature in Europe (SIGLE). Dissertations and theses were searched for using the ProQuest Dissertations and Theses Full Text database and the Periodicos Capes Theses database.

To locate unpublished and ongoing trials related to the review question, we searched the following

Table 1: *Electronic Database and Search Strategy*

Pubmed (April 14, 2016)	
#1 (tooth discoloration[MeSH Terms] OR "tooth staining"[Title/Abstract] OR "tooth stain"[Title/Abstract] OR "stained tooth"[Title/Abstract] OR "stained teeth"[Title/Abstract] OR "tooth discoloration"[Title/Abstract] OR "tooth discolouration"[Title/Abstract] OR "discolored tooth"[Title/Abstract] OR "discoloured tooth"[Title/Abstract] OR "discolored teeth"[Title/Abstract] OR "discoloured teeth"[Title/Abstract] OR "dental discoloration"[Title/Abstract] OR "dental discolouration"[Title/Abstract])	**#2** (peroxides[MeSH Terms] OR tooth bleaching[MeSH Terms] OR bleaching agents[MeSH Terms] OR carbamide peroxide[Supplementary Concept] OR bleaching[Title/Abstract] OR whitening[Title/Abstract] OR "carbamide peroxide"[Title/Abstract] OR "home-use"[Title/Abstract])
#1 AND #2	
Scopus (April 14, 2016)	
#1 (TITLE-ABS-KEY ("tooth discoloration") OR TITLE-ABS-KEY ("tooth staining") OR TITLE-ABS-KEY ("discolored tooth") OR TITLE-ABS-KEY ("stained tooth") OR TITLE-ABS-KEY ("dental discoloration"))	**#2** (TITLE-ABS-KEY (peroxides) 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 ("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 (April 28, 2016)	
#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") OR Topic: ("dental discolo*ration")	**#2** Topic: (peroxides) OR Topic: ("tooth bleaching") OR Topic: ("bleaching agents") OR Topic: ("tooth bleaching agents") 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: ("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")
#1 AND #2	
Lilacs and BBO (April 28, 2016)	
#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 "dental discoloration" 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 "carbamide peroxide" OR "peróxido de carbamida" OR "dental bleaching" OR "clareamento dental" OR "blanqueamiento dental" OR "tooth whitening" 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 "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")

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

Eligibility Criteria

We included parallel and split-mouth randomized clinical trials (RCTs) that compared the risk and intensity of TS and color change after at-home bleaching with different concentrations of CP in adult patients of any age-group. The efficacy of the

Table 1: Continued.

#1 AND #2	
Cochrane Library (April 28, 2016)	
#1 MeSH descriptor: [Tooth Discoloration] explode all trees #2 MeSH descriptor: [Peroxides] explode all trees #3"discoloured tooth":ti,ab,kw or "discoloured teeth":ti,ab,kw or "stained tooth":ti,ab,kw or "stained teeth":ti,ab,kw or "dental discoloration":ti,ab,kw or "dental discolouration":ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Bleaching Agents] explode all trees #4 MeSH descriptor: [Tooth Bleaching Agents] explode all trees #5 "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) #6 "discoloured tooth":ti,ab,kw or "discoloured teeth":ti,ab,kw or "stained tooth":ti,ab,kw or "stained teeth":ti,ab,kw or "dental discoloration":ti,ab,kw (Word variations have been searched)	#7 "dental discolouration":ti,ab,kw (Word variations have been searched) #8 "carbamide peroxide":ti,ab,kw or "dental bleaching":ti,ab,kw or "tooth whitening":ti,ab,kw or "bleaching techniques":ti,ab,kw or whitening:ti,ab,kw (Word variations have been searched) #9 bleaching:ti,ab,kw or "dental whitening":ti,ab,kw or "bleaching systems":ti,ab,kw or "whitening systems":ti,ab,kw or "vital bleaching":ti,ab,kw (Word variations have been searched) #10 "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) #11 "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) #12 #1 or #2 or #3 or #4 or #5 or #6 or #7 #13 #8 or #9 or #10 or #11 #14 #12 and #13

bleaching treatment was compared using the ΔSGU (shade guide units) and/or ΔE values.

RCT studies were excluded if studies compared 10% CP with 1) hydrogen peroxide, 2) in-office bleaching, 3) different placebos, 4) whitening toothpastes, 5) over-the-counter products, and 6) higher CP concentrations but did not measure any of the outcomes under investigation in this systematic review.

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 had insufficient information to make a clear decision. Subsequently, three reviewers (JLG, LMW, and TFB) classified those that met the inclusion criteria. To handle such a large number of studies, we used a study ID for each eligible study, combining first author and then year of publication. Data were extracted using customized extraction forms and the following data recorded for each included study:

- Details of the study, including year of publication and author(s)
- Details of study methods, including study design and setting
- Details of participants, including age and gender
- Details of bleaching protocol
- Details of concentration of the bleaching gels
- Details of TS perception using different types of scales
- Details of color evaluation using shade guides and/or spectrophotometers

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, we attempted to contact authors by e-mail at least twice to request the missing information.

When data from multiple bleaching sessions were provided, we made an average of the figures for each bleaching protocol. Concerning color change, we employed the data that represented the immediate result (up to three months postbleaching). When more than one concentrated CP agent was included in the study, their values were combined to make a single entry.

Risk of Bias in Individual Studies

Quality assessments of the selected trials were evaluated by three independent reviewers (JLG, LMW, and TFB) using the Cochrane Collaboration tool for assessing risk of bias in randomized trials.[20] 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 fourth reviewer (AR).

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 Version* 5.1.0 (http://handbook.cochrane.org). 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.

For the outcomes risk, intensity of TS, and color change in shade guide units, studies were at "low" risk of bias if there was adequate sequence generation, allocation concealment, and blinding (key domains). For the objective evaluation of color in ΔE*, examiner blinding was not considered a key domain, as the foreknowledge of the treatment would not affect the results produced by the instrument tool.

To summarize the risk of bias within a study for each outcome, we followed the directions of the Cochrane Collaboration. An outcome of a study is at low risk of bias when all key domains for that outcome are at low risk of bias. The study was considered at unclear risk when one or more key domain was also unclear, and, finally, the study was at high risk of bias when at least one key domain was at high risk.

Summary Measures and Synthesis of the Results

Data from studies at low or unclear risk of bias were meta-analyzed using Revman 5 (Review Manager version 5, Cochrane Collaboration, Copenhagen, Denmark). Data from eligible studies were either dichotomous (absolute risk of TS) or continuous (intensity of TS, ΔSGU, and ΔE).

The outcomes were summarized by calculating the standardized mean difference for the continuous data and the odds ratio along with the 95% confidence interval (CI) for the dichotomous data. The random effects models were employed. Heterogeneity was assessed using the Cochran Q-test and I^2 statistics. No subgroup analysis was performed. Sensitivity analyses were conducted to investigate the reasons for high heterogeneity whenever detected.

Assessment of the Quality of Evidence Using GRADE

We graded the quality of the evidence for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org) to determine the overall strength of evidence for each meta-analysis.[21] The GRADE approach is used to contextualize or justify intervention recommendations with four levels of evidence quality, ranging from high to very low.

The GRADE approach begins with the study design (RCTs or observational studies) and then addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) to possibly rate down the quality of the evidence (one or two levels) and three to possibly rate up the quality (large effect, management of confounding factors, and dose-response gradient).[21] Each one of these topics was assessed as "no limitation," "serious limitations," and "very serious limitations" to allow categorization of the quality of the evidence for each outcome into high, moderate, low, and very low. "High quality" suggests that we are very confident that the true effect lies close to the estimate of the effect. On the other extreme, "very low quality" suggests that we have very little confidence in the effect estimate and that the estimate reported can be substantially different from what it was measured.

The GRADEpro Guideline Development Tool available online at http://www.gradepro.org) was used to create a summary of finding tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*.[22]

RESULTS

Study Selection

After the database screening and removal of duplicates, 1418 studies were identified (Figure 1). After title screening, 182 studies remained, and this number was reduced to 22 after careful examination of the abstracts. After reading the articles, only 17 studies were included in the qualitative analysis.

Characteristics of the Included Articles

The characteristics of the 17 articles selected are listed in Table 2. Four articles were follow-ups of earlier studies, three from Meireles[23-25] and one from Matis,[12] totaling 13 studies from a total of 17 articles. The parallel study design was predominantly used in these studies.[4,5,10,11,15-17,26,27] Four out of the 13 studies used the split-mouth design.[13,14,18,28]

Three studies used a visual analog scale for pain evaluation,[10,17,18] and six studies used a numeric rating scale.[4,5,13,15,27,28] Three studies evaluated

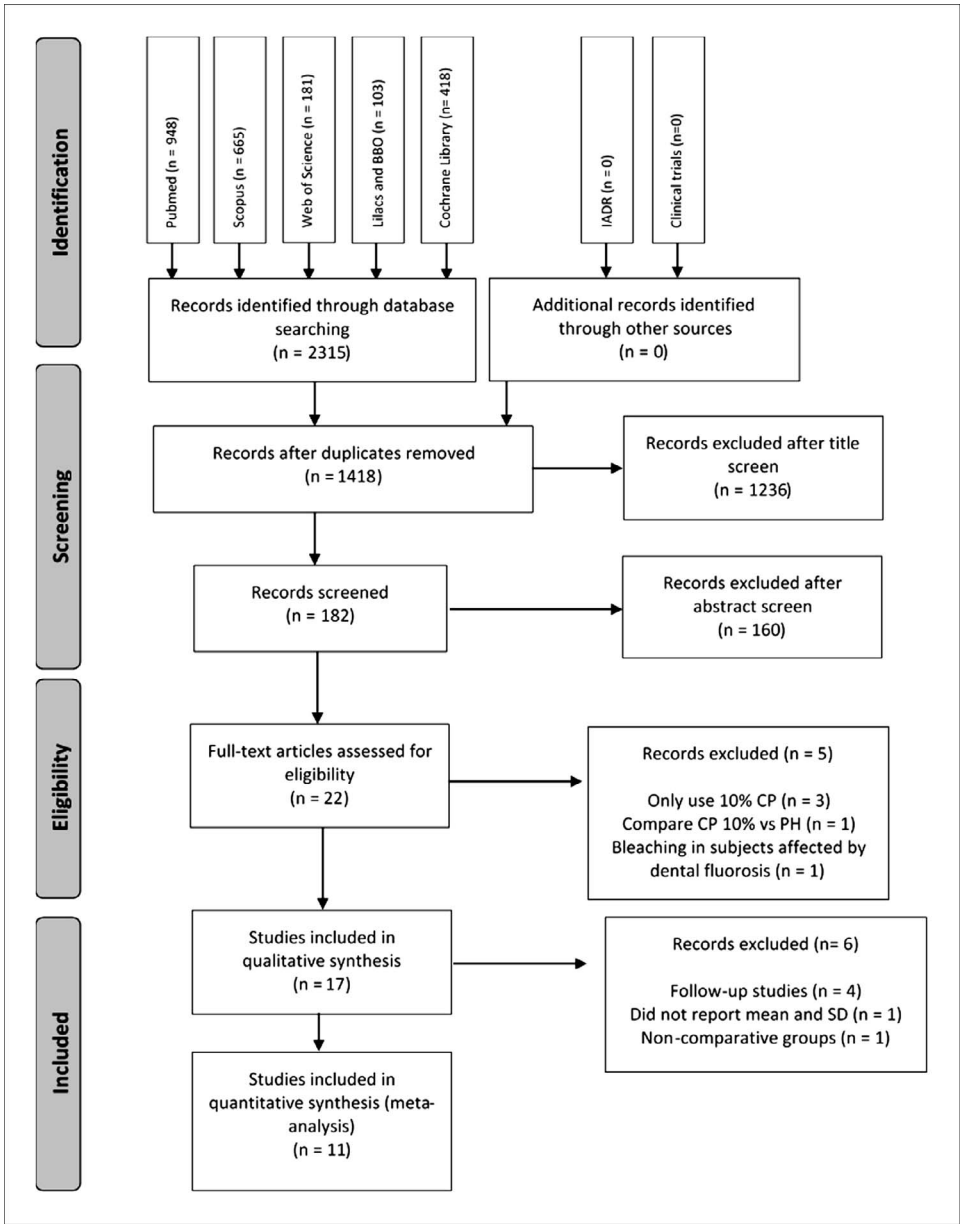

Figure 1. Flow diagram of study identification.

only the risk of TS,[14,16,26] and one study did not evaluate this outcome.[11]

For color evaluation, 10 studies used a shade guide.[4,5,10,11,13,15,17,18,26,28] Eight used an objective instrument (spectrophotometer or colorimeter) for color assessment.[4,11,13,15,17,18,27,28] Photographs or digital images were used in four studies.[13,16,27,28] One study did not evaluate the color change.[14]

The number of patients per group included in these studies ranged from 10 to 30. The average age of all participants included in the clinical trials was approximately 32.4 years.[4,13-17] Seven studies did not report this information.[5,10,11,18,26-28] In one study, most of the participants were male;[17] in six articles, females predominated.[4,5,13-16] Six studies did not report this information.[10,11,18,26-28]

Bleaching Protocol and Features

Bleaching trays with reservoir were used in most of the studies.[4,11,13,14,16,17,26-28] Three studies used custom-bleaching trays without reservoirs,[5,15,18] and one study did not report this information.[10]

Regarding the bleaching protocol (Table 2), CP with different concentrations, such as 12%,[26] 15%,[10,13,15,16,18,28] 16%,[4,14,18] 17%,[11,17] 20%,[5,16,28] and 28%,[27] were used for at-home bleaching.

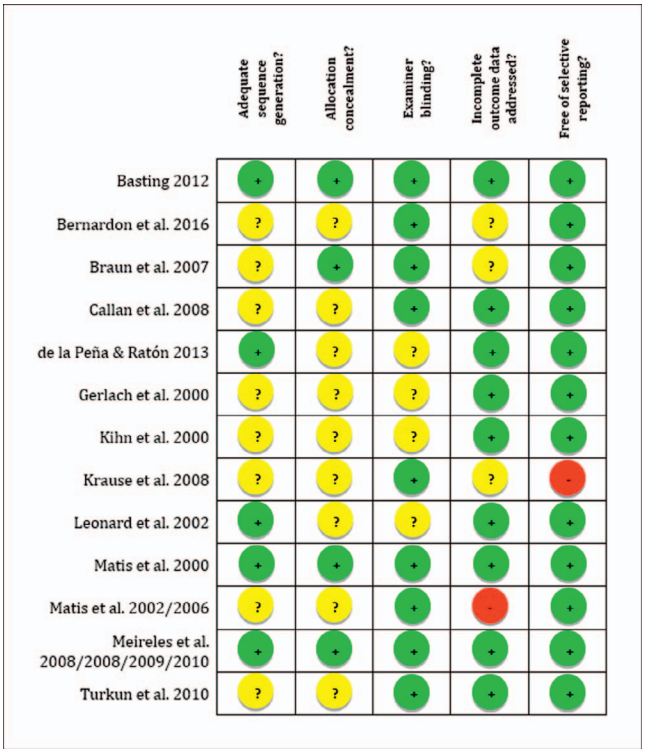

Figure 2. Summary of the risk of bias assessment according to the Cochrane Collaboration tool.

The daily usage time of at-home bleaching gels varied from 20 minutes to overnight and the duration of bleaching in days varied from seven days to six months, but most of the studies performed bleaching for 14 days.[10,13-16,26] (Table 2).

Assessment of the Risk of Bias

The risk of bias of the included studies is presented in Figure 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.

In summary, from the 13 studies, ten[10,11,14-18,26-28] were considered at unclear risk of bias in the key domains of the Cochrane risk of bias tool, and three studies[4,5,13] were classified at low risk of bias.

Meta-Analyses

All meta-analyses were performed on studies at low and unclear risk of bias and from which the information about the outcome could be extracted. For instance, we could not extract the data from the study of Leonard and others[14] for any of the outcomes. The study of Turkun and others[27] compared very different protocols between the two study groups, being four to six hours daily for 10% carbamide peroxide and only 20 minutes per day for 20% carbamide peroxide . Thus, from 13 studies, only 11 have data to be used at least in one of the outcomes of this study. This explains the variation in the number of studies in the forest plots of the different meta-analyses.

Risk of TS—This analysis was based on nine studies.[4,5,10,15-18,26,28] The odds ratio was 0.41 (95% CI 0.20 to 0.84; p=0.01), which means that two people from the PC 10% will experience the event for every five who will not (Figure 3). Data were not heterogeneous (χ^2 test, p=0.09; I^2=41%; Figure 3), which means that all studies included in the analysis share a common effect size.

Intensity of TS—This analysis was based on six studies.[4,5,10,15,17,28] The standardized difference in means was −0.44 (95% CI −0.67 to −0.20; p=0.0003). This provides evidence that there is a moderate difference,[29] with lower intensity of pain for CP 10% than CP with higher concentrations (Figure 4). Data were not heterogeneous (χ^2 test, p=0.34; I^2=12%; Figure 4).

Color Change in ΔSGU—This analysis was based on seven studies.[4,5,10,11,15,18,26] The standardized difference in means was 0.29, with a confidence interval varying from −0.25 to 0.83 (p=0.29). 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<0.00001; I^2=85%; Figure 5), which means that all studies included in the analysis did not share a common effect size. Through a sensitivity analysis, we did not identify the reason for this high heterogeneity.

*Color Change in ΔE**—This analysis was based on five studies.[4,13,15,16,18] The standardized difference in means was −0.16, with a confidence interval varying from −0.38 to 0.06 (p=0.16). These results show that there was no significant difference in the color change measured with a spectrophotometer (Figure 6). Data were not heterogeneous (χ^2 test, p=0.56; I^2=0%; Figure 5).

Assessment of the Quality of Evidence—In the summary of findings in Table 3, we can observe that except for the color change in ΔSGU, graded as low in the quality of evidence, the other outcomes were assessed as moderate quality using GRADE. The reasons for downgrading the evidence for ΔSGU were that most RCTs are at "unclear" risk of bias, presence of inconsistency with nonexplained statistical heterogeneity, and imprecision with a high 95% confidence interval, which does not exclude impor-

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] (y)	No. of Subjects Male[Total]	Dropouts
Basting (2012)[5]	Parallel [n.r.]	Shade guide unit (Vita Classical)	n.r. ± n.r. [18-42]	18 [94]	13
Bernardon and others (2016)[18]	Split-mouth [n.r.]	Shade guide unit (Vita Classical) and spectrophotometer	n.r. ± n.r. [18-40]	n.r. [50]	n.r.
Braun and others (2007)[11]	Parallel [n.r.]	Shade guide unit (Vitapan 3D) and spectrophotometer (Spectroshade)	n.r. ± n.r. [n.r.]	n.r. [30]	n.r.
Callan and others (2008)[26]	Parallel [n.r.]	Shade guide unit (Vita Classical)	n.r. ± n.r. [n.r.]	n.r. [46]	1
de la Peña & Ratón (2013)[15]	Parallel [University]	Shade guide unit (Vita Classical) and spectrophotometer (Vita Easyshade)	25.9 ± 5.6 [n.r.]	28 [96]	0
Gerlach and others (2000)[16]	Parallel [n.r.]	Digital images	39 ± 8.4 [24-57]	6 [36]	4
Kihn and others (2000)[10]	Parallel [University]	Shade guide unit (Vita Lumin)	n.r. ± n.r. [18-65]	n.r.[57]	4
Krause and others (2008)[17]	Parallel [n.r.]	Shade guide unit (Vitapan 3D) and spectrophotometer (SpectroShade)	31 ± 4 [n.r.]	16 [30]	n.r.
Leonard and others (2002)[14]	Split mouth [University]	n.r.	23. ± n.r. [20-30]	0 [20]	1
Matis and others (2000)[13]	Split-mouth [n.r.]	Shade guide unit (Trubyte bioform), colorimeter (Chroma Meter) and photographic means	50.4 ± n.r. [26-73]	8 [25]	n.r.
Matis and others (2002, 2006)[28, 12]	Split mouth [University]	Shade guide (Vitalescence Esthetic Restorative Masters), photographs and colorimeter (Minolta Chroma Meter)	n.r. ± n.r. [n.r.]	n.r.[59]	15
Meireles and others (2008, 2008, 2009, 2010)[4, 24, 23, 25]	Parallel [n.r.]	Shade guide unit (Vita Classical), and spectrophotometer (Vita Easyshade)	25.3 ± 7.9 [18-55]	31 [92]	11
Turkun and others (2010)[27]	Parallel [n.r.]	Spectrophotometer (Vita Easyshade) and digital images	n.r. ± n.r. [25-28]	n.r. [20]	0

Abbrevations: CP, carbamide peroxide; delta SGU, shade guide units; delta E (L, a*, and b*); ID, identification; n.r., not reported; NRS (numerical rating scale): none, mild, moderate, considerate, severe VAS (visual analog scale): a 10-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end; SD, standard deviation.*

[a] *Opalescence 10%, Ultradent (South Jordan, UT, USA).*
[b] *Opalescence 20%, Ultradent.*
[c] *Power Bleaching 10%, BM4 (Maringá, Brazil).*
[d] *Opalescence 15% (Ultradent).*
[e] *Power Bleaching 16%, BM4.*
[f] *Perfect Bleach 10% (Voco, Cuxhaven, Germany).*
[g] *Perfect Bleach 17%, Voco.*
[h] *NightWhite Classic 10% (Discus Dental, Culver City, CA, USA).*
[i] *Rembrandt Xtra-Comfort 12% (Den-Mat Corporation, Santa Maria, CA, USA).*
[j] *Illuminè Home 15% (Dentsply, Konstanz, Germany).*
[k] *Nupro White Gold 10% (Dentsply).*
[l] *Nupro White Gold 15% (Dentsply).*
[m] *NightWhite Classic 16% (Discus Dental).*
[n] *Whiteness Perfect 10% (FGM, Joinville, SC, Brazil).*
[o] *Whiteness Perfect 16% (FGM.*
[p] *Meta Tray 28% (Remedent, Deurle, Belgium).*

Table 2: Extended.

Study ID	Bleaching Tray	Groups/Materials [No. of Subjects]	Bleaching Protocol	Outcomes evaluated		
				Color Change	Tooth Sensitivity (Pain Scale)	Gingival Irritation
Basting (2012)[5]	Without reservoirs	10% CP[a] [19] 20% CP[b] [21]	2 h daily [21 d]	ΔSGU	Absolute risk and intensity (NRS 0-3)	n.r.
Bernardon and others (2016)[18]	Without reservoirs	10% CP[a] [25] 10% CP[c] [25] 15% CP[d] [25] 16% CP[e] [25]	2 h daily [45 d]	ΔSGU and ΔE*	Intensity (VAS 0-10)	Loe index scores 0-3
Braun and others (2007)[11]	With reservoirs	10 % CP[f] [10] 17% CP[g] [10]	2 h daily [7 d]	ΔSGU and ΔE*	n.r.	n.r.
Callan and others (2008)[26]	With reservoirs	10% CP[h] [23] 12% CP[i] [23]	10%: 2 h twice per day [14 d] 12%: 6-8 h daily [14 d]	ΔSGU	Absolute risk	Number of days
de la Peña & Ratón (2013)[15]	Without reservoirs	10% CP[a] [24] 15% CP[j] [24]	1 h daily [14 d]	ΔSGU and ΔE*	Absolute risk and intensity (NRS 0-4)	n.r.
Gerlach and others (2000)[16]	With reservoirs	10% CP[a] [10] 15% CP[d] [11] 20% CP[b] [5]	2 h daily [14 d]	ΔE*	Absolute risk	Absolute risk
Kihn and others (2000)[10]	n.r.	10% CP[k] [28] 15% CP[l] [28]	4 h daily-overnight [14 d]	ΔSGU	Intensity (VAS 0-20)	n.r.
Krause and others (2008)[17]	With reservoirs	10% CP[f] [10] 17% CP[g] [10]	2 h-daily [7 d]	n.r.	Intensity (VAS 0-10)	n.r.
Leonard and others (2002)[14]	With reservoirs	10% CP[h] [20] 16% CP[m] [20]	8-10 h overnight [14 d]	n.r.	Absolute risk	Absolute risk
Matis and others (2000)[13]	With reservoirs	10% CP[a] [25] 15% CP[d] [25]	Overnight [14 d]	ΔSGU and ΔE*	Intensity (NRS 0-4)	0-4 scale
Matis and others (2002, 2006)[28, 12]	With reservoirs	10% CP[a] [30] 15% CP[d] [28] 20% CP[b] [30]	Overnight [6 mo]	ΔE*	Intensity (NRS 0-4)	0-4 scale
Meireles and others (2008, 2008, 2009, 2010)[4, 24, 23, 25]	With reservoirs	10% CP[n] [46] 16% CP[o] [46]	2 h daily [21 d]	ΔSGU and ΔE*	Absolute risk and intensity (NRS 0-4)	0-4 scale
Turkun and others (2010)[27]	With reservoirs	10% CP[a] [10] 28% CP[p] [10]	10%: 6-8 h daily [10 d] 28%: 20 min daily [10 d]	ΔE*	Absolute risk and intensity (NRS 0-4)	Absolute risk

tant harm or benefit (Table 3). For the other outcomes, the evidence was downgraded only for the unclear risk of bias of most RCTs.

DISCUSSION

In the present systematic review, we observed that at-home bleaching with 10% CP produced similar color change and lower risk and intensity of TS than at-home bleaching performed with more concentrated CP concentrations.

From a theoretical point of view, a faster or higher degree of color change was expected to occur with more concentrated CP gels. Chemical theories state that in simplest chemical reactions, an increase in the concentration of reactants may increase the reaction rate. Indeed, a closer look of several primary studies indicated that more concentrated CP products yielded a higher degree of whitening in the first days or week of bleaching,[4,10,11] but this difference was not maintained at the end of the treatment.

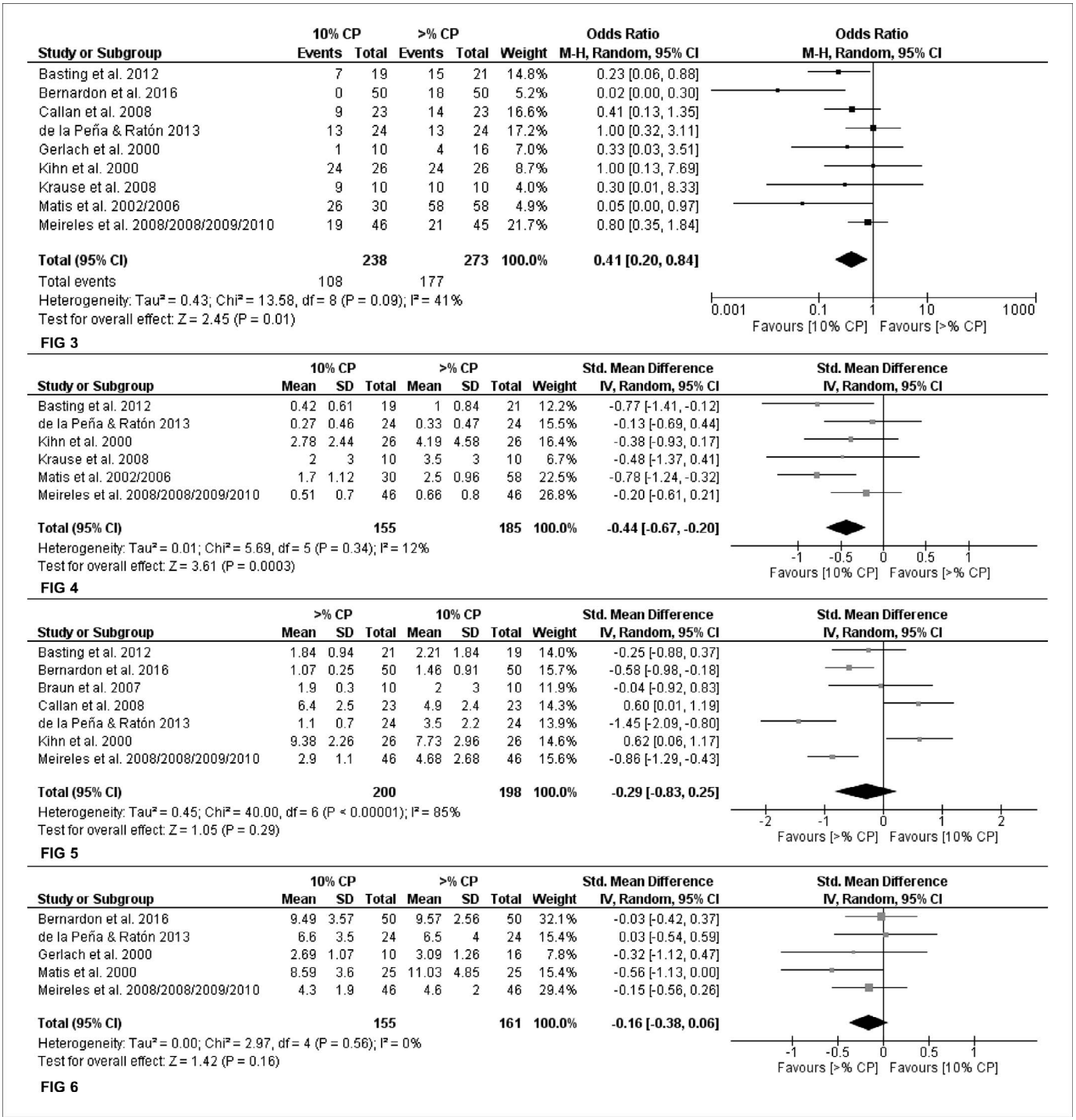

Figure 3. Forest plot of the risk of tooth sensitivity (TS) for 10% CP vs higher-concentration CP (>% CP).
Figure 4. Forest plot of the intensity of tooth sensitivity for 10% CP vs higher-concentration CP (>% CP).
Figure 5. Forest plot of the color change in shade guide units for 10% CP vs higher-concentration CP (>% CP).
Figure 6. Forest plot of the color change in ΔE^* for 10% CP vs higher-concentration CP (>% CP).

For instance, Matis and others[13] showed that a 15% CP gel achieved a higher degree of whitening than did the 10% CP gel after two weeks of use. However, by extending the treatment time to six weeks, the differences in color change or brightness were no longer statistically different. Similarly, Leonard and others[14] concluded that higher CP concentrations achieved faster bleaching, but the

Table 3: *Summary of Findings for At-Home Bleaching*[a]

Outcomes	Anticipated Absolute Effects[b] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)[c]
	Risk With More Concentrated CP	Risk With 10% CP			
Risk of TS assessed with dichotomous scale (yes/no) follow-up: mean 2-3 wk	648 per 1000	431 per 1000 (269-608)	OR 0.41 (0.20-0.84)	511 (9 RCTs)	⊕⊕⊕○ MODERATE[d]
Intensity of TS (intensity of TS) assessed with pain scales follow-up: mean 2-3 wk	—	SMD 0.44 SD fewer (0.67 fewer to 0.2 fewer)	—	340 (6 RCTs)	⊕⊕⊕○ MODERATE[d]
Delta SGU assessed with shade guide units follow-up: mean 2-3 wk	—	SMD 0.29 SD higher (0.25 lower to 0.83 higher)	—	398 (7 RCTs)	⊕○○○ VERY LOW[d,e,f]
Delta E assessed with spectrophotometer follow-up: mean 2-3 wk	—	SMD 1.04 SD lower (2.11 lower to 0.04 higher)	—	316 (5 RCTs)	⊕⊕⊕○ MODERATE[d]

Abbrevations: CI, confidence interval; CP, carbamide peroxide; OR, odds ratio; RCTs, randomized clinical trials; SGU, shade guide untis; SMD, standardized mean difference; TS, tooth sensitivity.
[a] Intervention: 10% CP; comparison: more concentrated CP.
[b] 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).
[c] High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[d] Most RCT are at "unclear" risk of bias.
[e] Nonexplained statistical heterogeneity.
[f] High 95% confidence interval, which does not exclude important harm or benefit.

results were equivalent, as longer application times were used for the lower CP concentrations.

When bleaching starts, the organic component of dentin has not been oxidized yet; therefore, a higher number of free radicals, available in highly concentrated CP products, have sufficient substrate for oxidization, leading to a higher degree of whitening at the beginning of bleaching. As time passes, the nonoxidized substrate reduces significantly, and the excess of active hydrogen peroxide in more concentrated CP products no longer has much substrate for action; while there are more available in dentin of those bleached with 10% CP. The lower concentration of active hydrogen peroxide in 10% CP gels is compensated for by the repetitive daily at-home bleaching protocol in a nonlinear trend. For instance, when 10% CP was applied in participants for eight hours daily, this group achieved faster bleaching than the group that used the product one hour daily; however, in just two more days, the color change of the one-hour group became similar to that of the eight-hour group.[30]

Analogously, this also help us understand why a higher risk and intensity of TS was observed for higher-concentrated CP products. The surplus of hydrogen peroxide from highly concentrated products without substrate to oxidize reaches the organic component of the pulp tissue, where it may induce the formation of reactive or reparative dentin.[31,32] Peroxides diffuse very quickly into dentin, reaching the pulp chamber, but the rate of penetration depends on the concentration and composition of the bleaching agent, the thickness of the hard tissue,[33-36] and the application protocol.[30] The higher the concentration of the bleaching agent, the greater the aggression to the pulp cells.[31,32,37]

The damage caused by the hydrogen peroxide leads to the expression of inflammatory mediators, such as substance-P[38] and prostaglandins, which have a recognized role in triggering nociceptive impulses for the perception of pain,[39] helping us explain why higher-concentrated hydrogen peroxide could be responsible for the higher absolute risk and intensity of TS.

Most of the studies in dental bleaching use shade guides for color evaluation.[4,5,10,11,13,17,18,26,28] Although these shade guides were designed primarily for shade matching with composite resins, their use is supported in the literature for evaluating bleaching efficacy.[34,40-42] Compared with the spectrophotometer, the shade guides show better visual correlation and have the potential to allow for more

accurate and consistent monitoring and reliable color of teeth.[43]

It is worth mentioning that the conclusions herein collected are of moderate quality of evidence, and this means that 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 different. The great limitation observed in this systematic review was the high number of studies at unclear risk of bias. Future studies with well-designed protocols, when added to the results collected so far in future systematic reviews of the same topic, may eventually lead the conclusions to high quality of evidence.

CONCLUSIONS

The 10% CP product demonstrated a significantly lower risk and intensity of TS when compared to higher CP concentrations without jeopardizing color change. In any case, these results should be interpreted with caution since most of the studies included in the meta-analysis were at unclear risk of bias.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of the State University of Ponta Grassa, Brazil.

Conflict of Interest

The authors of this article 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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