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Review Article

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Can carbamide peroxide be as effective as hydrogen peroxide for in-office tooth bleaching and cause less sensitivity? A systematic review

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ABSTRACT

This study aimed to answer the question through a systematic review: Can carbamide peroxide be as effective as hydrogen peroxide and cause less in-office bleaching sensitivity? A literature survey was performed in PubMed/MEDLINE, Embase, Scopus, ISI Web of Science, and gray literature. Primary clinical trials that compared the efficacy or the in-office bleaching sensitivity between carbamide and hydrogen peroxides were included. The risk of bias was evaluated using the RoB2. The certainty of the evidence was assessed using the GRADE approach. DPI training significantly improved the mean scores of the dental undergraduates from 7.53 in the pre-DPI-training test to 9.01 in the post-DPI-training test ($p < 0.001$). After 6 weeks, the mean scores decreased marginally to 8.87 in the retention test ($p = 0.563$). DPI training increased their confidence level from 5.68 pre-DPI training to 7.09 post-DPI training. The limited evidence suggests that the 37% carbamide peroxide may be similarly effective to the 35% hydrogen peroxide for bleaching teeth in-office and causes less bleaching sensitivity. However, more well-designed split-mouth clinical trials are necessary to strengthen the evidence.

Keywords: Carbamide peroxide; Systematic review; Tooth bleaching; Zydrogen peroxide

INTRODUCTION

Cosmetic dentistry is part of any clinical specialty and has grown greatly in the last hundred years [1]. Tooth bleaching is the elective dental procedure most sought by the general population. Commonly disseminated by professionals and the media, it can improve aesthetic perception and patient confidence [2-4]. In addition, the main advantage of tooth bleaching is that it is minimally invasive, eliminating the need to remove healthy dental tissues [4,5].

There are 3 professional approaches to bleaching teeth: at home (supervised by a dentist), in-office and combined [6]. The at-home tooth bleaching usually employs less concentrated peroxides, and its effectiveness depends on the volunteer collaboration to apply the gel daily in individualized trays [6]. Conversely, in-office tooth bleaching requires the professional's application of highly concentrated gels so that the bleaching efficacy is not dependent on patient collaboration and does not require trays [6]. However, the main disadvantage of the

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No potential conflict of interest relevant to this article was reported.

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last technique is a higher occurrence of bleaching sensitivity, which can mostly occur during bleaching sessions [7,8].

Primary studies evaluated if using a highly concentrated carbamide peroxide for in-office tooth bleaching can promote similar efficacy (color change) to the hydrogen peroxide, causing less bleaching sensitivity [7-9]. However, it is essential that synthesis studies, such as systematic reviews, are performed to summarize the primary data. Systematic reviews compile the methods, results and conclusions of primary studies over specific questions in the literature, establish the certainty of the evidence and can provide the highest evidence concerning interventions in biomedical sciences [10].

Therefore, this systematic review aimed to answer the question: Can carbamide peroxide be as effective as hydrogen peroxide and cause less in-office bleaching sensitivity?

MATERIALS AND METHODS

Protocol and registration

This systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42022382154) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [11].

Eligibility criteria

The studies included in this systematic review were according to the Population, Intervention, Control, and Outcome (PICO) question:

- P: 18 years older individuals undergoing in-office tooth bleaching.
- I: Carbamide peroxide.
- C: Hydrogen peroxide.
- O: Efficacy (color change) and bleaching sensitivity.

Thus, clinical trials were included comparing the in-office bleaching efficacy (color change) and sensitivity between carbamide and hydrogen peroxides. Studies that compared in-office and at-home bleaching approaches or used light activation, ultrasonic activation, and desensitization protocols were also excluded.

Information sources and search strategy

At first, the search strategy was defined for the MEDLINE database and applied to PubMed using controlled vocabulary – MeSH (Medical Subject Headings) terms – and free keywords to embrace the PICO question. Adapted versions of the search strategy were used in other databases (Cochrane Library, Embase, LILACS, Scielo, Scopus, Web of Science) (**Table 1**). The search included articles published up to January 2023.

1. Selection process and gathering data

After running the search strategy, a reference manager (RAYYAN, Intelligent Systematic Review) was used to store and select all data from databases [12]. Two authors were calibrated (P.W.M.B and K.S.S.) using 150 articles on the RAYYAN platform. The inter-examiner agreement was calculated through the Kappa coefficient using the SPSS statistical software (Statistical Package for the Social Sciences, version 21.0, IBM Corp., Armonk, NY, USA) (K = 0.91; confidence interval, 0.87–0.95).

Table 1. Electronic search strategies

Database	Search strategies
PubMed	(tooth bleaching[MeSH Terms] OR “tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “tooth whitening” OR “dental whitening”) AND (dental office[MeSH Terms] OR dental offices[MeSH Terms] OR “dental office” OR “dental offices” OR “in-office” OR "in office" OR office OR professional) AND (carbamide peroxide[MeSH Terms] OR carbamide[MeSH Terms] OR “carbamide peroxide” OR carbamide OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (hydrogen peroxide[MeSH Terms] OR “hydrogen peroxide” OR hydroperoxide OR perhydrol OR oxydol OR superoxol) AND (“tooth sensitivity” OR efficacy OR effectiveness OR sensitivity OR “color change” OR “shade change” OR longevity OR “color stability” OR “shade stability” OR “clinical behavior”)
Scopus	(“tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “tooth whitening” OR “dental whitening”) AND (“dental office” OR “dental offices” OR “in-office” OR "in office" OR office OR professional) AND (“carbamide peroxide” OR carbamide OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (hydrogen peroxide OR hydroperoxide OR perhydrol OR oxydol OR superoxol) AND (“tooth sensitivity” OR efficacy OR effectiveness OR sensitivity OR “color change” OR “shade change” OR longevity OR “color stability” OR “shade stability” OR “clinical behavior”)
Web of science	(“tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “tooth whitening” OR “dental whitening”) AND (“dental office” OR “dental offices” OR “in-office” OR "in office" OR office OR professional) AND (“carbamide peroxide” OR carbamide OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (hydrogen peroxide OR hydroperoxide OR perhydrol OR oxydol OR superoxol) AND (“tooth sensitivity” OR efficacy OR effectiveness OR sensitivity OR “color change” OR “shade change” OR longevity OR “color stability” OR “shade stability” OR “clinical behavior”)
Lilacs/BVS	(“tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “tooth whitening” OR “dental whitening”) AND (“dental office” OR “dental offices” OR “in-office” OR "in office" OR office OR professional) AND (“carbamide peroxide” OR carbamide OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (hydrogen peroxide OR hydroperoxide OR perhydrol OR oxydol OR superoxol) AND (“tooth sensitivity” OR efficacy OR effectiveness OR sensitivity OR “color change” OR “shade change” OR longevity OR “color stability” OR “shade stability” OR “clinical behavior”)
Embase	(“dental procedure”/exp OR “teeth bleaching agent/exp” OR “tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “dental bleaching”/exp OR “tooth whitening” OR “tooth whitening”/exp OR “dental whitening”) AND (“dental office” OR “dental facility”/exp OR “dental offices” OR “in-office” OR "in office" OR office OR “office”/exp OR professional) AND (“carbamide peroxide” OR “carbamide peroxide”/exp OR carbamide OR urea/exp OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (“hydrogen peroxide” OR “hydrogen peroxide”/exp OR hydroperoxide OR hydroperoxide/exp OR perhydrol OR oxydol OR superoxol) AND (“tooth sensitivity” OR “dentin hypersensitivity”/exp OR efficacy OR efficacy/exp OR effectiveness OR “clinical effectiveness”/exp OR sensitivity OR sensitivity/exp OR “color change” OR “color change”/exp OR “shade change” OR longevity OR “longevity” OR “color stability” OR “color stability”/exp OR “shade stability” OR “clinical behavior”)
Cochrane library	(“tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “tooth whitening” OR “dental whitening”) AND (“dental office” OR “dental offices” OR “in-office” OR "in office" OR office OR professional) AND (“carbamide peroxide” OR carbamide OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (hydrogen peroxide OR hydroperoxide OR perhydrol OR oxydol OR superoxol) AND (“tooth sensitivity” OR efficacy OR efectiveness OR sensitivity OR “color change” OR “shade change” OR longevity OR “color stability” OR “shade stability” OR “clinical behavior”)
Scielo	(“tooth bleaching” OR “teeth whitening” OR “teeth bleaching” OR “dental bleaching” OR “tooth whitening” OR “dental whitening”) AND (“dental office” OR “dental offices” OR “in-office” OR "in office" OR “office” OR “professional”) AND (“carbamide peroxide” OR “carbamide” OR “urea peroxide” OR “perhydrol urea” OR “urea hydrogen peroxide”) AND (“hydrogen peroxide” OR “hydroperoxide” OR “perhydrol” OR “oxydol” OR “superoxol”) AND (“tooth sensitivity” OR “efficacy” OR “effectiveness” OR “sensitivity” OR “color change” OR “shade change” OR “longevity” OR “color stability” OR “shade stability” OR “clinical behavior”)

After calibration, the studies had their duplicates removed and were selected by title and abstract. The articles were selected when they met the eligibility criteria. Two independent reviewers (P.W.M.B and K.S.S.) carried out the selection process. The electronic search was complemented by a manual search within the references of the selected articles for reading in full. The reviewers discussed any disagreement and solved the question by a consensus.

The same 2 reviewers summarized and extracted data from the articles, including study design, purpose, subjects, interventions, follow-up, outcomes and main results. A third reviewer (B.C.D.B.) was consulted to decide the case of any disagreement.

Risk of bias assessment

The risk of bias was evaluated using the Risk of Bias 2.0 (RoB2) tool for efficacy (color change) and bleaching sensitivity. Two reviewers (P.W.M.B and K.S.S.) independently assessed the risk of bias. Any disagreements were solved through discussion and consulting a third reviewer (B.C.D.B.). The risk of bias assessment consists of 5 domains that evaluate bias from the randomization process (domain 1), the bias of deviations from intended interventions (domain 2), bias due to missing outcome data (domain 3), bias from measuring the outcome (domain 4), bias due to selections of the reported result (domain 5), and overall

bias. In each domain, bias could be defined as low, some concerns and high, depending on the signaling questions' answers [13]. A study was considered as having a low risk of bias when the algorithm defined all domains as low after answering the signaling questions.

Certainty of the evidence

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool for efficacy (color change) and bleaching sensitivity. Two reviewers (P.W.M.B and K.S.S.) independently assessed the tool to rank the quality of the evidence. Any disagreements were solved through discussion and consulting a third reviewer (B.C.D.B.). With the GRADE tool, included randomized clinical trials (RCTs) are initially considered to provide high-quality evidence; however, the certainty of the evidence decreases to moderate, low, or very low if serious or very serious problems related to the risk of bias, imprecision, inconsistency, indirectness, and publication bias are identified [14]. Each outcome was analyzed separately and graded as very low, low, moderate, and high, considering a grouped analysis of studies.

RESULTS

Study selection

The search strategy was conducted on January 16, 2023. After database screening and duplicate removal, 1,510 studies were identified from January 1992 to January 2023. After title screening, 3 studies remained and were kept for full-text inspection after the abstract screening. All studies selected after applying inclusion criteria in this systematic review have been published in the last 5 years. The exclusion criteria, the number of excluded articles, and details on the search strategy are shown in **Figure 1**.

Characteristics of the included studies

The characteristics of the 3 selected studies are listed in **Table 2**. All selected studies were RCTs. Two studies used a parallel design, whereas the other used a split-mouth design [7-9].

The blindness of subjects, operators and examiner about the intervention during the trial is important. One study reported double blinding (subjects and examiner), one study reported single blinding (subjects), and one did not report any blinding [7-9]. In all selected studies, the population was individuals without caries and having good oral health, restoration-free anterior teeth who desired to bleach the teeth.

The number of patients per group included in these studies ranged from 40 to 45. The reported age range of individuals included in the clinical trials was approximately 19 to 27 years old, and the minimum age to participate in the study was 18. Most participants were female in all studies [7-9].

Regarding the bleaching protocol, 35% hydrogen peroxide and 37% carbamide peroxide gels were used in all studies [7-9]. The studies reported 2 or 3 bleaching sessions, with the application time of bleaching agents ranging from 40 to 50 minutes per session. The 35% hydrogen peroxide was applied once a week in all the studies [7-9]. The 37% carbamide peroxide was applied once a day with a 1-week interval [7,8] and twice daily for 3 consecutive days [9].

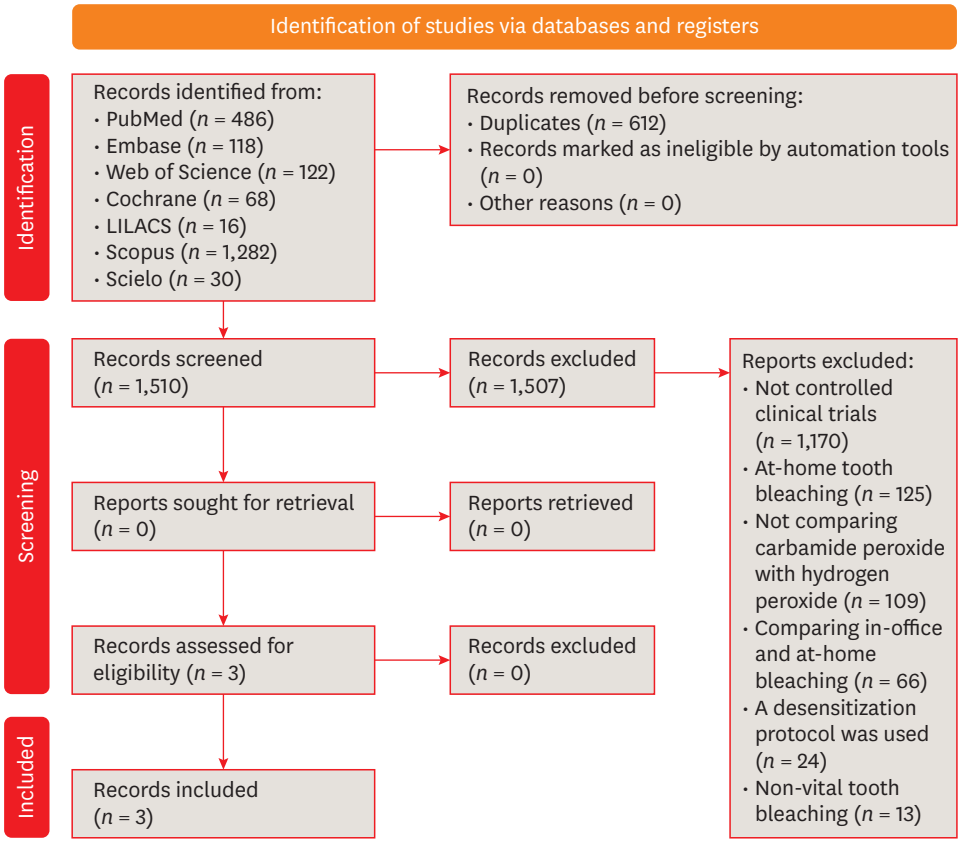

Figure 1. Flow diagram of the search process.

Efficacy (color change)

The efficacy (color change) was evaluated in all studies using different methods and time points [7-9]. One study used only a visual shade guide to assess color change [8]. Sixteen Vitapan Classical shade guide shades were displayed from the highest (B1) to the lowest (C4) value and converted to a number from 1 (B1) to 16 (C4) for statistical purposes. The assessment was made before and after 3 bleaching sessions, 3 and 6 months after the last bleaching session. After the last bleaching session, 3 and 6 months after the last bleaching session, the color change promoted by the 35% hydrogen peroxide and the 37% carbamide peroxide was statistically similar.

In contrast, others used a spectrophotometer to assess variations of luminosity (ΔL*), red-green axis (Δa*), blue-yellow axis (Δb*) and color change (ΔE) [7,9]. The study by Monteiro *et al.* [9] assessed ΔL*, Δa*, Δb*, and ΔE by comparing results immediately after the last bleaching section, 24 hours, 72 hours, 7 days and 15 days after the last bleaching session with baseline. The 37% carbamide peroxide showed statistically similar ΔE to the 35% hydrogen peroxide in all time points assessed. Peixoto *et al.* [7] assessed ΔL*, Δa*, Δb*, and ΔE by comparing results after the first bleaching session, after the second bleaching session and 30 days after the second bleaching session with baseline. The 35% hydrogen peroxide showed statistically higher ΔE than the 37% carbamide peroxide in all time points assessed.

In the studies that performed 3 bleaching sessions, the color change promoted by the 37% carbamide peroxide was similar to the 35% hydrogen peroxide from the end of the procedure

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Table 2. Main results of the articles included in this systematic review

Study	Study design, purpose, and subjects	Intervention and follow-up	Measurement of the outcomes	Main results
Abrantes *et al.* [8]	Study design - Split-mouth, randomized double-blinded (examiner and participants) clinical trial Purpose - To evaluate the efficacy (color change), longevity, and bleaching sensitivity of in-office bleaching with 37% CP compared with 35% HP Subjects - 45 subjects - 60% female and 40% male - Ranging from 19 to 27 yr	Intervention - 37% CP and 35% HP - One 40 minutes application once a wk for 3 Follow-up - Up to 6 mon	Efficacy (color change) - VCSG - Before and after 3 bleaching sessions, 3 and 6 months after the last bleaching session Bleaching sensitivity - Intensity of bleaching sensitivity in a 0–10 cm VAS immediately after each bleaching session (corresponding to the pain felt during the session), from one to 7 days after each bleaching session, 3 and 6 months after the last bleaching session - GIS: calculated by summing 3 values reported by the individuals immediately after each bleaching session (corresponding to the pain felt during the session)	Efficacy (color change) - 37% CP and 35% HP provided statistically similar color to the teeth at the end of the last bleaching session and 3 and 6 mon after the last bleaching session Bleaching sensitivity - 35% HP had statistically higher GIS than CP - 37% CP showed statistically lower sensitivity levels during bleaching sessions and in 2 subsequent days than 35% HP
Monteiro *et al.* [9]	Study design - Parallel, randomized clinical trial Purpose - To evaluate the efficacy (color change) of in-office bleaching with 37% CP compared with 35% HP Subjects - 40 subjects - 72.5% female and 27.5% male (not informed by group) - Age range not informed	Intervention - 37% CP and 35% HP - 35% HP: One 45 min application once a wk for 3 wk - CP: One 50 min application twice a day for 3 consecutive days Follow-up - Up to 15 days	Efficacy (color change) - Spectrophotometer - ΔL*, Δa*, Δb*, and ΔE by comparing results immediately after the last bleaching section, 24 hr, 72 hr, 7 days, and 15 days after the last bleaching session with baseline Bleaching sensitivity - Not evaluated	Efficacy (color change) - 37% CP and 35% HP provided statistically similar color change in all time points Bleaching sensitivity - Not evaluated

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Table 2. (Continued) Main results of the articles included in this systematic review

Study	Study design, purpose, and subjects	Intervention and follow-up	Measurement of the outcomes	Main results
Peixoto *et al.* [7]	Study design - Parallel, randomized, single-blinded (participants) clinical trial Purpose - Evaluate the efficacy (color change) and bleaching sensitivity of in office bleaching with 37% CP compared with 35% HP Subjects - 40 subjects - HP group: 60% female and 40% male, 23.5 ± 4.5 yr old - CP group: 45% female and 55% male, 23.8 ± 3.5 yr old	Intervention - 37% CP and 35% HP - 35% HP: 3 15 min applications (45 min), once a wk for 2 wk - 37% CP: One 40 min application once a wk for 2 wk Follow-up - Color change: up to 30 days - Bleaching sensitivity: up to 24 hr after the last bleaching session	Efficacy (color change) - Spectrophotometer - ΔL*, Δa*, Δb*, and ΔE by comparing results after the first bleaching session, after the second bleaching session and 30 days after the second bleaching session with baseline Bleaching sensitivity - Relative risk during the first bleaching session, 24 hr after the first bleaching session, during the second bleaching session, and 24 hr after the second bleaching session - Reported bleaching sensitivity score (none, mild, moderate, considerable, severe) during, the peak after and 24 hr after the first bleaching session, during, the peak after and 24 hr after the second bleaching session - Intensity of bleaching sensitivity in a 0–10 cm VAS during, the peak after and 24 hr after the first bleaching session, during, the peak after and 24 hr after the second bleaching session	Efficacy (color change) - The 35% HP showed statistically higher ΔE than the 37% carbamide peroxide in all time points Bleaching sensitivity - The relative risk of individuals reporting bleaching sensitivity was statistically higher for 35% HP than the 37% CP during bleaching sessions - The score of bleaching sensitivity was statistically higher for the 35% HP during the bleaching sessions and in the peak after the bleaching sessions - The intensity of bleaching sensitivity was also statistically higher for the 35% HP during the bleaching sessions and in the peak after the bleaching sessions

CP, carbamide peroxide; HP, hydrogen peroxide; VCSG, vitapan classical shade guide; VAS, visual analog scale; GIS, global immediate sensitivity; BP, bleaching procedure.

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to the last time point analyzed [8,9]. Conversely, the 37% carbamide peroxide promoted lower tooth bleaching efficacy than the 35% hydrogen peroxide during and at the end of the procedure in the study that enrolled 2 bleaching sessions [7]. A meta-analysis could not be executed due to the different experimental designs of primary studies.

Bleaching sensitivity

The bleaching sensitivity was evaluated in 2 studies [7,8]. One study assessed bleaching sensitivity through 3 parameters at different time points [7]: 1) relative risk during the first bleaching session, 24 hours after the first bleaching session, during the second bleaching session, and 24 hours after the second bleaching session; 2) reported bleaching sensitivity score (none, mild, moderate, considerable, severe) during, the peak after and 24 hours after the first bleaching session, during, the peak after and 24 hours after the second bleaching session; and 3) intensity of bleaching sensitivity in a 0–10 cm visual analog scale (VAS) during, the peak after and 24 hours after the first bleaching session, during, the peak after and 24 hours after the second bleaching session. The study also related the self-perception of individuals to bleaching procedures performed using questions not exactly related to color change and bleaching sensitivity. The relative risk of individuals reporting bleaching sensitivity was statistically higher for 35% hydrogen peroxide than the 37% carbamide peroxide during the first and second bleaching sessions [7]. The score of bleaching sensitivity was statistically higher for the 35% hydrogen peroxide during the first and second bleaching sessions and in the peak after the first and second bleaching sessions [7]. The intensity of bleaching sensitivity was also statistically higher for the 35% hydrogen peroxide during the first and second bleaching sessions and in the peak after the first and second bleaching sessions [7].

The other study assessed bleaching sensitivity through 2 parameters at different time points [8]: 1) intensity of bleaching sensitivity in a 0–10 cm VAS immediately after each bleaching session (corresponding to the pain felt during the session), from one to 7 days after each bleaching session, 3 and 6 months after the last bleaching session; and 2) the global immediate sensitivity (GIS), calculated by summing 3 values reported by the individuals immediately after each bleaching session (corresponding to the pain felt during the session). The intensity of bleaching sensitivity was statistically higher for the 35% hydrogen peroxide during the first, second, and third bleaching sessions, 24 hours and 48 hours after the first, second, and third bleaching sessions [8]. The GIS promoted by the 35% hydrogen peroxide was statistically higher than the 37% carbamide peroxide. A meta-analysis could not be executed due to the different experimental designs of primary studies.

Assessment of the risk of bias

Regarding randomization, 2 out of the 3 studies reported the randomization method used [7,8]. Only one of the 3 studies reported allocation concealment, and one needed to report more information about the randomization process, although it was mentioned [8,9]. Blinding was reported only in 2 studies [7,8].

For the color change risk of bias assessment, 2 studies were judged as having a low risk of bias [7,8]. For bleaching sensitivity, Peixoto *et al.* [7] and Abrantes *et al.* [8] were classified as low risk of bias studies (**Figure 2**). One study was judged as having some concerns due to the absence of information about the randomization process and the high risk of bias for deviations from the intended interventions, missing outcome data and selective outcome reporting (**Figure 3**) [9].

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Certainty of the evidence

The certainty of the evidence for the included studies that assessed color change and bleaching sensitivity was low and moderate, respectively (**Table 3**). The level was downgraded by serious inconsistency due to high heterogeneity across the studies and serious imprecision of estimates, hindering the evidence's accuracy.

DISCUSSION

This pioneer systematic review aimed to summarize and analyze the methods and results from clinical trials assessing the efficacy of carbamide peroxide for in-office tooth bleaching and bleaching sensitivity levels compared to hydrogen peroxide. After compiling, analyzing and summarizing the primary studies, the 37% carbamide peroxide showed similar efficacy

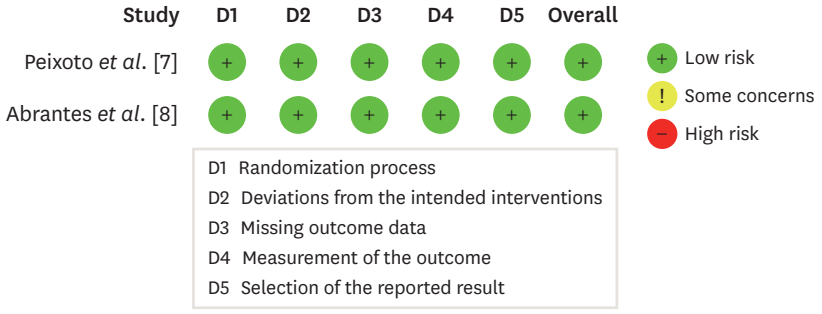

Figure 2. Summary of risk of bias assessment for color change.

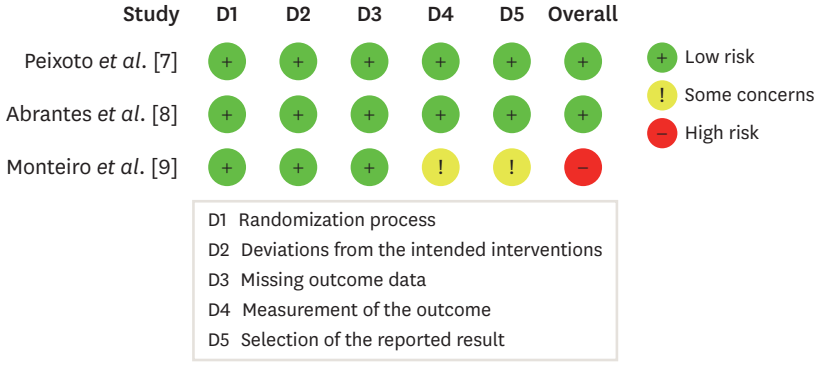

Figure 3. Summary of risk of bias assessment for bleaching sensitivity.

Table 3. Certainty of the evidence

Outcome	Certainty assessment							Number of subjects		Certainty
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CP	HP	
Color change	3	Randomized trials	Serious*	Not serious†	Not serious	Serious†	None	85/170 (50.0%)	85/170 (50.0%)	⊕⊕○○ Low
Bleaching sensitivity	2	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	65/130 (50.0%)	65/135 (50.0%)	⊕⊕⊕○ Moderate

CP, carbamide peroxide; HP, hydrogen peroxide.
*Moderate and serious risk of bias on the included studies.
†Imprecise estimates.

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to the 35% hydrogen peroxide once more than 2 bleaching sessions were performed and less bleaching sensitivity. However, the certainty of the evidence was not high. Once isolated data from primary studies were compiled, analyzed, and summarized and certainty of the evidence formulated, novel data was obtained to make this result innovative and original.

Two studies employed 3 clinical bleaching sessions, and 1 employed 2 sessions [7-9]. Despite the variation in the number of sessions, this is a common characteristic in tooth bleaching clinical studies, and this diversity does not necessarily imply bias in the studies. However, the variety in the methods adopted by the authors of primary studies included was considered not to establish a high certainty of the evidence of the present synthesis.

Despite differences regarding the mode/method of application of the bleaching gel employed in each study, these reflect the multifaceted reality of clinical practice involving tooth bleaching [7-9,15]. However, despite the absence of a standardized method, a reflection of this same reality, in all studies, the method followed the manufacturer's guidelines to obtain results for efficacy (color change) and bleaching sensitivity [15,16].

Several reports have provided explanations for the etiology of bleaching sensitivity, such as increased flow of dentinal fluid with consequent mechanical excitation of the nerve fibers, as well as the oxidative effects of the treatment products on the pulp tissue [17-19]. When the bleaching gel comes in contact with the dental structures, reactive oxygen species (ROS) are released and may reach the dentin-pulp complex, triggering an inflammatory process in pulp cells such as dental pulp stem cells [19]. The bleaching gel can stimulate intracellular Ca^{2+}, ATP, and extracellular ATP release in a dose-dependent manner and increase the mRNA and protein levels of hyperalgesia (TRPA1 and PANX1) and inflammation (TNFα and IL6) factors [20]. A highly concentrated 40% hydrogen peroxide increased the release of hyperalgesia and inflammation factors more than a 15% carbamide peroxide [20]. Once the decrease in intracellular Ca^{2+}, ATP, and extracellular ATP expression was obtained when the TRPA1 inhibitor (HC030031) was administrated, it was concluded that TRPA1 plays a critical role in sensitivity and inflammation after tooth bleaching [20].

The breakdown of carbamide peroxide generates approximately 1-third of hydrogen peroxide [21]. Likely, the 37% carbamide peroxide used in the studies included in this review resulted in approximately 12% hydrogen peroxide, which would stimulate the production of less ROS, hyperalgesia and inflammation factors than the 35% hydrogen peroxide. This difference in the kinetics of active oxygen release implies the need for more sessions with carbamide peroxide to achieve results similar to hydrogen peroxide. Despite the requirement for more sessions, the lower formation of ROS from peroxide decomposition minimizes the primary side effect of tooth bleaching: tooth sensitivity [7,22]. Thus, the results of studies that assessed bleaching sensitivity and found decreased levels caused by the 37% carbamide peroxide compared to the 35% peroxide can be associated with the decreased production of ROS and hyperalgesia and inflammation factors [21].

One can highlight that the critical time point to generate bleaching sensitivity began during bleaching sessions and continued up to 48 hours in the studies included [7,8]. Thus, choosing 37% carbamide peroxide as an in-office bleaching agent might provide more comfortable bleaching sessions for individuals undergoing in-office tooth bleaching. On the other hand, the interpretation of this data should be made with caution. Although the studies were classified as having a low risk of bias, the certainty of the evidence was moderate, not high [7,8].

The studies by Peixoto *et al.* [7] and Abrantes *et al.* [8] did not mention the confidence interval, increasing its inaccuracy. The longer the confidence interval is, the more inaccurate the effect estimation. That is, less certainty that a real effect will be applied to the patient [14]. If the confidence interval is shorter, it might have no effect or an effect favorable to another substance [14]. This justified downgrading the level of evidence due to imprecision. By that, it is highly advised that confidence intervals should be reported. Also, the split-mouth design might be recommendable, in which both interventions are applied to the same patient, allowing a more accurate response concerning the interventions' effect, as adopted in Abrantes *et al.* [8] These results highlight the importance of better-described methodological parameters related to quality assessment in future studies. In addition, since studies with a low risk of bias are more reliable, future studies need to be more cautiously planned to avoid an increase in the risk of bias.

Concerning bleaching efficacy, this systematic review's results showed that 37% carbamide peroxide and 35% hydrogen peroxide can promote a similar bleaching effect after 3 bleaching sessions. Since carbamide peroxide generates less and slower ROS than hydrogen peroxide, the 2 bleaching sessions were insufficient to get teeth as white as hydrogen peroxide. The professional should choose the 37% carbamide peroxide for in-office tooth bleaching after considering how fast the individual expects tooth bleaching to occur. Using the 37% carbamide peroxide instead of the 35% hydrogen peroxide might guarantee a less bleaching sensitivity procedure but involves at least 3 bleaching sessions. However, as it was reported by Monteiro *et al.* [9], using 37% carbamide peroxide on 3 consecutive days twice a day provided similar bleaching efficacy to 35% hydrogen peroxide applied in 3 bleaching sessions with a 1-week interval and might be an option for obtaining faster results.

To assess color change, shade guides and electronic devices can measure the tooth color in at least 2 moments. While color assessment with electronic devices provides objective and accurate data, they involve a higher cost, and some factors such as contour, translucency and texture of teeth may influence their color measurements [23]. Indeed, visual assessment of tooth color using the Vitapan Classical shade guide was found to be a valid and suitable method for color matching of teeth in comparison with digital devices such as Vita EasyShade spectrophotometer (Vita Zahnfabrik, Bad Säckingen, Germany) [24-26]. Thus, the fact that Abrantes *et al.* [8] used a visual and not a digital method to assess the color change does not negatively affect the results' certainty.

Two of the 3 studies included in the color change analysis were classified as low risk of bias [7,8]. They correctly reported the randomization process, which needs to be prepared previously, concealed until the application, and described in detail in the methods section [7,8]. However, another study had a high risk of bias due to the absence of data about the randomization process, deviations from the intended interventions, missing outcome data and selection of the reported result [9]. When data from the randomization process is absent, it may result in the unknowingness of prognostic features. Therefore, no cause-effect associations can be established from a RCT [13]. Randomization process failures can result in a selection bias that compromises safety and confidence in the obtained results and confuses assertive clinical decision-making in professional practice [13]. In addition, 1 study gave no information on the number of subjects lost to follow-up, implying a serious concern over the availability and accuracy of obtained results [9,14]. Due to the inconsistencies reported, the certainty of the evidence for efficacy (color change) needed to be graded as low. Thus, the results of this outcome should be interpreted with caution. Further randomized split-mouth

clinical trials should be performed to provide data to strengthen the evidence that the 37% carbamide peroxide is as effective as the 35% hydrogen peroxide after 3 bleaching sessions.

The great variation in the methods used by the authors of primary studies included in this systematic review impaired the data metanalysis. Although the present investigation included a few studies ($n = 3$), the great variation in the methods of tooth bleaching clinical trials evaluating color change was already reported in the literature, making a metanalysis difficult [16].

The present systematic review included at most 3 studies previously published in the literature to answer the question: Can carbamide peroxide be as effective as hydrogen peroxide and cause less in-office bleaching sensitivity? Due to a low number of studies compiled, inconsistencies in the methods and data interpretation of one of them greatly impact the overall certainty of the evidence of the outcomes analyzed. Thus, further well-designed split-mouth RCTs that detail the methods used are necessary to strengthen the evidence regarding the efficacy and induced bleaching sensitivity of the 37% carbamide peroxide compared with 35% hydrogen peroxide for in-office tooth bleaching.

The present systematic review focused on specific aspects of the literature and did not directly address the comparison between high-concentration carbamide peroxides and low-concentration hydrogen peroxides. Thus, further synthesis studies should compare bleaching efficacy and sensitivity between high-concentration carbamide peroxides and low-concentration hydrogen peroxides.

CONCLUSIONS

Within the limitations of this study, the evidence from this systematic review suggested that the efficacy of 37% carbamide peroxide might be similar to the 35% hydrogen peroxide for in-office tooth bleaching when at least 3 applications are performed. Using 37% carbamide may promote less sensitive in-office tooth bleaching. However, these results should be interpreted with caution before any decision is made due to the low and moderate certainty of the evidence, respectively.

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