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**Desempenho do peróxido de hidrogênio no
clareamento interno de dentes descoloridos:
uma revisão sistemática**

Araçatuba – SP

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Barbara de Moura Pereira

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uma revisão sistemática**

Dissertação apresentada ao programa de Pós-Graduação da Faculdade de Odontologia de Araçatuba, Universidade Estadual Paulista “Júlio Mesquita Filho” – UNESP, como parte dos requisitos para obtenção do título de Mestre em Ciência Odontológica, Área de concentração em Endodontia.

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Shirley e Marcelo, que sempre
acreditaram em mim. E ao meu avô,
Manoel Saraiva, que nos deixou ao longo
dessa jornada e deixou saudade.*

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*Você não pode ser tudo o que você quer ser antes do
seu tempo.*

(Billy Joel)

Resumo

Pereira, BM. **Desempenho do peróxido de hidrogênio no clareamento interno de dentes descoloridos: uma revisão sistemática.** [Dissertação](Mestrado). Araçatuba: UNESP — Univ. Estadual Paulista; 2022.

Esta revisão sistemática (PROSPERO CRD42022304257) avaliou o desempenho do gel clareador à base de peróxido de hidrogênio (HP) no clareamento interno de dentes escurecidos em comparação com outros géis clareadores. Foi realizada uma busca sistemática (PubMed/MEDLINE, Scopus, Embase e Cochrane Library) até dezembro/2021, sendo elegíveis apenas estudos clínicos que comparassem o HP como clareador interno. O desfecho primário foi a eficácia do clareamento, enquanto a citocina do fluido crevicular gengival e a avaliação da satisfação do paciente foram desfechos secundários. O risco de viés foi avaliado. Dos 449 estudos encontrados, 8 foram incluídos. A eficácia do clareamento foi avaliada por escalas de cores (3 estudos), por espectrofotômetro (2 estudos) ou pela combinação dos dois (3 estudos). Três estudos analisaram citocinas no fluido crevicular gengival. Quatro estudos avaliaram a satisfação do paciente usando o Oral Health Impact Profile (OHIPQ) e o questionário Psychosocial Impact of Dental Aesthetics (PIDAQ). Todos os estudos compararam HP com peróxido de carbamida (CP), mas um desses estudos utilizou uma combinação de HP e perborato de sódio (SP). O peróxido de hidrogênio teve maior eficácia de clareamento do que o CP em três estudos e foi semelhante ao CP nos outros quatro estudos. Em um estudo, o HP foi mais eficaz ou semelhante ao CP, dependendo da análise realizada. Tanto o HP quanto o CP aumentaram as citocinas no fluido crevicular gengival sem diferença entre eles e foram satisfatoriamente semelhantes na qualidade de vida/satisfação do paciente. Baixo risco de viés foi observado.

Concluimos, que o Peróxido de Hidrogênio é mais eficaz que o CP quanto à eficácia clareadora ao promover um aumento na qualidade de vida/satisfação do paciente e de citocinas no fluido crevicular gengival, semelhante ao CP.

Palavras-chave: Clareamento dental, descoloração dentária, peróxido de hidrogênio, clareamento interno, clareamento intracoronal.

Abstract

Pereira, BM. **Performance of hydrogen peroxide on internal whitening of teeth discolored: a systematic review.** [Dissertação](Mestrado). Araçatuba: UNESP — Univ. Estadual Paulista; 2022.

This systematic review (PROSPERO CRD42022304257) evaluated the performance of hydrogen peroxide (HP)-based whitening gel in internal whitening of discolored teeth compared to other whitening gels. A systematic search was performed (PubMed/MEDLINE, Scopus, Embase, and Cochrane Library) until December/2021, and only clinical studies that compared HP as an internal bleacher were eligible. The primary outcome was whitening efficacy, while gingival crevicular fluid cytokine and patient satisfaction assessment were secondary outcomes. The risk of bias was evaluated. Of 449 studies found, 8 were included. Whitening efficacy was assessed by color scales (3 studies), by spectrophotometer (2 studies), or a combination of both (3 studies). Three studies analyzed cytokines in the gingival crevicular fluid. Four studies evaluated patient satisfaction using the Oral Health Impact Profile (OHIPQ) and Psychosocial Impact of Dental Aesthetics (PIDAQ) questionnaire. All studies compared HP with carbamide peroxide (CP) but one of these studies used a combination of HP and sodium perborate (SP). Hydrogen Peroxide had higher whitening efficacy than CP in three studies and was similar to CP in the other four studies. In one study, HP was more effective or similar to CP depending on the analysis performed. Both HP and CP increased cytokines in gingival crevicular fluid with no difference between them and were satisfactorily similar in quality of life/patient satisfaction. Low risk of bias was observed. Concluded, the Hydrogen Peroxide is more effective than CP regarding whitening efficacy while promoting an increase in the patient's quality of life/satisfaction and of cytokines in the gingival crevicular fluid, similar to CP.

Keywords: Tooth whitening, tooth discoloration, hydrogen peroxide, internal whitening, intracoronal whitening.

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Performance of hydrogen peroxide on internal whitening of teeth discolored: a systematic review

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Performance of hydrogen peroxide on internal whitening of teeth discolored: a systematic review

Abstract

Introduction: This systematic review (PROSPERO CRD42022304257) evaluated the performance of hydrogen peroxide (HP)-based whitening gel in internal whitening of discolored teeth compared to other whitening gels.

Methods: A systematic search was performed (PubMed/MEDLINE, Scopus, Embase, and Cochrane Library) until December/2021, and only clinical studies that compared HP as an internal bleacher were eligible. The primary outcome was whitening efficacy, while gingival crevicular fluid cytokine and patient satisfaction assessment were secondary outcomes. The risk of bias was evaluated.

Results: Of 449 studies found, 8 were included. Whitening efficacy was assessed by color scales (3 studies), by spectrophotometer (2 studies), or a combination of both (3 studies). Three studies analyzed cytokines in the gingival crevicular fluid. Four studies evaluated patient satisfaction using the Oral Health Impact Profile (OHIPQ) and Psychosocial Impact of Dental Aesthetics (PIDAQ) questionnaire. All studies compared HP with carbamide peroxide (CP) but one of these studies used a combination of HP and sodium perborate (SP). Hydrogen Peroxide had higher whitening efficacy than CP in three studies and was similar to CP in the other four studies. In one study, HP was more effective or similar to CP depending on the analysis performed. Both HP and CP increased cytokines in gingival crevicular fluid with no difference between them and were satisfactorily similar in quality of life/patient satisfaction. Low risk of bias was observed.

Conclusion: Hydrogen Peroxide can be more effective than CP regarding whitening efficacy while promoting an increase in the patient's quality of life/satisfaction and of cytokines in the gingival crevicular fluid, similar to CP.

Keywords: Tooth whitening, tooth discoloration, hydrogen peroxide, internal whitening, intracoronar whitening.

Introduction

Dental esthetics is associated with quality of life, and dental discoloration is a negative factor with high psychosocial impact^{1,2}. Tooth discoloration depends on the accumulation of pigments present on the surface or in its structure for different causes being classified as intrinsic or extrinsic, or even a combination of the two^{3,4}. When differentiating tooth discoloration, extrinsic discoloration occurs by the external deposition of chromogens on the tooth surface derived from some foods with pigments ingestion, tobacco, mouthwashes, or bacterial plaque. On the other hand, intrinsic ones can occur in a systemic, metabolic, genetic, or local way^{5,6}.

In non-vital teeth, intrinsic local discoloration is associated with trauma, pulp necrosis, intrapulpal hemorrhage, pulp tissue remnants after endodontic therapy, root resorption, aging, presence of endodontic materials, restorative materials, filling materials, and intracanal medications⁶. The teeth become darkened or grayish due to the extravasation of blood components into the dentinal tubules, undergoing hemolysis and release of iron, which when reacting with hydrogen sulfide forms iron sulfide⁷. The presence of root canal filling materials in contact with the coronal dentin of the pulp chamber is another source of pigmentation, the substances in the composition of the materials used in the treatment are capable to induce discolorations⁸.

When they are not removed only with brushing or mechanical procedures, to reverse them it is necessary to opt for tooth whitening or restorative procedures, and depending on the need, performing both⁹. Internal whitening is the treatment of discolored non-vital teeth, it is the least invasive option and the treatment of choice for these cases¹⁰. In summary, it comprises placing the whitening agent temporarily in the pulp chamber until the desired color is reached, which is a simple, low-cost, and conservative method that can be applied to permanent and deciduous teeth¹¹.

Among the most commonly used whitening agents are hydrogen peroxide (HP) in concentrations from 10% to 45%, sodium perborate (SP) which can be dissolved in water or HP, and carbamide peroxide (CP) in concentrations from 10% to 100% ready-to-use powder or gel¹². Intracoronary whitening agents act by producing free radicals that degrade the chromophore structure of organic molecules that darken teeth¹³. The whitening agent concentration, application time, type, and tooth discoloration intensity are important factors for whitening effectiveness and the final outcome¹⁴.

Hydrogen Peroxide is a thermally unstable, low molecular weight free radical that penetrates enamel and dentin by diffusion. The mechanism of action occurs by the breakdown of

complex molecules of organic pigments in the tissues that are broken into simpler hydrophilic molecules through an oxidation-reduction reaction by the action of perhydroxyl ions originating from the degradation of HP inside the dentinal tubules, resulting in the whitening of teeth¹⁵.

However, the use of this internal whitening agent is related to cervical resorptions¹⁶. The SP also releases oxygen, and so, it has been discussing the effectiveness but also the damage of whitening agents, especially the external cervical resorption¹⁷. A previous study showed that the incidence of external cervical resorption was 6.9% after use of SP and 30% after use of HP¹⁸, while other study showed that SP with water presented similar whitening effectiveness compared to other whitening materials, and prevented the occurrence of cervical resorption¹⁶. Thus, as HP is one of the most used whitening agents by dentists, it is important to evaluate the patient's satisfaction regarding its internal whitening effectiveness associated to the presence of cytokine in gingival crevicular fluid. A recent systematic review¹⁹ concluded that there is not a direct relationship between the effectiveness of HP compared to other whitening agents remaining the question about the most effective agent. Furthermore, patient satisfaction and the presence of cytokines in the crevicular fluid were not considered in the previous review as the secondary outcome.

Thus, this systematic review aims to evaluate the whitening efficacy of HP compared to other whitening agents as the primary and patient satisfaction and the presence of cytokines in the crevicular fluid as the secondary outcome. Only clinical studies were considered eligible.

Materials and Methods

The reporting of this present study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^{20,21}. This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42022304257.

Eligibility Criteria

The inclusion criteria were 1) randomized clinical trial studies; 2) studies that evaluated the effectiveness of the HP whitening gel on internal whitening; and 3) studies that present a bleached group with another whitening agent. The exclusion criteria were 1) studies that analyzed internal whitening without HP as comparison; 2) whitening protocols of vital teeth; 3) studies for which the full text was not available.

The PICO (population-intervention-comparison-outcome) approach was used to address the following question: “Is the hydrogen peroxide whitening agent efficient in the internal whitening compared to other whitening agents?”. In this process, the population (P) was patients with teeth undergoing internal whitening. The intervention (I) was internal whitening with HP. The comparison (C) was internal whitening with another whitening agent. The primary outcomes (O) evaluated was the whitening effectiveness. The cytokine in the gingival crevicular fluid and patient satisfaction assessments were found as secondary outcomes.

Search Strategy and Information Sources

Electronic searches were conducted in PubMed/MEDLINE, Scopus, Embase, and Cochrane Library until December-2021. The grey literature was also consulted through OpenGrey. The search strategy was firstly defined for the MEDLINE database via PubMed using a controlled vocabulary (MeSH terms) and free keywords. The MEDLINE search was also adapted to the other databases, as shown in Supplementary Table S1. Manual searches were also performed in the reference lists of the included articles to find additional studies. No restrictions to publication date or language were considered.

Study selection

The articles retrieved by the literature search were selected by two independent authors (B.M.P. and V.G.O.) in a two-step procedure. In Step 1, the two authors appraised the titles and abstracts of studies that met the eligibility criteria. The studies were arranged alphabetically by title, and duplicates were identified and removed manually. In Step 2, the two authors assessed the full texts of each study. Only studies in which the full text fulfilled the proposed eligibility criteria were included in this review. Any disagreements between the two authors were resolved through discussion, and when necessary, a third author (F.B.) was consulted.

Data Collection and Analyses

One author collected data (B.M.P.) from the included studies and tabulated it to analyze the results. The following data were retrieved: author and year, cause of tooth discoloration, groups and internal whitening protocol, period of follow-up, outcomes of color assessment, cytokine in gingival crevicular fluid assessment, and patient satisfaction. A second author (V.G.O.) revised the collected data.

Risk of bias assessment

Two investigators (B.M.P. and V.G.O.) independently assessed the methodological quality of the selected studies, according to their levels of evidence as proposed by the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Randomized Controlled Trials. The assessed items of the JBI tool were: adequate randomization, allocation concealment, baseline equivalence of treatments, blinding, similarity of groups, satisfactory follow-up, patient evaluation in the groups, measurement standardization, method treatment, adequate statistical analysis, adequate trial design. Each item was scored using a 3-point scale: 0, content not reported; 1, content reported inadequately; and 2, content sufficiently reported²². Doubts and discrepancies between the investigators were discussed to enter consensus, and if not resolved, a third examiner (A.H.R.P.) was consulted.

Results

Selected Studies

The selection process of the articles is presented in Figure 1. A total of 449 articles were found in the databases 'search. After the first screening and removal of duplicates, 18 studies were selected. These studies were then subjected to full-text evaluation that resulted in the exclusion of 10 studies²³⁻³² for not having a bleaching group with HP^{24, 25, 31, 32}, in vitro study²⁸⁻³⁰ or not having a group with bleaching with another bleaching agent for comparison²⁵⁻²⁷. Finally, 8 studies were included in this review³³⁻⁴⁰.

The assessed Cohen kappa coefficient value for the inter-investigator agreement was equal to 0.959 for PubMed, 0.837 for Scopus, 0.889 for Embase, 1.000 for the Cochrane Library, and 1.000 for OpenGrey. These values indicated an almost perfect agreement among reviewers according to the scale of Landis & Koch (1977)⁴¹.

Characteristics of the Included Studies

The characteristics of the studies are depicted in Table 1. Six studies used n of 50 patients³³⁻³⁹, one study used a n of 47 patients³⁷, and one study used n of 14 patients⁴⁰. The age of the patients ranged from 18 to 65 years. Regarding the teeth selected for the intervention, only one article reported using only anterior teeth⁴⁰, while the other studies³³⁻³⁹ did not identify the teeth that were evaluated.

The baseline color used in studies was A2 or darker³³⁻⁴⁰. The cause of tooth discoloration was reported as trauma or caries. The majority of studies (7 studies)³³⁻³⁹ compared whitening gels

of 35% HP with 37% CP, and one study used a combination of HP and SP⁴⁰. The gels were used in different protocols.

To report the color changes, three studies used the Shade guide - Bleached color scale^{33,37,39}, two studies used just Spectrophotometer - Vita EasyShade Compact^{38,40}, while three studies associated both spectrophotometer and color scale Shade guide - Classic Vita^{35,36} and Bleached³⁴.

The inflammatory response to the whitening procedure was described by evaluating the cytokine in gingival crevicular fluid assessment of interleukin (IL)-1 β and Receptor Activator for Nuclear Factor Kappa β Ligand (RANK-L), in three studies^{33,37,39}. To assess patient satisfaction, four articles^{34-36,38} used the Oral Health Impact Profile (OHIPQ) and Psychosocial Impact of Dental Aesthetics (PIDAQ) questionnaires.

The post-intervention follow-up ranged from immediately after whitening to 5 years and was followed up weekly, monthly, and annually. The data regarding study outcomes are summarized in Table 2 and described below.

Color assessment

The color evaluation showed a higher whitening efficacy of HP in comparison with CP in three studies^{33,37,39}, and similar to CP in others four studies^{34-36,38}. In one study, HP was more effective in all periods, but depending on the analysis performed was similar to CP.

Cytokine in gingival crevicular fluid assessment

All studies observed an increase of cytokines in crevicular fluid gingival, in relation to the follow-up time 35% HP showed values higher than 37% CP in two studies^{33,37}. One study showed that the increase of IL-1 β on crevicular fluid gingival was higher for 37% CP than 35% HP³⁹.

Patient's satisfaction

All studies evaluated the patient's satisfaction using OHIPQ and PIDAQ comparing HP and CP^{35,36,38,39}, and they both showed similar and positive impacts in self-perception and psychosocial impact independent of the follow-up period.

Risk of bias assessment

Critical appraisal of eligible studies is presented in Supplementary Table 2 and Figure 2 ranging from high risk to low overall. All the included studies showed a similarity of groups,

measurement standardization, and a reliable method of analysis. Conversely, information regarding blinding procedures among participants, operators, and evaluators was frequently missing or reported inadequately. Low risk of bias was observed in the remaining domains among most studies.

Discussion

According to the articles included in this systematic review, it is possible to state that HP has significant internal whitening efficacy which is higher in some studies when compared to the CP whitening gel. Regarding crevicular fluid cytokines, and in relation to patient satisfaction, there was no significant difference between HP and CP. This way, it is possible to infer that HP may be superior to CP because it is more efficient on the whitening process and has the same influence on cytokine expression. However, despite the concern about the harmful effects of HP gel, the studies carried out have not compared this whitening agent with any other than CP. Thus, despite the low risk of bias found in this systematic review, the importance of comparing HP with other bleaching gels in randomized clinical trials is highlighted.

The color change (ΔE) was compared between 35% HP and 37% CP in seven studies³³⁻³⁹, and HP was more statistically significant in four of them. This corroborates with the previous systematic review that evaluated the efficacy of internal whitening agents and found HP to have a significant whitening effect on discolored teeth¹⁹. However, HP was similar to CP in the others three studies of this present review, demonstrating that there is no strong difference between the agents. This result is also observed in laboratory studies. Lim et al. (2004)⁴¹ described that 35% CP and 35% HP were equally effective for internal whitening of artificially blood-stained and obturated roots, while Behl et al. (2020)¹¹ evaluated the effectiveness of 10% CP, 9.5% HP and 10% SP on internal bleaching of permanent and primary teeth artificially blood-stained, and all bleaching agents were also equally effective.

The evaluation of whitening efficacy was performed by color scales in most of the selected studies³³⁻³⁹, or by spectrophotometer^{34-38,40}. Although the visual method is widely used through color scales, it is a very subjective and can lead to a compromised final result differently from that obtained using spectrophotometry or chromometer⁴². The difference in the results of these analyzes can be observed in one study where HP was more effective in the visual color scale but it was similar to CP in the spectrophotometer data³⁶. Thus, this review highlights the importance of further studies with non-subjective analyzes in the assessment of whitening efficacy.

Patient satisfaction was found as secondary outcome in the present review. To assess patient satisfaction four studies applied the OHIPQ and PIDAQ questionnaires, where they compared HP and CP performance^{34-36,38}. The PIDAQ assesses the impact of oral problems on the patient's daily life. This questionnaire is composed of 23 items distributed into four psychosocial impact subscales (dental self-confidence, social impact, psychological impact, and esthetic concern)^{43,44}. The OHIPQ consists of 49 questions used in several countries that assess the impact of oral health on quality of life⁴⁵. This systematic review observed that the OHIPQ and PIDAQ showed significantly different from the beginning of the treatment in the studies when compared to the ends of the treatment, at different follow-up periods. Moreover, there were no differences between the results of the questionnaire when used HP or CP, exhibiting the similar and satisfactory quality of life/patient satisfaction results.

The OHIPQ and PIDAQ were used to evaluate the psychosocial effects and the effects on self-perception in a study of color stability and recovery comparing 6% and 37.5% HP in-office whitening in vital teeth, and HP showed significant differences at 1-year follow-up in both questionnaires, providing a positive effect on self-perception and psychosocial, although the decrease in these scores at one-year post-whitening⁴⁶. This difference between the baseline and the end of follow-up in the test results with the color recurrence that occasionally happens after internal whitening in some cases^{6,47}, so the importance of indication when determining the most appropriate treatment.

Despite the favorable aesthetic results, it is believed that when the internal whitening agent reaches the dentin exposed in the region of the cementum-enamel junction where there is damaged or absent cementum, an inflammatory reaction occurs⁴⁸, so the internal whitening technique requires periodontal health and well-closed canals⁴⁹. Three studies of this systematic review observed elevated levels of inflammatory markers associated with root resorption in the gingival crevicular fluid with the use of 35% HP or 37% CP, at one and six-month periods that were considered another secondary outcome. The use of HP leads to oxygen-reactive species diffusion through the dentinal tubules, which can lead to cervical root resorption⁵⁰.

Then, the HP replacement with CP was recommended, which releases HP more slowly⁵¹, or HP can also be replaced by SP associated with water in the whitening of non-vital teeth¹⁵. However, it does not present results as satisfactory as when associated with hydrogen peroxide⁵². Despite these recommendations, the studies in this systematic review show that CP also leads to an increase in inflammatory markers in the crevicular fluid, similarly to HP^{33,37}. Thus, the replacement of HP by CP should be further studied, in order to assess

whether it can prevent future cervical resorptions. In addition, few cytokines were evaluated (IL-1 β and RANK-L), and few studies were performed, which strongly demonstrates the need for more randomized clinical evaluations.

As one of the main whitening agents used, the aim of this review was to systematically investigate the efficiency of HP in whitening discolored nonvital teeth, providing a review with complete information on internal whitening with HP. However, our study had limitations: the first is the fact that it does not have a meta-analysis, because the selected studies do not have sufficient homogeneity for this type of analysis; second, the follow-up periods differ among themselves, which compromises the comparison of HP with other whitening agents; yet, only the CP-based gel was compared with the HP; the majority of the selected studies were published by the same group of authors; and finally, there were few randomized clinical studies performed.

Conclusion

HP is more effective than CP regarding whitening efficacy while promoting an increase in the patient's quality of life/satisfaction and of cytokines in the gingival crevicular fluid similar to CP.

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Conflict of Interest statement

The authors deny any conflicts of interest related to this study.

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Figure Legends

Figure 1 Flow diagram of the search strategy of the systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Figure 2 Assessment of the risk of bias in the included studies according to the percentage of the scores attributed to each evaluated item.

Statement of Clinical Relevance

Hydrogen peroxide is one of the most used whitening agents by dentists in the internal bleaching of discolored non-vital teeth. However, there has not been a direct comparison between the effectiveness of HP, the patient's satisfaction, and the presence of cytokine in gingival crevicular fluid, compared to other whitening agents.

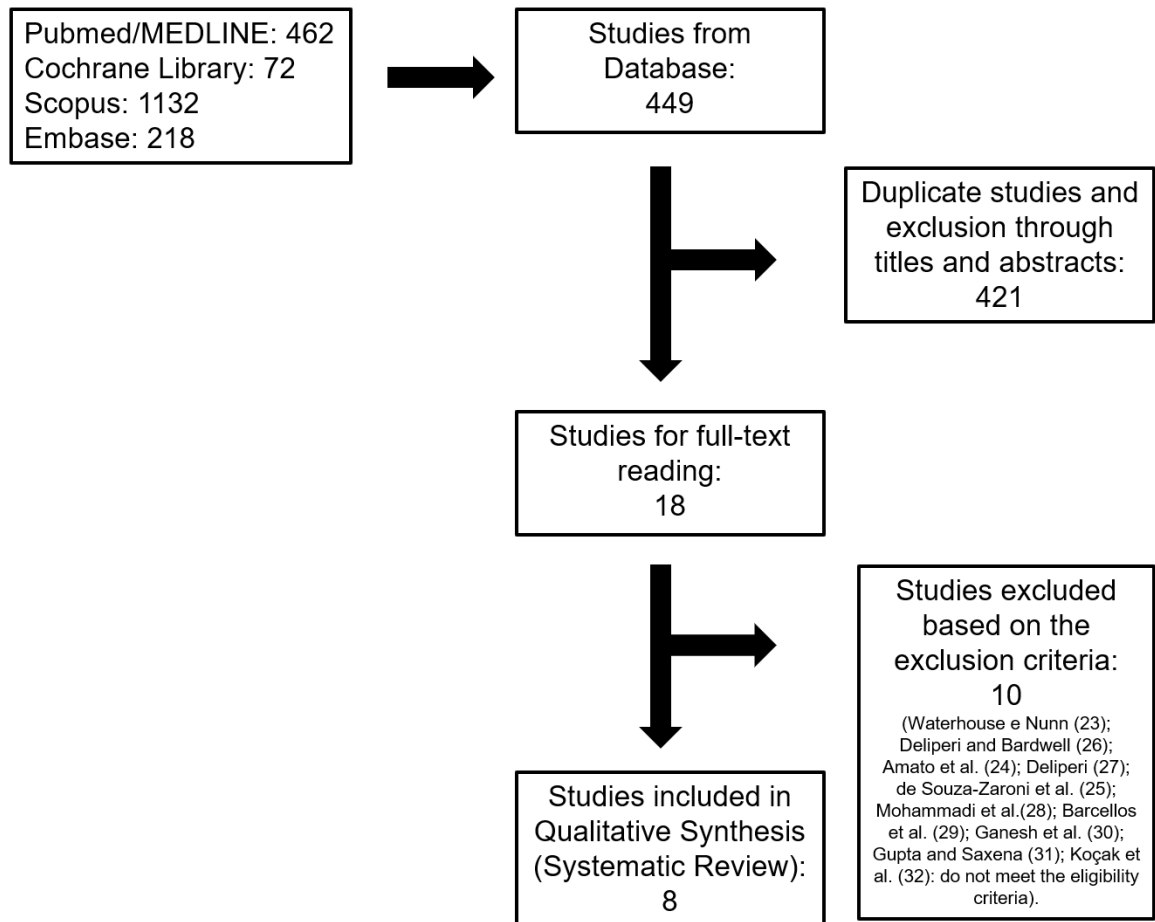
Figure 1

Figure 2



Table 1. Characteristics of the studies included in the review

Author	Nº of patients	Age mean $\pm$ SD [range] (years)	Baseline color	Evaluated tooth	Reason for endodontic treatment	Bleaching agent (n)	Bleaching protocol	Color assessment	Patient's satisfaction	Cytokine in gingival crevicular fluid	Follow-up
Bersezio et al. 2020	50	G1: 30 $\pm$ 12 [19-65], G2: 31 $\pm$ 11 [20-65]	A2 or darker	-	Trauma and caries	G1: 35% HP (n = 21), G2: 37% CP (n = 23)	4 sessions / 1 week of interval	Shade guide - Vita Bleach Guide color scale	-	IL-1 β and RANK-L	Immediate, 1 week, 1 month, and 3 months
Bersezio et al. 2019a	50	G1: 30.6 $\pm$ 11.7 [19-65], G2: 30.8 $\pm$ 11.3 [20-65]	A2 or darker	-	Trauma and caries	G1: 35% HP (n = 19), G2: 37% CP (n = 19)	4 sessions / 1 week of interval	Shade guide - Vita Bleach Guide color scale	-	IL-1 β and RANK-L	Immediate, 1 week, 1 month, and 6 months
Bersezio et al. 2019b	50	G1: 30.47 $\pm$ 11.71 [19-65], G2: 30.82 $\pm$ 12.14 [20-65]	A2 or darker	Incisors	Trauma and caries	G1: 35% HP (n = 17), G2: 37% CP (n = 17)	4 sessions / 1 week of interval	Shade guide - Classic Vita and Bleachedguide 3D-MASTER, Spectrophotometer-Vita EasyShade Compact	Questionnaire - OHIPQ and PIDAQ	-	Immediate, 1 week, 1 month, 6 months, and 12 months
Bersezio et al. 2018a	50	G1: 30.24 $\pm$ 12.26 [19-65], G2: 30.83 $\pm$ 11.25 [20-65]	A2 or darker	Incisors	Trauma and caries	G1: 35% HP (n = 21), G2: 37% CP (n = 23)	4 sessions / 1 week of interval	Spectrophotometer-Vita EasyShade Compact	Questionnaire - OHIPQ and PIDAQ	-	Immediate, 1 week, 1 month, and 3 months
Bersezio et al. 2018b	50	G1: 30.6 $\pm$ 11.7 [19-65], G2: 30.8 $\pm$ 11.3 [20-65],	C2 or darker	-	Trauma and caries	G1: 35% HP (n = 24), G2: 37% CP (n = 23)	4 sessions / 1 week of interval	Shade guide - Vita Bleachedguide 3D-MASTER	-	IL-1 β and RANK-L	Immediate after each bleaching session, 1 week, and 1 month
Bersezio et al. 2018c	50	G1: 31.37 $\pm$ 12.59 [19-65], G2: 30.84 $\pm$ 12.1 [20-65]	A2 or darker	-	Trauma	G1: 35% HP (n = 19), G2: 37% CP, (n = 19)	4 sessions / 1 week of interval	Spectrophotometer - Vita EasyShade Compact, Shade guide - Vita Classical Guide	Questionnaire - OHIPQ and PIDAQ	-	Immediate, 1 week (before and after restoration), 1 and 6 months

Pedrollo Lise et al. 2018	14	At least 18	A2 or darker	Maxillary incisors and canines, and mandibular incisors	-	WB: 2 g SP + 1 mL 20% HP (n = 9), I-O: 10% CP gel (n = 8)	4 sessions / WB: 1 for week, I-O: 1 session of 1 hour per day	Spectrophotometer - Vita EasyShade Compact	-	-	During bleaching (1, 2, 3, and 4 weeks), and 1 year
Bersezio et al. 2017	47	G1: 30.88 ± 11.58 [19-65], G2: 30.83 ± 11.25 [20 - 65]	A2 or darker	Maxillary central incisors	Trauma and caries	G1: 35% HP (n = 25), G2: 37% CP (n = 25)	4 sessions / 1 week of interval	Shade Guide- Vita Classic Spectrophotometer - Vita EasyShade Compact	Questionnaire - OHIPQ and PIDAQ	-	Immediate after each bleaching session, 1 week, and 1 month

CP: carbamide peroxide, G: groups, g: gram, HP: hydrogen peroxide, I-O: inside-outside, mL: milliliter, n = number, OHIPQ: Oral Health Impact Profile Questionnaire, PIDAQ: Psychosocial Impact of Dental Aesthetics Questionnaire, SD: standard deviation, SP: sodium perborate, WB: walking bleaching.

Table 2. Color assessment and cytokine in gingival crevicular fluid assessment of the studies included in the review.

Author	Color assessment	Cytokine in gingival crevicular fluid assessment
Bersezio et al. 2020	G1 = 35% HP; G2 = 37% CP. ΔSGU Vita Classic Scale: 1w - BS x BC: G1: 3, G2: 1; 2w - BS x BC: G1: 4*, G2: 3*; 3w - BS x BC: G1: 5*, G2: 4*; 4w - BS x BC: G1: 6*, G2: 4* BS x 1 w(BR): G1: 5, G2: 4; BS x 1 w (AR): G1: 5, G2: 4; BS x 1 m: G1: 5, G2: 4; BS x 3 m: G1 : 5, G2: 4 * = significative difference <i>Summary: HP is more effective than CP.</i>	Delta (Δ) IL-1β: 1 w - BC x BS: G1: 2.8a, G2: 2.6a; 2 w - BC x BS: G1: 9.8a, G2: 8.6a; 3 w - BC x BS: G1: 21.5a, G2: 18.3a; 4 w - BC x BS: G1: 40.4a, G2: 34.2a; 1 w (AR) BC x BS: G1: 67a, G2: 62.6a; 1 m x BS: G1: 81.7a, G2: 79.4a Delta (Δ) RANK-L: 1 w - BC x BS: G1: 0.5a, G2: 0.5a; 2 w - BC x BS: G1: 1.9a, G2: 1.7a; 3 w - BC x BS: G1: 4.2a, G2: 3.4a; 4 w BC x BS: G1: 8.0a, G2: 6.6a; 1 w (AR) BC x BS: G1: 12.2a, G2: 11.2a; 1 m x BS: G1: 15.2a, G2: 14.6a <i>Summary: HP or CP promotes similar increase of IL-1β and RANK-L.</i>
Bersezio et al. 2019a	G1 = 35% HP; G2 = 37% CP. ΔSGU Vita Bleach Guide: BS x 1 w(BR): G1: 5.00 ± 2.26*, G2: 4.16 ± 1.26; BS x 1 w (AR): G1: 5.00 ± 2.24*, G2: 4.16 ± 1.26; BS x 1 m: G1: 4.84 ± 2.14*, G2: 3.89 ± 1.20; BS x 6 m: G1: 4.37 ± 2.29, G2: 3.89 ± 1.15 * = significative difference <i>Summary: HP is more effective than CP.</i>	IL-1β (pg/μL): BS: G1: 102.20 ± 48.61, G2: 114.81 ± 52.50 1 w: G1: 160.02 ± 70.74 b,c; G2: 174.91 ± 76.71 b,c 1 m: G1: 177.35 ± 76.00 b,c; G2: 193.74 ± 83.26 b,c 6 m: G1: 192.19 ± 79.17 b,c; G2: 213.20 ± 88.79 b,c b = statistical difference from BS; c = statistical difference from the previous time. <i>Summary: HP or CP promotes similar increase of RANK-L and IL-1β, persisting for up to six m.</i>
Bersezio et al. 2019b	G1 = 35% HP; G2 = 37% CP. ΔE:	

BS x immediate bleaching: G1 > G2 (showed incomplete results).*

* = significant difference after immediate bleaching.

ΔSGU Vita Classic Scale:

Homologous teeth: G1: 5, G2: 3;

BS: G1: 15a, G2: 12a

Immediate (subsequent BC): G1: 4b, G2: 5b; 1 w (BR): G1: 5b, G2: 4b; 1 w (AR): G1 (35%HP): 5b, G2: 3b; 1 m: G1: 5b, G2: 4b; 6 m: G1: 5b, G2: 4b; 12 m: G1: 5b, G2: 5b

ΔSGU Vita Bleach Guide:

Homologous teeth: G1: 7, G2: 7

BS: G1: 12a, G2: 11a

Immediate (subsequent BC): G1: 5b, G2: 7b; 1 w (BR): G1: 6b, G2: 7b; 1 w (AF): G1: 5b, G2: 7b; 1 m: G1: 7b, G2: 7b; 6 m: G1: 7b, G2: 6b; 12 m: G1: 8b, G2: 7b

a = statistically significant difference intragroup x homologous teeth.

b = statistically significant difference intragroup x baseline.

The values were not significantly different intergroups.

Summary: HP and CP are similar.

Bersezio et al. 2018a	G1 = 35% HP; G2 = 37% CP. ΔE: BS x 1 w: G1: 10.08 ± 4.83, G2: 7.24 ± 4.79 BS x 1 m: G1: 16.04 ± 4.88, G2: 14.09 ± 4.83 BS x 3 m: G1: 15.25 ± 5.28, G2: 13.71 ± 4.58 <i>Summary: HP and CP are similar.</i>	
Bersezio et al. 2018b	G1 = 35% HP; G2 = 37% CP. ΔSGU Vita Bleach Guide: BS x 1 w of BC: G1: 3a, G2: 1a; BS x 2 w of BC: G1: 4a, G2: 2a; BS x 3 w of BC: G1: 5, G2: 4a; BS x 4 w of BC: G1: 5.5, G2: 4; BS x 1 w (BR): G1: 5, G2: 4; BS x 1 w (AR): G1: 5, G2: 4 a = statistical difference with previous time <i>Summary: HP is more effective than CP.</i>	G1 = 35% HP; G2 = 37% CP. Delta (Δ) IL-1β: BS x 1 w of BC: G1: 2.77, G2: 2.64; 2 weeks of BC x BS: G1: 9.78a, G2: 8.64a; BS x 3 w of BC: G1: 21.53a, G2: 18.27a; BS x 3 w of BC: G1: 40.38a, G2: 34.23a; 1 w after BC x BS: G1: 66.98a, G2: 62.62a; 1 m x BS: G1: 81.74a, G2: 79.37a Delta (Δ) RANK-L: 1 week of BC x BS: G1: 0.52, G2: 0.54; 2 weeks of BC x BS: G1: 1.92a, G2: 1.71a; 3 weeks of BC x BS: G1: 4.17a, G2: 3.40a; 4 weeks of BC x BS: G1: 8.02a, G2: 6.62a; 1 week after BC x BS: G1: 12.17a, G2: 11.19a; 1 m x BS: G1: 15.20a, G2: 14.57a a = statistical difference with previous time <i>Summary: HP or CP promotes similar increase of RANK-L and IL-1β.</i>
Bersezio et al. 2018c	G1 = 35% HP; G2 = 37% CP. ΔE: BS x 1 w of BC: G1: 8.77 ± 1.60, G2: 7.32 ± 4.75; BS x 2 w of BC: G1: 12.87 ± 5.58^a, G2: $10.93 \pm 5.42a$; BS x 3 w of BC: G1: 15.58 ± 6.03^a, G2: $12.33 \pm 5.20a$; BS x 4 w of BC: G1: $16.65 \pm 6.76a$, G2: $13.01 \pm 4.71a$; BS x 1 w(BR): G1: 15.94 ± 7.01, G2: 13.33 ± 4.95; BS x 1 w (AR): G1: 16.31 ± 6.80, G2: 14.25	

± 5.28 ; BS x 1 m: G1: 15.01 ± 5.01 , G2: 13.62 ± 5.13 ; BS x 6 m: G1: 14.53 ± 5.07 , G2: 14.09 ± 6.61

Δ SGU Vita Bleach Guide:

BS x 1 w of BC: G1: 2.89 ± 2.56 , G2: 2.84 ± 2.93 ; BS x 2 w of BC: G1: $6.68 \pm 4.27a$, G2: $4.53 \pm 3.75a$; BS x 3 w of BC: G1: $8.21 \pm 4.37a$, G2: $5.95 \pm 3.78a$; BS x 4 w of BC: G1: $9.26 \pm 4.01a$, G2: 6.89 ± 3.57 ; BS x 1 w (BR): G1: $8.53 \pm 4.13a$, G2: 6.79 ± 3.72 ; BS x 1 w (AR): G1: 8.74 ± 3.90 , G2: 6.89 ± 3.56 ; BS x 1 m: G1: 8.16 ± 3.75 , G2: 6.58 ± 3.75 ; BS x 6 m: G1:

8.21 ± 3.66 , G2: 6.58 ± 3.72

a = statistical difference with previous time

Summary: HP and CP are similar.

Lise et al.
2018

G1: WB; G2: I-O

ΔE :

BS x 1 w of BC: G1: 7.8 ± 3.7 , G2: $8.6 \pm 3.6aA$

BS x 2 w of BC: G1: $12.0 \pm 6.4^*$, G2: $12.9 \pm 4.6^*$

BS x 3 w of BC: G1: $13.8 \pm 6.1^*$, G2: $12.2 \pm 5.0^*$

BS x 4 w of BC: G1: $12.4 \pm 3.4^*$, G2: $12.7 \pm 5.9^*$

BS x 1 y: G1: $11.3 \pm 3.9^*$, G2: $10.9 \pm 3.3^*$

* = statistical difference with 1 w time

Summary: There is no difference in bleaching effectiveness between WB (HP+SP) and I-O (CP).

Bersezio et
al. 2017

G1 = 35% HP; G2 = 37% CP.

ΔSGU Vita Classic Scale:

BS x 1 w of BC: G1: 3.5, G2: 3; BS x 2 w of BC: G1: 8, G2: 4; BS x 3 w of
BC: G1: 9.5, G2: 7; BS x 4 w of BC: G1: 11, G2: 7; BS x 1 w(BR): G1: 10,
G2: 7; BS x 1 w (AR): G1: 9.5, G2: 7; BS x 1 m: G1: 9.5, G2: 7

ΔE:

BS x 1 w of BC: G1: 9.67 ± 4.79 , G2: 7.40 ± 4.64 ; BS x 2 w of BC: G1:
 13.24 ± 5.94 , G2: 11.04 ± 5.19 ; BS x 3 w of BC: G1: 15.69 ± 5.79 , G2:
 12.17 ± 4.93 ; BS x 4 w of BC: G1: 17.19 ± 6.55 , G2: 13.31 ± 4.67 ; BS x 1 w
(BR): G1: 16.44 ± 7.10 , G2: 14.36 ± 4.74 ; BS x 1 w (AR): G1: 16.22 ± 6.46 ,
G2: 14.45 ± 4.88 ; BS x 1 m: G1: 15.48 ± 5.17 , G2: 14.02 ± 4.85

*Summary: Vita Classic Scale: HP is more effective in all periods; ΔE: HP
and CP are similar, except only longer period.*

AR: after restoration, BC: bleaching, BR: before restoration, BS: baseline, CP: Carbamide peroxide, G: groups, HP: Hydrogen peroxide, I-O: inside-outside, m = month(s), SP: Sodium perborate, w: week, WB: walking bleach, y: year.

Table 3. Patient satisfaction assessment of the studies included in the review.

Author	Patient's satisfaction
Bersezio et al. 2019b	G1 = 35% HP; G2 = 37% CP. PIDAQ: BS: G1: DSC: 17; SI: 24; PI: 18; ECAC: 9. G2: DSC: 15; SI: 23; PI: 17; ECAC: 9. PostBC: G1: DSC: 21a; SI: 17a; PI: 13a; ECAC: 6a. G2: DSC: 22.5a; SI: 16a; PI: 14.5; ECAC: 4.5a. 1 month: G1: DSC: 22a; SI: 12a; PI: 12a; ECAC: 4ab. G2: DSC: 21.5a; SI: 17 a; PI: 14; ECAC: 6ab. 6 month: G1: DSC: 19.5; SI: 15; PI: 15.5; ECAC: 7. G2: DSC: 21a; SI: 19a; PI: 15a; ECAC: 8a. 12 month: G1: DSC: 21ab; SI: 15a; PI: 13a; ECAC: 8a. G2: DSC: 19a; SI: 16.5a; PI: 14a; ECAC: 8.5b. OHIPQ: BS: G1: FL: 5; PP: 3; PD: 4; PDB: 1; PCDB: 2; SD: 0; Handicap: 1; Sum: 17. G2 : FL: 5; PP: 3; PD: 5; PDB: 2; PCDB: 3; SD: 1; Handicap: 1; Sum: 19. PostBC: G1: FL: 3a; PP: 3; PD: 4; PDB: 1; PCDB: 2; SD: 0a; Handicap: 0a; Sum: 13a. G2: FL: 4a; PP: 3; PD: 3; PDB: 1; PCDB: 2; SD: 0a; Handicap: 0a; Sum: 15a. 1 month: G1: FL: 2a; PP: 2a; PD: 4; PDB: 1; PCDB: 1a; SD: 0; Handicap: 0a; Sum: 14a. G2: FL: 4a; PP: 2; PD: 4; PDB: 0; PCDB: 2a; SD: 0; Handicap: 0; Sum: 13a. 6 months: G1: FL: 2a; PP: 2ab; PD: 4a; PDB: 0; PCDB: 1; SD: 0; Handicap: 0; Sum: 10a. G2: FL: 3a; PP: 3; PD: 4a; PDB: 1; PCDB: 2a; SD: 0 a; Handicap: 0; Sum: 12ab. 12 months: G1: FL: 3a; PP: 2; PD: 4; PDB: 1; PCDB: 1; SD: 0; Handicap: 0; Sum: 15. G2 : FL: 3a; PP: 3; PD: 3; PDB: 0; PCDB: 1a; SD: 0; Handicap: 1; Sum: 12a.
a = statistically significant difference x BS; b = statistically significant difference x 1w after bleaching. <i>Summary: There were no statistically significant differences between groups at the one-year follow-up: each gel produced a positive impact on patients' psychosocial impact.</i>	
Bersezio et al. 2018a	G1 = 35% HP; G2 = 37% CP. OHIPQ: BS: G1 : FL: 5; PP: 4; PD: 5; PDB: 2; PCDB: 3; SD: 0; Handicap: 1; Sum/Scores: 19. G2 : FL: 5; PP: 3; PD: 5; PDB: 2; PCDB: 3; SD: 0.5; Handicap: 0.5; Sum/Scores: 19

1 : G1: FL: 3a; PP: 3; PD: 4a; PDB: 2; PCDB: 2; SD: 0a; Handicap: 0a; Sum/Scores: 13. G2: FL: 4a; PP: 3; PD: 3.5a; PDB: 1; PCDB: 1.5a; SD: 0; Handicap: 0; Sum/Scores: 14a

1 month: G1 : FL: 2a; PP: 3; PD: 4a; PDB: 1; PCDB: 2a; SD: 0; Handicap: 0a; Sum/Scores: 14a. G2: FL: 4a; PP: 2; PD: 4; PDB: 0; PCDB: 2a; SD: 0; Handicap: 0a; Sum/Scores: 14a.

3 months: G1: FL: 4a; PP: 2ab; PD: 4abc; PDB: 1; PCDB: 2a; SD: 0; Handicap: 0; Sum/Scores: 13a. G2: FL: 3.5a; PP: 2.5ab; PD: 3a; PDB: 1; PCDB: 1; SD: 0b; Handicap: 0a; Sum/Scores: 11ab

PIDAQ:

BS: G1: DSC: 16; SI 24; PI: 20; EC: 10. G2: DSC: 14; SI 22.5; PI: 17; EC: 9.5.

1 w: G1: DSC: 21a; SI 18a; PI: 14a; EC: 9a. G2: DSC: 23a; SI 16a; PI: 14.5a; EC: 4.5a.

1 month: G1: DSC: 19a; SI 17a; PI: 14a; EC: 6ab. G2: DSC: 22.5a; SI 17a; PI: 13.5; EC: 6ab.

3 months: G1: DSC: 21.5b; SI 17a; PI: 15ac; EC: 9a. G2: DSC: 22a; SI 15ac; PI: 13.5ab; EC: 6a.

a = statistically significant difference x BS; b = statistically significant difference x 1 w after bleaching; c = statistically significant difference x 1 m after bleaching.

Summary: HP or CP generates a positive impact on aesthetic self-perception and psychosocial impact.

Bersezio

et al.

2018c

G1 = 35% HP; G2 = 37% CP.

OHIPQ:

BS: G1: FL: 4; PP: 2; PD: 4; PDB: 1; PCDB: 1; SD: 0; Handicap: 0; Sum/Scores: 14. G2: FL: 5; PP: 3; PD: 5; PDB: 2; PCDB: 4; SD: 1; Handicap: 1; Sum/Scores: 20

1 month: G1: FL: 2a; PP: 2a; PD: 4a; PDB: 1; PCDB: 1a; SD: 0; Handicap: 0; Sum/Scores: 12a. G2: FL: 4a; PP: 2; PD: 4; PDB: 0; PCDB: 2a; SD: 0; Handicap: 0; Sum/Scores: 13a.

6 months: G1: FL: 2a; PP: 2a; PD: 4a; PDB: 0; PCDB: 1a; SD: 0; Handicap: 0a; Sum/Scores: 10a. G2: FL: 3a; PP: 3; PD: 4; PDB: 1; PCDB: 2a; SD: 0; Handicap: 0a; Sum/Scores: 13^a.

PIDAQ:

BS: G1: DSC: 17; SI 19; PI: 18; EC: 9. G2: DSC: 14; SI 23; PI: 19; EC: 10.

1 month: G1: DSC: 19a; SI 15a; PI: 14a; EC: 5a. G2: DSC: 21a; SI 19a; PI: 14a; EC: 6a.

6 months: G1: DSC: 20; SI 12; PI: 15; EC: 6. G2: DSC: 21a; SI 18a; PI: 14; EC: 6a.

a = statistically significant difference x BS; b = statistically significant difference x 1 m.

Summary: There is a positive impact on the esthetic perception and psychosocial impact of patients, and it is consistent over time.

Bersezio	G1 = 35% HP; G2 = 37% CP.
et al.	OHIPQ:
2017	BS: G1: FL: 5; PP: 3.5; PD: 5; PDB: 1.5; PCDB: 2.5; SD: 0; Handicap: 1; Sum: 18. G2 : FL: 5; PP: 3; PD: 5; PDB: 2; PCDB: 3; SD: 1; Handicap: 1; Sum: 19
	1 w: G1: FL: 3a; PP: 3; PD: 4a; PDB: 1.5; PCDB: 2a; SD: 0a; Handicap: 0a; Sum: 13a. G2: FL: 4a; PP: 3; PD: 3; PDB: 1; PCDB: 2a; SD: 0; Handicap: 0; Sum: 15a.
	1 months: G1: FL: 2.5a; PP: 2.5; PD: 4a; PDB: 1; PCDB: 1.5a; SD: 0; Handicap: 0a; Sum: 14a. G2: FL: 4a; PP: 2; PD: 4; PDB: 0; PCDB: 2a; SD: 0; Handicap: 0a; Sum/Scores: 13a.
	PIDAQ:
	BS: G1: DSC: 16.5; SI 24; PI: 19.5; EC: 9.5; Sum: 71. G2: DSC: 14; SI 23; PI: 17; EC: 9; Sum: 66.
	1 week: G1: DSC: 21a; SI 17.5a; PI: 13.5a; EC: 8a; Sum: 57a. G2: DSC: 23a; SI 16a; PI: 15a; EC: 5a; Sum: 57a.
	1 months: G1: DSC: 19ab; SI 15.5a; PI: 14a; EC: 5.5ab; Sum: 54a. G2: DSC: 22a; SI 17a; PI: 14; EC: 6a; Sum: 58.

a = statistically significant difference x BS; b = statistically significant difference x 1 w after bleaching.

Summary: Summary: HP or CP generates a positive impact on aesthetic self-perception and psychosocial impact.

AC: aesthetic concern; BC: bleaching; BS: baseline; CP: carbamide peroxide; DSC: dental self-confidence; EC: esthetic concern; FL: functional limitation; G: groups; HP: hydrogen peroxide; OHIPQ: oral health impact profile; PD: psychological discomfort; PDB: physical disability; PCDB: psychological disability; PI: psychological impact; PIDAQ: psychosocial impact of dental aesthetics; PP: physical pain; SD: social disability; SI: social impact; w: week.

Supplementary Table 1. Search strategy used for the electronic databases

Database	Search strategy
Medline through PubMed (http://www.ncbi.nlm.nih.gov/pubmed), OpenGrey (http://www.opengrey.eu/)	((internal bleaching[MeSH Terms]) OR (internal bleaching[Title/Abstract]) OR (non vital bleaching[MeSH Terms]) OR (non vital bleaching[Title/Abstract]) OR (non vital whitening[MeSH Terms]) OR (non vital whitening[Title/Abstract]) OR (internal whitening[MeSH Terms]) OR (internal whitening[Title/Abstract]) OR (non vital tooth bleaching[MeSH Terms]) OR (non vital tooth bleaching[Title/Abstract]) OR (nonvital tooth whitening[MeSH Terms]) OR (nonvital tooth whitening[Title/Abstract]) OR (intracoronal bleaching[MeSH Terms]) OR (intracoronal bleaching[Title/Abstract]) OR (intracoronal whitening[MeSH Terms]) OR (intracoronal whitening[Title/Abstract]))
Scopus (http://www.scopus.com/)	TITLE-ABS-KEY (Internal bleaching) OR TITLE-ABS-KEY (Non vital bleaching) OR TITLE-ABS-KEY (Non vital whitening) OR TITLE-ABS-KEY (Internal whitening) OR TITLE-ABS-KEY (Non vital tooth bleaching) OR TITLE-ABS-KEY (Non vital tooth whitening) OR TITLE-ABS-KEY (Intracoronal bleaching) OR TITLE-ABS-KEY (Intracoronal whitening)
Embase (https://www.embase.com)	'internal bleaching':ab,ti OR 'non vital bleaching':ab,ti OR 'non vital whitening':ab,ti OR 'internal whitening':ab,ti OR 'non vital tooth bleaching':ab,ti OR 'non vital tooth whitening':ab,ti OR 'intracoronal bleaching':ab,ti OR 'intracoronal whitening':ab,ti
Cochrane (https://www.cochranelibrary.com/)	((Internal bleaching) OR (Non vital bleaching) OR (Non vital whitening) OR (Internal whitening) OR (Non vital tooth bleaching) OR (Non vital tooth whitening) OR (Intracoronal bleaching) OR (Intracoronal whitening)):ti,ab,kw

MeSH – Medical Subject Heading.

Supplementary Table 2. Risk of bias of included studies

Quality criteria	Bersezio <i>et al.</i> 2020	2	2	2	2	0	2	2	2	0	2	2	2	2	22
	Bersezio <i>et al.</i> 2019a	2	2	2	2	0	2	2	2	0	2	2	2	2	22
	Bersezio <i>et al.</i> 2019b	2	2	2	2	0	2	2	2	0	2	2	2	2	22
	Bersezio <i>et al.</i> 2018a	2	2	2	2	0	2	2	2	0	2	2	2	2	22
	Bersezio <i>et al.</i> 2018b	2	2	2	2	1	2	2	2	0	2	2	2	2	23
	Bersezio <i>et al.</i> 2018c	2	2	2	2	0	2	2	2	0	2	2	2	2	22
	Lise <i>et al.</i> 2018	2	2	2	2	0	1	2	2	0	2	2	2	2	21
	Bersezio <i>et al.</i> 2017	2	2	2	2	0	2	2	2	0	2	2	2	2	22
	0: not reported, 1: reported but unclear, 2: reported and adequate.														
	Was true randomization used for assignment of participants to treatment groups?														
	Was allocation to treatment groups concealed?														
	Were treatment groups similar at the baseline?														
	Were participants blind to treatment assignment?														
Were those delivering treatment blind to treatment assignment?															
Were outcomes assessors blind to treatment assignment?															
Were treatment groups treated identically other than the intervention of interest?															
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analvzed?															
Were participants analyzed in the groups to which they were randomized?															
Were outcomes measured in the same way for treatment groups?															
Were outcomes measured in a reliable way?															
Was appropriate statistical analysis used?															
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?															
Total score															

0: not reported, 1: reported but unclear, 2: reported and adequate.

Guidelines for Publishing Papers in the JOE

Writing an effective article is a challenging assignment. The following guidelines are provided to assist authors in submitting manuscripts.

The *JOE* publishes original and reviews articles related to the scientific and applied aspects of endodontics. Moreover, the *JOE* has a diverse readership that includes full-time clinicians, full-time academicians, residents, students, and scientists. Effective communication with this diverse readership requires careful attention to writing style.

General Points on Composition

Organization of Original Research Manuscripts

Manuscripts Category Classifications and Requirements

Available Resources

General Points on Composition

1. Authors are strongly encouraged to analyze their final draft with both software (e.g., spelling and grammar programs) and colleagues who have expertise in English grammar. References listed at the end of this section provide a more extensive review of rules of English grammar and guidelines for writing a scientific article. Always remember that clarity is the most important feature of scientific writing. Scientific articles must be clear and precise in their content and concise in their delivery since their purpose is to inform the reader. The Editor reserves the right to edit all manuscripts or to reject those manuscripts that lack clarity or precision, or have unacceptable grammar or syntax. The following list represents common errors in manuscripts submitted to the *JOE*:
2. The paragraph is the ideal unit of organization. Paragraphs typically start with an introductory sentence that is followed by sentences that describe additional detail or examples. The last sentence of the paragraph provides conclusions and forms a transition to the next paragraph. Common problems include one-sentence paragraphs, sentences that do not develop the theme of the paragraph (see also section “c” below), or sentences with little to no transition within a paragraph.
3. Keep to the point. The subject of the sentence should support the subject of the paragraph. For example, the introduction of authors’ names in a sentence changes the subject and lengthens the text. In a paragraph on sodium hypochlorite, the sentence, “In 1983, Langeland et al., reported that sodium hypochlorite acts as a lubricating factor during instrumentation and helps to flush debris from the root canals” can be edited to: “Sodium hypochlorite acts as a lubricant during instrumentation and as a vehicle for flushing the generated debris (Langeland et al., 1983).” In this example, the paragraph’s subject is sodium hypochlorite and sentences should focus on this subject.
4. Sentences are stronger when written in the active voice, *i.e.*, the subject performs the action. Passive sentences are identified by the use of passive verbs such as “was,” “were,” “could,” etc. For example: “Dexamethasone was found in this study to be a factor that was associated with reduced inflammation,” can be edited to: “Our results demonstrated that dexamethasone reduced inflammation.” Sentences written in a

direct and active voice are generally more powerful and shorter than sentences written in the passive voice.

5. Reduce verbiage. Short sentences are easier to understand. The inclusion of unnecessary words is often associated with the use of a passive voice, a lack of focus or run-on sentences. This is not to imply that all sentences need be short or even the same length. Indeed, variation in sentence structure and length often helps to maintain reader interest. However, make all words count. A more formal way of stating this point is that the use of subordinate clauses adds variety and information when constructing a paragraph. (This section was written deliberately with sentences of varying length to illustrate this point.)
6. Use parallel construction to express related ideas. For example, the sentence, “Formerly, endodontics was taught by hand instrumentation, while now rotary instrumentation is the common method,” can be edited to “Formerly, endodontics was taught using hand instrumentation; now it is commonly taught using rotary instrumentation.” The use of parallel construction in sentences simply means that similar ideas are expressed in similar ways, and this helps the reader recognize that the ideas are related.
7. Keep modifying phrases close to the word that they modify. This is a common problem in complex sentences that may confuse the reader. For example, the statement, “Accordingly, when conclusions are drawn from the results of this study, caution must be used,” can be edited to “Caution must be used when conclusions are drawn from the results of this study.”
8. To summarize these points, effective sentences are clear and precise, and often are short, simple and focused on one key point that supports the paragraph’s theme.
9. Authors should be aware that the *JOE* uses iThenticate, plagiarism detection software, to assure originality and integrity of material published in the *Journal*. The use of copied sentences, even when present within quotation marks, is highly discouraged. Instead, the information of the original research should be expressed by new manuscript author’s own words, and a proper citation given at the end of the sentence. Plagiarism will not be tolerated and manuscripts will be rejected, or papers withdrawn after publication based on unethical actions by the authors. In addition, authors may be sanctioned for future publication.

Organization of Original Research Manuscripts

Please Note: *All abstracts should be organized into sections that start with a one-word title (in bold), i.e., Introduction, Methods, Results, Conclusions, etc., and should not exceed more than 250 words in length.*

1. **Title Page:** The title should describe the major emphasis of the paper. It should be as short as possible without loss of clarity. Remember that the title is your advertising billboard—it represents your major opportunity to solicit readers to spend the time to read your paper. It is best not to use abbreviations in the title since this may lead to imprecise coding by electronic citation programs such as PubMed (e.g., use “sodium hypochlorite” rather than NaOCl). The author list must conform to published standards on authorship (see authorship criteria in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals at icmje.org). The manuscript title, name and address (including email) of one author designated as the corresponding author. This author will be responsible for editing proofs and order reprints when

applicable. The contribution of each author should also be highlighted in the cover letter.

2. **Abstract:** The abstract should concisely describe the purpose of the study, the hypothesis, methods, major findings, and conclusions. The abstract should describe the new contributions made by this study. The word limitations (250 words) and the wide distribution of the abstract (*e.g.*, PubMed) make this section challenging to write clearly. This section often is written last by many authors since they can draw on the rest of the manuscript. Write the abstract in past tense since the study has been completed. Three to ten keywords should be listed below the abstract.
3. **Introduction:** The introduction should briefly review the pertinent literature in order to identify the gap in knowledge that the study is intended to address and the limitations of previous studies in the area. The purpose of the study, the tested hypothesis and its scope should be clearly described. Authors should realize that this section of the paper is their primary opportunity to establish communication with the diverse readership of the *JOE*. Readers who are not expert in the topic of the manuscript are likely to skip the paper if the introduction fails to succinctly summarize the gap in knowledge that the study addresses. It is important to note that many successful manuscripts require no more than a few paragraphs to accomplish these goals. Therefore, authors should refrain from performing the extensive review of the literature, and discuss the results of the study in this section.
4. **Materials and Methods:** The objective of the materials and methods section is to permit other investigators to repeat your experiments. The four components of this section are the detailed description of the materials used and their components, the experimental design, the procedures employed, and the statistical tests used to analyze the results. The vast majority of manuscripts should cite prior studies using similar methods and succinctly describe the essential aspects used in the present study. Thus, the reader should still be able to understand the method used in the experimental approach and concentration of the main reagents (*e.g.*, antibodies, drugs, etc.) even when citing a previously published method. The inclusion of a “methods figure” will be rejected unless the procedure is novel and requires an illustration for comprehension. If the method is novel, then the authors should carefully describe the method and include validation experiments. If the study utilized a **commercial product**, the manuscript must state that they either followed manufacturer’s protocol or specify any changes made to the protocol. If the study used an *in vitro* model to simulate a clinical outcome, the authors must describe experiments made to validate the **model**, or previous literature that proved the clinical relevance of the model. Studies on **humans** must conform to the Helsinki Declaration of 1975 and state that the institutional IRB/equivalent committee(s) approved the protocol and that informed consent was obtained after the risks and benefits of participation were described to the subjects or patients recruited. Studies involving **animals** must state that the institutional animal care and use committee approved the protocol. The statistical analysis section should describe which tests were used to analyze which dependent measures; p-values should be specified. Additional details may include randomization scheme, stratification (if any), power analysis as a basis for sample size computation, drop-outs from clinical trials, the effects of important confounding variables, and bivariate versus multivariate analysis.
5. **Results:** Only experimental results are appropriate in this section (*i.e.*, neither methods, discussion, nor conclusions should be in this section). Include only those data that are critical for the study, as defined by the aim(s). Do not include all available data without justification; any repetitive findings will be rejected from

publication. All Figures, Charts, and Tables should be described in their order of numbering with a brief description of the major findings. The author may consider the use of supplemental figures, tables or video clips that will be published online. Supplemental material is often used to provide additional information or control experiments that support the results section (*e.g.*, microarray data).

6. **Figures:** There are two general types of figures. The first type of figures includes photographs, radiographs or micrographs. Include only essential figures, and even if essential, the use of composite figures containing several panels of photographs is encouraged. For example, most photos, radio- or micrographs take up one column-width, or about 185 mm wide X 185 mm tall. If instead, you construct a two columns-width figure (*i.e.*, about 175 mm wide X 125 mm high when published in the *JOE*), you would be able to place about 12 panels of photomicrographs (or radiographs, etc.) as an array of four columns across and three rows down (with each panel about 40 X 40 mm). This will require some editing to emphasize the most important feature of each photomicrograph, but it greatly increases the total number of illustrations that you can present in your paper. Remember that each panel must be clearly identified with a letter (*e.g.*, “A,” “B,” etc.), in order for the reader to understand each individual panel. Several nice examples of composite figures are seen in recent articles by Jeger et al (J Endod 2012;38:884–888); Olivieri et al., (J Endod 2012;38:1007–1011); Tsai et al (J Endod 2012;38:965–970). Please note that color figures may be published at no cost to the authors and authors are encouraged to use color to enhance the value of the illustration. Please note that a multi-panel, composite figure only counts as one figure when considering the total number of figures in a manuscript (see section 3, below, for the maximum number of allowable figures). The second type of figures is graphs (*i.e.*, line drawings including bar graphs) that plot a dependent measure (on the Y-axis) as a function of an independent measure (usually plotted on the X axis). Examples include a graph depicting pain scores over time, etc. Graphs should be used when the overall trend of the results are more important than the exact numerical values of the results. For example, a graph is a convenient way of reporting that an ibuprofen-treated group reported less pain than a placebo group over the first 24 hours, but was the same as the placebo group for the next 96 hours. In this case, the trend of the results is the primary finding; the actual pain scores are not as critical as the relative differences between the NSAID and placebo groups.
7. **Tables:** Tables are appropriate when it is critical to present exact numerical values. However, not all results need be placed in either a table or figure. For example, the following table may not be necessary: Instead, the results could simply state that there was no inhibition of growth from 0.001-0.03% NaOCl, and a 100% inhibition of growth from 0.03-3% NaOCl (N=5/group). Similarly, if the results are not significant, then it is probably not necessary to include the results in either a table or as a figure. These and many other suggestions on figure and table construction are described in additional detail in Day (1998).

% NaOCl N/Group % Inhibition of Growth

0.001	5	0
0.003	5	0
0.01	5	0
0.03	5	0
0.1	5	100
0.3	5	100

% NaOCl N/Group % Inhibition of Growth

1	5	100
3	5	100

8. **Discussion:** This section should be used to interpret and explain the results. Both the strengths and weaknesses of the observations should be discussed. How do these findings compare to the published literature? What are the clinical implications? Although this last section might be tentative given the nature of a particular study, the authors should realize that even preliminary clinical implications might have value for the clinical leadership. Ideally, a review of the potential clinical significance is the last section of the discussion. What are the major conclusions of the study? How does the data support these conclusions
9. **Acknowledgments:** All authors must affirm that they have no financial affiliation (e.g., employment, direct payment, stock holdings, retainers, consultantships, patent licensing arrangements or honoraria), or involvement with any commercial organization with direct financial interest in the subject or materials discussed in this manuscript, nor have any such arrangements existed in the past three years. Any other potential conflict of interest should be disclosed. Any author for whom this statement is not true must append a paragraph to the manuscript that fully discloses any financial or other interest that poses a conflict. Likewise, the sources and correct attributions of all other grants, contracts or donations that funded the study must be disclosed
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Manuscripts Category Classifications and Requirements

Manuscripts submitted to the *JOE* must fall into one of the following categories. The abstracts for all these categories would have a maximum word count of 250 words:

1. **CONSORT Randomized Clinical Trial-Manuscripts** in this category must strictly adhere to the Consolidated Standards of Reporting Trials-CONSORT- minimum guidelines for the publication of randomized clinical trials. These guidelines can be found at consort-statement.org. These manuscripts have a limit of 3,500 words, [including abstract, introduction, materials and methods, results, discussion, and acknowledgments; excluding figure legends and references]. In addition, there is a limit of a total of 4 figures and 4 tables*.
2. **Review Article-Manuscripts** in this category is either narrative articles, or systematic reviews/meta-analyses. Case report/Clinical Technique articles even when followed by the extensive review of the literature will be categorized as “Case Report/Clinical Technique”. These manuscripts have a limit of 3,500 words, [including abstract, introduction, discussion, and acknowledgments; excluding figure legends and references]. In addition, there is a limit of a total of 4 figures and 4 tables*.
3. **Clinical Research** (e.g., prospective or retrospective studies on patients or patient records, or research on biopsies, excluding the use of human teeth for technique

studies). These manuscripts have a limit of 3,500 words [including abstract, introduction, materials and methods, results, discussion, and acknowledgments; excluding figure legends and references]. In addition, there is a limit of a total of 4 figures and 4 tables*.

4. Basic Research Biology (animal or culture studies on biological research on physiology, development, stem cell differentiation, inflammation or pathology). Manuscripts that have a primary focus on biology should be submitted in this category while manuscripts that have a primary focus on materials should be submitted in the Basic Research Technology category. For example, a study on cytotoxicity of a material should be submitted in the Basic Research Technology category, even if it was performed in animals with histological analyses. These manuscripts have a limit of 2,500 words [including abstract, introduction, materials and methods, results, discussion, and acknowledgments; excluding figure legends and references]. In addition, there is a limit of a total of 4 figures or 4 tables*.
5. Basic Research Technology (Manuscripts submitted in this category focus primarily on research related to techniques and materials used, or with potential clinical use, in endodontics). These manuscripts have a limit of 2,500 words [including abstract, introduction, materials and methods, results, discussion, and acknowledgments; excluding figure legends and references]. In addition, there is a limit of a total of 3 figures and tables*.
6. Case Report/Clinical Technique (*e.g.*, report of an unusual clinical case or the use of cutting-edge technology in a clinical case). These manuscripts have a limit of 2,500 words [including abstract, introduction, materials and methods, results, discussion, and acknowledgments; excluding figure legends and references]. In addition, there is a limit of a total of 4 figures or tables*.* Figures, if submitted as multi-panel figures must not exceed 1-page length. Manuscripts submitted with more than the allowed number of figures or tables will require the approval of the JOE Editor or associate editors. If you are not sure whether your manuscript falls within one of the categories above, or would like to request preapproval for submission of additional figures please contact the Editor by email at jendodontics@uthscsa.edu. Importantly, adhering to the general writing methods described in these guidelines (and in the resources listed below) will help to reduce the size of the manuscript while maintaining its focus and significance. Authors are encouraged to focus on only the essential aspects of the study and to avoid inclusion of extraneous text and figures. The Editor may reject manuscripts that exceed these limitations.

Available Resources

Strunk W, White EB. *The Elements of Style*. Allyn & Bacon, 4th ed, 2000, ISBN 020530902X.

Day R. *How to Write and Publish a Scientific Paper*. Oryx Press, 5th ed. 1998. ISBN 1-57356-164-9.

Woods G. *English Grammar for Dummies*. Hungry Minds:NY, 2001 (an entertaining review of grammar).

Alley M. *The Craft of Scientific Writing*. Springer, 3rd edition 1996 SBN 0-387-94766-3.

Alley M. *The Craft of Editing*. Springer, 2000 SBN 0-387-98964-1.