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LARISSA PEREIRA NUNES

USO DA FOTOTERAPIA COMO MÉTODO COMPLEMENTAR NO RETRATAMENTO ENDODÔNTICO: REVISÕES SISTEMÁTICAS E META-ANÁLISE DE ENSAIOS CLÍNICOS

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Epigrafe

"...E aprendi que se depende sempre

De tanta, muita, diferente gente

Toda pessoa sempre é as marcas

Das lições diárias de outras tantas pessoas

E é tão bonito quando a gente entende

Que a gente é tanta gente onde quer que a gente vá

É tão bonito quando a gente sente

Que nunca está sozinho por mais que pense estar."

Gonzaguinha

Resumo Geral

Nunes, LP. **Uso da fototerapia como método complementar no retratamento endodôntico: revisões sistemáticas e meta-análise de ensaios clínicos.** Dissertação (Mestrado) – Faculdade de Odontologia, Universidade Estadual Paulista, Araçatuba 2022.

Este trabalho objetivou realizar duas revisões sistemáticas com as seguintes propostas: 1) Avaliar se a fototerapia com laser resultaria em menor dor pós-operatória (PP) em pacientes submetidos a reintervenção endodôntica; e 2) Avaliar se o uso da terapia fotodinâmica antimicrobiana (aPDT) seria eficaz na desinfecção de canais radiculares em casos de reintervenção endodôntica. As Revisões Sistemáticas foram registradas no PROSPERO (CRD42021243500 e CRD42021260013, respectivamente) e seguiram as diretrizes dos Itens de Relatório Preferenciais para Revisões Sistemáticas e Meta-análise (PRISMA). As buscas foram realizadas nas bases de dados eletrônicas PubMeb, Scopus, Web of Science, Embase, Web of Science, Clinical Trials e Cochrane Library e nos bancos de dados da literatura cinza. A qualidade metodológica e o risco de viés foram avaliados pela ferramenta Cochrane Risk of Bias para ensaios clínicos randomizados (RCT) e pelo qualificador Newcastle-Ottawa (NOS) para estudos não RCT (prospectivos). A análise da qualidade de evidência foi realizada com base na abordagem GRADE. A meta-análise foi realizada com o R software Meta package, utilizando um intervalo de confiança (IC) de 95%. Quanto aos resultados do Artigo 1: Cinco artigos foram incluídos para análise. Os estudos foram classificados como "baixo" risco de viés. Dos cinco estudos clínicos, quatro estudos mostraram uma diminuição significativa da PP após a reintervenção endodôntica nos grupos de fototerapia a laser quando comparados ao grupo controle, principalmente nos primeiros dias após a intervenção. A certeza de evidência foi classificada como baixa. Devido à alta heterogeneidade clínica entre os estudos, não foi possível realizar qualquer meta-análise. Apesar das limitações desta revisão sistemática, a fototerapia se mostrou uma alternativa promissora na redução e controle da PP na reintervenção endodôntica não cirúrgica. Nos resultados do Artigo 2, dez estudos atenderam aos critérios de elegibilidade e foram incluídos, sendo 8 utilizados na síntese quantitativa. A meta-análise mostrou que todos os dados dos estudos apresentaram diferença significativa antes e depois da terapia fotodinâmica antimicrobiana na redução da carga microbiana em infecções endondônticas secundárias (OR 0,15 [0,07; 0,32], $p < 0,0001$). No geral, os estudos apresentaram baixo risco de viés e a análise das evidências foi classificada como moderada. Sugerese que a terapia fotodinâmica seja uma ferramenta benéfica e promissora, mostrando eficácia na redução da carga microbiana nos casos de reintervenção endodôntica. Em suma, a abordagem da utilização da fototerapia se demonstrou eficaz na diminuição da dor pós-operatória e na desinfecção dos canais radiculares, podendo ser uma terapia indicada nos casos de reintervenção endodôntica.

Palavras-Chave: Tratamento do canal radicular – Retratamento; Fototerapia; Fotoquimioterapia; Revisão sistemática; Meta-análise.

General Abstract

Nunes, LP. **Use of phototherapy as a complementary method in endodontic reintervention: systematic reviews and meta-analysis of clinical trials**. Dissertation (Master) – School of Dentistry, São Paulo State University, Araçatuba 2022.

This study aimed to carry out two systematic reviews with the following proposals: 1) Evaluate whether laser phototherapy would result in less postoperative pain (PP) in patients undergoing endodontic reintervention; and 2) Evaluate whether the use of antimicrobial photodynamic therapy (aPDT) would be effective in disinfection of root canals in cases of endodontic reintervention. Systematic Reviews were registered in PROSPERO (CRD42021243500 and CRD42021260013, respectively) and followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Searches were performed in the electronic databases PubMeb, Scopus, Web of Science, Embase, Web of Science, Clinical Trials and Cochrane Library and in the gray literature databases. Methodological quality and risk of bias were assessed by the Cochrane Risk of Bias tool for randomized clinical trials (RCT) and by the Newcastle-Ottawa (NOS) qualifier for non-RCT (prospective) studies. The analysis of the quality of evidence was performed based on the GRADE approach. The meta-analysis was performed using the R Meta package software, using a 95% confidence interval (CI). As for the results of Article 1: Five articles were included for analysis. Studies were classified as "low" risk of bias. Of the five clinical studies, four studies showed a significant decrease in PP after endodontic reintervention in the laser phototherapy groups when compared to the control group, mainly in the first days after the intervention. The certainty of evidence was rated low. Due to the high clinical heterogeneity between studies, it was not possible to perform any meta-analysis. Despite the limitations of this systematic review, phototherapy proved to be a promising alternative for the reduction and control of PP in conventional endodontic reintervention. In the results of Article 2, ten studies met the eligibility criteria and were included, being 8 used in the quantitative synthesis. The meta-analysis showed that all data from the studies showed a significant difference before and after antimicrobial photodynamic therapy in reducing the microbial load in secondary endodontic infections (OR 0.15 [0.07; 0.32], $p < 0.0001$). Overall, the studies presented a low risk of bias and the analysis of evidence was rated as moderate. It is suggested that photodynamic therapy is a beneficial and promising tool, showing efficacy in reducing the microbial load in cases of endodontic reintervention. In summary, the approach to the use of phototherapy has been shown to be effective in reducing postoperative pain and disinfection of root canals, and may be an indicated therapy in cases of endodontic reintervention.

Keywords: Root canal treatment – Retreatment; Phototherapy; Photochemotherapy; Systematic review; Meta-analysis.

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Introdução Geral

1. INTRODUÇÃO GERAL

O tratamento endodôntico tem como principais objetivos a limpeza, modelagem, desinfecção e preenchimento do sistema da canais radiculares para obtenção de cicatrização dos tecidos periapicais e prevenção de reinfecções [1]. No entanto, embora a terapia endodôntica apresente uma alta taxa de sucesso, por volta de 85 a 98%, em alguns casos ainda acontecem algumas falhas que acabam acarretando no insucesso da terapia [2].

Quando o sucesso no tratamento endodôntico primário não é obtido, a reintervenção deve ser realizada, sendo a abordagem não cirúrgica a primeira opção de tratamento para eliminar a infecção [3]. É importante ressaltar que as taxas de sucesso dos casos de reintervenção endodôntica são mais baixas do que do tratamento inicial [1], uma vez estes casos normalmente apresentam algumas condições capazes de diminuir a taxa de sucesso da terapia, como por exemplo, a presença de sintomatologia pré-operatória, extrusão apical da obturação do canal radicular, presença e/ou aumento do tamanho da lesão periapical, persistência de cepas microbianas, complicações intra-operatórias, entre outros [1,3, 4, 5].

Somado a isso, estudos também evidenciaram que casos de reintervenção endodôntica apresentam uma maior ocorrência de dor pós-operatória e com maior severidade do que no tratamento inicial [6], além de possuir uma microbiota mais complexa com espécies microbianas persistentes e capazes de resistir em condições extremas com poucos nutrientes, variações bruscas de pH, apresentando dessa forma, resistência a agentes antimicrobianos comumente utilizados na terapia endodôntica [7,8,9].

Desta maneira, nos últimos anos autores têm buscado cada vez mais investigar métodos complementares e/ou coadjuvantes com o objetivo de proporcionar vantagens e aumentar o índice de sucesso da terapia endodôntica [10,11,12]. Dentre esses métodos, a fototerapia com utilização de aparelhos de lasers de baixa ou alta potência, aparelhos de LED's, associados ou não a substâncias fotossensibilizadoras, foi citada como ferramenta promissora tanto no sentido de reduzir e modular a dor pós-operatória, quanto na redução de microrganismos e erradicação da infecção intracanal nos casos de tratamento primário e de reintervenção [7, 12, 14, 15]

Todavia, apesar de haver alguns estudos avaliando o uso da fototerapia na terapia endodôntica, as evidências a respeito da sua eficácia e adequados parâmetros de uso ainda são limitadas, não havendo um consenso na literatura quanto a sua correta indicação se tratando dos casos de infecção endodôntica secundária/persistente. Assim, tendo em vista que a reintervenção é uma etapa complexa e que requer o uso de métodos complementares para que o sucesso seja alcançado, é de suma importância avaliar: 1) se a fototerapia com laser resulta em menor dor pós operatória em comparação ao laser simulado em pacientes submetidos a reintervenção endodôntica, e 2) se o uso da terapia fotodinâmica antimicrobiana (aPDT) é eficaz na desinfecção de canais radiculares em casos de reintervenção endodôntica.

Artigo 1

2. Postoperative pain in conventional endodontic reintervention versus combined laser therapy: a systematic review

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2.1 ABSTRACT

BACKGROUND: This systematic review (SR) aimed to evaluate the efficacy of laser phototherapy (LPT) on the reduction in postoperative pain (PP) of endodontic origin after conventional/non-surgical reintervention of root canals.

METHODS: This SR was registered with PROSPERO (CRD42021243500) and followed the guidelines of the PRISMA. The PICOS strategy was used to locate randomized clinical trials comparing laser phototherapy and mock laser therapy in the management of endodontic pain after reintervention of root canals. The searches were performed in the PubMeb, Scopus, Web of Science, Embase, Web of Science, Clinical Trials, and the Cochrane Library. The methodological quality and risk of bias of the included studies were analyzed using the Cochrane Collaboration tool for risk of bias analysis. The quality of evidence was rated on the basis of the GRADE approach.

RESULTS: Five articles were included for analysis. The studies were classified as "low" risk of bias. Of the five clinical studies, foure studies showed a significant decrease in PP after endodontic reintervention in the laser phototherapy groups when compared to the control group, especially in the first days after the intervention. The certainty of the evidence was classified as low.

CONCLUSIONS: Despite the limitations of this systematic review, LPT was shown to be a promising alternative in reducing and controlling PP in conventional endodontic reintervention.

CLINICAL RELEVANCE: Suggests that use of Phototherapy in endodontic reintervention may be a safe and promising alternative to clinically efficacious agent for use in the management of postoperative pain in this procedure.

KEYWORDS: Endodontic retreatment; Phototherapy; Lasers; Postoperative pain; Systematic review.

2.2 INTRODUCTION

Even with technical-scientific advances, conventional endodontic therapies are still the “gold standard” therapy [1]. Despite this, the incidence of endodontic failure rates and the presence of postoperative pain are still observed [2]. Pain after endodontic procedures is commonly reported and undesirable occurrence for patients and professionals, affecting 3 to 58% of patients [2]. Although postoperative pain can occur both after primary endodontic treatment and after reintervention [3], studies show that reintervention is a contributing factor to postoperative complications, since it is more complex procedure, as it requires the solution to difficulties arising from the previous treatment [4,5].

The literature reports that postoperative pain after endodontic reintervention presents greater severity and with more significant occurrence than after the initial treatment [6,7]. This fact highlights the importance of investigating an adequate method of postoperative pain management in cases of reintervention, in order to prevent complications, provide more comfort to the patient, and increase the predictability and success of the endodontic treatments, since pain interferes negatively in the patient's daily activities [8,9].

Studies reveal some strategies aimed controlling postoperative endodontic pain, such as the prescription of analgesics, non-steroidal anti-inflammatory drugs, and corticosteroids [10,11]. However, added to the fact that drug therapy alone is not always sufficient to eliminate the painful process, the use of these drugs can cause certain adverse effects [12], requiring the use of alternative and/or complementary methods [13]. In this context, phototherapy using laser source has recently been cited as a promising and supporting tool in the sense of moderating and modulating pain after root canal treatment [8,14,15,16].

Phototherapy consists of the use of lasers, light-emitting diodes, and/or polarized light that has been widely investigated in different areas of Dentistry as an alternative to provide analgesia, biomodulation of inflammatory parameters, improvement in tissue repair and healing processes, and regenerative effects [8,17,18,19]. The use of laser provides an increase in the production of endogenous endorphins, reduces the histamine and bradykinin release, and promotes vasodilation and alteration in the synthesis of prostaglandins [20,21]. Recent studies used low-level laser phototherapy to manage postoperative endodontic pain and reported beneficial and satisfactory results, with significantly reduced pain levels [8,14,15,22].

However, although some studies evaluated phototherapy in the postoperative pain condition soon after endodontic reintervention, evidence regarding its efficacy is still scarce, and there is no consensus in the literature as to its correct indication. Thus, considering that cases of postoperative pain in endodontic reintervention are recurrent in clinical practice, and due to the absence of systematic reviews that assess the effect of phototherapy on postoperative pain in the respective cases, the objective of this systematic review was to answer this question, investigating whether laser phototherapy is effective in reducing pain of endodontic origin after reintervention of root canals.

2.3 MATERIALS AND METHODS

2.3.1 Protocol and registry

This systematic review was structured according to the Preferred Report Items checklist for Systematic Reviews and Meta-Analyses (PRISMA), according to the guidelines of the Cochrane Handbook [23], and different published studies [4,24,25]. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO - CRD42021243500).

2.3.2 Eligibility criteria

Inclusion criteria were: controlled and randomized clinical trials that evaluated postoperative pain in non-surgical / conventional endodontic reintervention associated or not with laser therapy, compared to conventional endodontic reintervention with simulated laser therapy / placebo, studies that evaluated pain using an analogue scale, studies that evaluated at least 12 patients per group and studies including a period of up to 7 days after endodontic reinterventions, as well as studies with patients without alterations or systemic diseases. A specific question was asked based on the population, intervention, comparison, outcome and design criteria (PICOS): "Is postoperative pain in patients who received phototherapy application lesser than in those who received mock laser application after endodontic reintervention?", according to the PICOS strategy described below:

(P) Population: Patients in need of endodontic reintervention;

(I) Intervention: Conventional endodontic reintervention associated with laser therapy;

(C) Comparison: Conventional endodontic reintervention with simulated laser therapy / placebo;

(O) Outcome: Postoperative pain

(S) Study design: Randomized controlled clinical trials (RCTs)

Prospective, retrospective studies, editorial letters, case series, case reports, non-human studies, literature review articles, and studies based on research or expert opinions were excluded. No language restrictions were applied and with no publication time restrictions. The study also excluded investigations that evaluated surgical endodontic reintervention.

2.3.3 Database sources and search strategy

An electronic search was performed in the following databases: PubMeb, Scopus, Web of Science, Embase, Clinical Trials, and the Cochrane Library. A specialized librarian guided the entire electronic search strategy. A manual search was also performed to identify manuscripts that might not have been retrieved by the electronic search in the following journals: Journal of Endodontics; International Endodontic Journal; Photodiagnosis and Photodynamic Therapy; Lasers in Medical Science; Journal of Photochemistry and Photobiology. B Biology; and Brazilian Oral Research.

To find unpublished or ongoing studies, the registry of clinical trials was investigated on the website ClinicalTrials.gov (www.clinicaltrials.gov). Additionally, the grey literature (produced at governmental, academic, entrepreneurial, and industrial levels, in printed or electronic format, yet not controlled by commercial publishers) was searched using the grey literature database OpenGrey (http://www.opengrey.eu/http://www.opengrey.eu/).

Two independent authors (LPN and GPN) conducted the electronic search for articles indexed until September 17, 2021 (Appendix A).

2.3.4 Study selection and data collection

Initially, the articles were selected by title and abstract according to the pre-established eligibility criteria. The articles were read in full if they were considered potentially eligible or if there was not enough information in the titles and abstracts. All discrepancies in the searches carried out in the databases were analyzed by a third reviewer.

One of the authors collected relevant data from the articles and a second author reviewed all the information collected. The variables collected from the articles were: author / year, country of study, study type, groups (n), mean age (age range), tooth root, status PAI, outcomes evaluated, number of patients needing medication, follow-up, results, and conclusion. If there was a lack of information, the authors of the article were contacted by e-mail.

2.3.5 Additional analysis

The kappa score was used to calculate the inter-reader agreement during the inclusion process for publication-evaluated databases. Any disagreements were resolved by discussion and consensus of all authors.

2.3.6 Evaluation of the risk of bias

The methodological quality and risk of bias of the included studies were analyzed by two independent reviewers (LPN and GPN), using the Cochrane Collaboration tool for analysis of risk of bias (http://handbook.cochrane.org). The evaluation criteria comprised six items: random sequence generation, allocation concealment, blinded evaluations of results, blinding of participants and staff, results with incomplete data, selective outcome reporting, and other possible sources of bias. The six domains were evaluated and the included studies were classified.

During evaluation of the risk of bias, any divergences between reviewers were solved by discussion and consensus and, if necessary, with the aid of a third reviewer (GSA). For each aspect of quality analysis, the risk of bias for each domain was identified following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org). Each criterion was scored as "yes", indicating low risk of bias; "no", indicating high risk of bias; and "unclear", indicating lack of information or uncertainty about the potential of bias.

If blinding was applied for patients, the domains "blinding of participants and personnel" and "blinding of outcome" were considered low risk since the operator cannot be blinded to the procedure and the patients themselves recorded their pain experience on a visual analogue scale. If the study evaluated swelling and postoperative pain on palpation and percussion, it was considered a low risk of bias if a separate and wholly blinded investigator evaluated these parameters.

2.3.7 Quality of evidence

The certainty of the evidence (certainty in the estimates of effect) was determined for the outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Randomized clinical studies start as strong evidence, and the quality of, or certainty in, the body of evidence decreases to moderate, low, or very low if serious or very serious issues, related to the risk of bias, inconsistency, indirectness, imprecision, and publication bias, are present [26]. The evaluations were carried out by two researchers independently (LPN and GPN) and then compared.

2.4 RESULTS

2.4.1 Literature search

The database search retrieved 629 studies, including 175 from PubMed / MEDLINE, 70 from Scopus, 166 from Embase, 77 from Web of Science, 139 from the Cochrane Library, and 2 in the manual searches. After removing the duplicates, a total of 597 studies remained for evaluation of Titles and Abstracts. After evaluating the Titles and Abstracts 586 articles were excluded and nine articles were selected to apply the Eligibility Criteria (Figure 1). After reading the full texts of these articles, four were excluded (Table 1). Thus, five studies were included, all of which were randomized clinical trials [6,27,28,29; 30]. The kappa agreement between investigators for the articles included in all databases (k = 0.93) showed an acceptable level of agreement.

2.4.2. Description of the studies

The characteristics of the five included studies are listed in Table 2. All of the included studies were randomized controlled clinical trials. Two studies were carried out in Turkey [27,28], and the others were performed in Iran [6,30] and Korea [29]. The time for pain assessment ranged from 4 hours to 7 days. The number of participants involved in these studies ranged from 33 to 73 patients, totaling 243 evaluated patients, with an average age ranging from 25.76 ± 8.14 to 46.4 ± 11.3 years.

Three studies performed endodontic treatment in a single session [6,27,30], and in the other two studies, treatment was carried out in two sessions [28,29]. To assess postoperative pain, all studies used pain assessment scales completed by the patients themselves, with four studies using the Visual Analogue Scale (VAS), and one study the Numerical Rating Scale (NRS) [27].

As for the number of roots, one article analyzed single-root teeth [27], three articles were performed with multi-root teeth [6,28,30], and one article evaluated both root morphologies [29]. With regard to preoperative symptoms, among the studies included, three evaluated symptomatic teeth [28,29,30], one analyzed asymptomatic teeth [27], and one study included teeth with both conditions [6]. According to the apical periodontitis index, three studies had teeth with a Periapical Index (PAI) score 2-3 [27,28,30], and the other studies did not report this information [6,29].

The parameters for using the laser are described in Table 3. All studies used phototherapy without the use of photosensitizing agents (photodynamic therapy), that is, phototherapy was performed and not photodynamic therapy. The diode laser was the most commonly used type of laser [6,27,28,30], with a wavelength ranging from 808 to 970 ± 15 nm. Only one study [29] used the neodymium laser (Nd: YAG) with a wavelength of 1440 nm. The power output ranged from 100 mW to 1000 mW, the energy from 70 J/cm^2 to 200 J/cm^2, and the duration of laser application ranged from 10 s to 80 s. All studies reported fiber optic diameter as 0.2 mm [27,28], 0.3 mm [29] 0.6 mm [6] and 10 mm [30]. Most studies applied the laser regimen only once, immediately after the biomechanical preparation of the root canals.

2.4.3 Characteristics of included studies related to reintervention

Regarding the studies included, three studies evaluated postoperative pain on percussion [27,28,29], and showed that endodontic reintervention associated with the use of laser therapy was able to reduce the levels of post-retreatment pain. Arslan et al. [2017] reported a significant reduction in pain in the laser group in the first four days ($P < 0.05$), with no significant difference between the two groups after five days [28]. The study evaluated by Fazlyab et al. [2021], observed that the pain index in patients in the laser group was lower in the first 4 hours after endodontic reintervention, and after this period, no significant difference was detected between the groups [30]. Only one study found no statistical difference between groups at any time when reintervention associated with laser therapy was performed compared to simulated laser [6].

Regarding medication consumption, all included studies reported this outcome [6,27,28,29,30]. In two studies [27,28] the consumption of analgesics after reintervention was significantly lower in the laser groups when compared to the simulated laser groups. Two studies [6,29] did not observe a statistical difference between the comparative groups, andin the study by Fazlyab et al. [2021], the patients did not use medication either before or after the endodontic procedure. Ibuprofen was prescribed in all studies analyzed, when necessary.

2.4.4 Assessment of risk bias

According to the Cochrane scale, the RCTs demonstrated a “low risk of bias” for generating a random sequence (selection bias). Two studies did not report enough information for allocation concealment, thus being considered as having an “unclear risk of bias” [6,29]. All included studies presented a low risk of bias for the domains: blinding of participants, personnel and outcome; incomplete outcome data; and selective outcome reporting. One study [6] presented a “high risk” in “other bias” because of the significant difference in the number of participants in each group (41 patients in the laser group and 20 patients in the mock laser group) (Figure 2).

2.4.5 Quality of evidence

The quality of evidence was classified as low. The reasons for each GRADE criterion are described in Table 4.

2.5 DISCUSSION

In recent years studies have shown possible beneficial effects of the use of a laser in preventing the development of postoperative endodontic pain, however, scientific evidence is needed to support the therapeutic choice regarding the use or not of laser therapy. The present study was based on the hypothesis that laser therapy provides satisfactory effects in the prevention/reduction in postoperative pain, immediately after conventional endodontic reintervention. A total of five randomized clinical studies were included, of which four [27,28,29,30] demonstrated a statistically significant improvement in reducing pain after endodontic reintervention. A single study [6] showed no difference in relation to the corresponding control group, but also did not demonstrate any adverse effects, suggesting that lasers can be suggested as an appropriate adjuvant tool.

The scientific literature reports that laser phototherapy has the potential to increase the amount of immunoglobulins, prostaglandins (such as I2, which has an anti-inflammatory effect), lymphokines, and endogenous endorphins (β-endorphins), decreasing the activity of C fibers and bradykinin, and playing an analgesic role [21,30]. In addition, laser phototherapy also inhibits the synthesis of neurotransmitters linked to pain [32], affects the local microcirculation and cellular metabolism causing regenerative effects [8,33], and induces the reduction in pain-inducing substances, such as histamine, substance P, and dopamine [20]. In addition to this, it presents a biological mechanism, since photonic energy is transformed into chemical energy inside the cell, in the form of ATP, which leads to the normalization of cellular function, and to pain relief [34]. All of these characteristics justify the beneficial results found in the studies evaluated.

The study by Asnaashari et al. [2017] was the only one among those evaluated which found no difference between the laser and placebo groups, both in reducing pain and reducing consumption of analgesics after endodontic reintervention [6]. However, it is important to note that this study has some biases, such as, for example, the lack of sample standardization, with a considerable discrepancy between the number of patients evaluated in the laser group (n = 41) and in the placebo group (n = 20) [6]. Another important limitation is the fact that this study evaluated symptomatic and asymptomatic teeth and did not isolate these variables in the outcome analysis. Added to this, approximately 25% of the patients included in the sample had been administering drugs to control pain prior to endodontic reintervention, which may possibly have influenced the results.

The studies by Arslan et al. [2017] and Yoo et al. [2014] evaluated symptomatic teeth in the preoperative period and showed that there was a significant reduction in pain in the first four postoperative days in the laser group [28,29], a period in which the highest occurrence of post-treatment pain is reported in the literature [35]. Previously, some authors observed that patients who already had symptoms prior to endodontic reintervention presented a significant incidence of postoperative pain [36]. This information can be justified, because biologically, preoperative pain may indicate the occurrence of infection of the root canal system of inflammation of the periapical tissues, which may accentuate after the procedure [37].

The study by Yoo et al. [2014] evaluated laser for pain relief in relation to levels of inflammatory cytokines and neuropeptides - calcitonin gene-related peptide (CGRP) and metalloproteinases-8 (MMP-8) in tooth root canal exudates with persistence of periodontitis symptomatic apical [29]. CGRP is a pro-inflammatory mediator that activates neurogenic blood vessel vasodilation, with a role in inflammation and immunomodulation, lowering the pain threshold and increasing pain sensitivity [38]. The authors found that the laser was able to decrease CGRP levels ($p = .049$), in addition to substance P ($p = .002$) and MMP-8 ($p = .002$). These findings corroborate the results already described by Arslan et al. [2018], where a diode laser was used after endodontic treatment and the authors concluded that the laser had a biomodulatory effect, modifying CGRP levels and identifying a positive association between VAS percussion pain scores and CGRP levels [39].

Other studies have established possible variables that can influence postoperative endodontic pain [37,40,41,42]. However, the approach to postoperative pain after endodontic reintervention is limited, since there are some difficulties related to the assessment of the occurrence of postoperative pain, as this is multifactorial and can vary both due to aspects related to the patients themselves and to the individual characteristics or conditions of the teeth. It is known that teeth requiring endodontic reintervention, present recurrent infections with more resistant microbial strains compared to the primary treatment [43,44], periapical lesions [45], and other difficulties inherent to the previous treatment that need to be overcome and can lead to a greater occurrence of postoperative pain. In addition, endodontic reintervention involves a series of complex processes, and each step has the potential to trigger post-treatment pain.

In relation to the consumption of medications, in the studies when it was necessary to use any medication, the prescribed medication was Ibuprofen, which comprises the class of non-steroidal anti-inflammatory drugs (NSAIDs) [6,27,28,29]. NSAIDs are widely used in the control of postoperative pain resulting from endodontic therapy and have the effect of relieving pain by reducing the chemical inflammatory mediators that activate nociceptors [46]. However, despite being recommended, these drugs have considerable side effects that may be unfavorable in tissue repair after treatment of root canals, such as a delay in the tissue repair process [12]. In most of the included studies, patients ingested NSAIDs even with laser irradiation. In two of the studies [27,28] the consumption of painkillers after treatment was significantly lower in the laser groups than in the simulated laser groups, while in the other studies [6,29,30] there was no difference between the groups. Authors report that laser therapy shows a favorable effect on tissue repair, and may be an alternative option to the use of medications [15], or in some cases, used as a complementary measure to NSAIDs in order to reduce their consumption [15].

Regarding to the parameters of laser use, some variables such as wavelength, time, power output, irradiance and place of application, can be factors of methodological variation, as well as being able to influence the results [47,48]. Although there is no wavelength considered standard and universally accepted. In Dentistry, low intensity lasers have the objective of generating a biomodulator and biostimulator effect and vary in the range of 600-900 nm [49]. Some authors believe that differences in wavelengths do not negatively affect the result obtained [49], however, there is a possibility that some wavelengths are more effective than others depending on the cell type [49]. In the studies included in this review, the wavelengths varied from 808 to 1440 nm. The time of use is also an important factor, as a time that is less than that required may have no effect on the pathologies, while an exacerbated time may cause inhibitory effects, requiring a balance of the irradiation time in order to obtain a beneficial effect [50]. The literature shows that treatment times in Dentistry vary from 30 - 60 s per treatment site [47]. In the included studies, the time ranged from 10 - 80 s.

It is worth mentioning that there are some limitations in this systematic review. The limited number of clinical studies included in the review, inconsistency and inaccuracy of the data meant that the quality of evidence was classified as low. Other important limitations are the variability and methodological differences that the included studies presented. The studies differ in terms of the parameters of lasers used, administration regime, selection and number of patients, and prescription of medications. In addition, it was not possible to perform any meta-analysis, since there is a high clinical heterogeneity among the studies, with no standardization of the methodological approach, which makes it impossible to compare results in quantitative form.

Thus, the results are presented only with qualitative outcomes, and these suggested that phototherapy may be an important and promising therapeutic tool in reducing postoperative pain in patients undergoing root canal reintervention. However, it is necessary to conduct more robust randomized clinical trials with standardization and high methodological quality, with clear, comprehensive, and pre-established protocols with regard to the parameters of laser to be used, pain scales, medication administration, randomization, and blinding, to further confirm the evidence base and elucidate the findings of this systematic review.

Although studies have observed that laser therapy is a promising alternative for postoperative pain reduction and control in conventional endodontic reintervention, this does not allow us to safely say that laser is an effective and assertive method. Since, due to the high heterogeneity, lack of methodological standardization among the included studies and the absence of a meta-analysis, future clinical studies are needed to investigate the efficacy of phototherapy in the treatment of post-retreatment pain to provide concrete evidence and allow clinical decisions to be taken with greater certainty.

2.6 REFERENCES

1. Torabinejad M, White SN (2016) Endodontic treatment options after unsuccessful initial root canal treatment: Alternatives to single-tooth implants. J Am Dent Assoc 147:214-20.

2. Shamszadeh S, Shirvani A, Eghbal MJ, Asgary S (2018) Efficacy of corticosteroids on postoperative endodontic pain: a systematic review and meta-analysis. J Endod 44:1057-65.
3. Gotler M, Bar-Gil B, Ashkenazi M (2012) Postoperative pain after root canal treatment: a prospective cohort study. Int J Dent 310467.
4. Nunes GP, Delbem ACB, Gomes JML, Lemos CAA, Pellizzer EP (2021) Postoperative pain in endodontic retreatment of one visit versus multiple visits: a systematic review and meta-analysis of randomized controlled trials. Clin Oral Investig 25:455-68.
5. Genc Sen O, Erdemir A, Canakci BC (2020) Effect of solvent use on postoperative pain in root canal retreatment: a randomized, controlled clinical trial. Clin Oral Investig 24:257-63.
6. Asnaashari M, Ashraf H, Daghayeghi AH, Mojahedi SM, Azari-Marhabi S (2017) Management of post endodontic retreatment pain with low level laser therapy. J Lasers Med Sci 8:128-31.
7. Wang C, Xu P, Ren L, Dong G, Ye L (2010) Comparison of post-obturation pain experience following one-visit and two-visit root canal treatment on teeth with vital pulps: a randomized controlled trial. Int Endod J 43:692-97.
8. Lopes LPB, Herkrath FJ, Vianna ECB, Gualberto Júnior EC, Marques AAF, Sponchiado Júnior EC. Effect of photobiomodulation therapy on postoperative pain after endodontic treatment: a randomized, controlled, clinical study (2019) Clin Oral Investig 23:285-92.
9. Monteiro LPB, Guerreiro MYR, de Castro Valino R, Magno MB, Maia LC, da Silva Brandão JM (2021) Effect of intracanal cryotherapy application on postoperative endodontic pain: a systematic review and metaanalysis. Clin Oral Investig 25(1):23-35.
10. Nagendrababu V, Gutmann JL (2017) Factors associated with postobturation pain following single-visit nonsurgical root canal treatment: A systematic review. Quintessence Int 48:193-208.
11. Arslan H, Gündoğdu EC, Sümbüllü M (2016) The effect of preoperative administration of antihistamine, analgesic and placebo on postoperative pain in teeth with symptomatic apical periodontitis: a randomized controlled trial. Eur Endod J 1:1-5.
12. Iwamoto S, Koga T, Ohba M, Okuno T, Koike M, Murakami A, et al (2017) Non-steroidal anti-inflammatory drug delays corneal wound healing by reducing production of 12-hydroxyheptadecatrienoic acid, a ligand for leukotriene B4 receptor 2. Sci Rep 7:13267.
13. Shirvani A, Shamszadeh S, Eghbal MJ, Asgary S (2017) The efficacy of non-narcotic analgesics on post-operative endodontic pain: A systematic review and meta-analysis: The efficacy of non-steroidal anti-inflammatory drugs and/or paracetamol on post-operative endodontic pain. J Oral Rehabil 44:709-21.

14. Doğanay Yıldız E, Arslan H (2018) Effect of low-level laser therapy on postoperative pain in molars with symptomatic apical periodontitis: a randomized placebo-controlled clinical trial. J Endod 44:1610-5.
15. Nabi S, Amin K, Masoodi A, Farooq R, Purra AR, Ahangar FA (2018) Effect of preoperative ibuprofen in controlling postendodontic pain with and without low-level laser therapy in single visit endodontics: A randomized clinical study. Indian J12 Dent Res 29:46-50.
16. Asnaashari M, Mohebi S, Paymanpour P (2011) Pain reduction using low level laser irradiation in single-visit endodontic treatment. j laser med sci [Internet]. 2011Nov.1 [cited 2021Feb.18];2(4):139-143.
17. Engel Naves Freire A, Macedo Iunes Carrera T, de Oliveira GJPL, Pigossi SC, Vital Ribeiro Júnior N (2020) Comparison between antimicrobial photodynamic therapy and low-level laser therapy on non-surgical periodontal treatment: a clinical study. Photodiagnosis Photodyn Ther 31:101756.
18. Nimbalkar M, Yawalkar M, Mahajan N, Dhoble SJ (2021) Potential of luminescent materials in phototherapy. Photodiagnosis Photodyn Ther 33:102082.
19. Hoseinpour Jajarm H, Asadi R, Bardideh E, Shafaee H, Khazaei Y, Emadzadeh M (2018) The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus-A systematic review and meta-analysis. Photodiagnosis Photodyn Ther 23:254-60.
20. Palaia G, Tenore G, Tribolati L, Russo C, Gaimari G, Del Vecchio A, Romeo U (2019) Evaluation of wound healing and postoperative pain after oral mucosa laser biopsy with the aid of compound with chlorhexidine and sodium hyaluronate: a randomized double blind clinical trial. Clin Oral Investig 23(8):3141-3151.
21. Kamal A, Salman B, Ar NH, Samsudin AR (2021) Management of dry socket with low-level laser therapy. Clin Oral Investig 25(3):1029-1033.
22. Coelho MS, Vilas-Boas L, Tawil PZ (2019) The effects of photodynamic therapy on postoperative pain in teeth with necrotic pulps. Photodiagnosis Photodyn Ther 27:396-401.
23. Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011). The Cochrane Collaboration. Available at: www.handbook.cochrane.org.
24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement. Syst Rev 4:1.
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700.
26. Ryan R, Hill S. How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group (2019) https://cccrg.cochrane.org/author-resources Version 30 March 2019. Accessed 17 February2020.

27. Genc Sen O, Kaya M (2019) Effect of root canal disinfection with a diode laser on postoperative pain after endodontic retreatment. Photobiomodul Photomed Laser Surg 37:85-90.
28. Arslan H, Doğanay E, Karataş E, Ünlü MA, Ahmed HMA (2017) Effect of low-level laser therapy on postoperative pain after root canal retreatment: a preliminary placebo-controlled, triple-blind, randomized clinical trial. J Endod 43:1765-9.
29. Yoo YJ, Shon WJ, Baek SH, Kang MK, Kim HC, Lee W (2014) Effect of 1440-nanometer neodymium:yttrium-aluminum-garnet laser irradiation on pain and neuropeptide reduction: a randomized prospective clinical trial. J Endod 40:28-32.
30. Fazlyab M, Esmaeili Shahmirzadi S, Esnaashari E, Azizi A, Moshari AA. Effect of low-level laser therapy on postoperative pain after single-visit root canal retreatment of mandibular molars: A randomized controlled clinical trial. Int Endod J. 2021 Nov;54(11):2006-2015. doi: 10.1111/iej.13608.
31. Gama SK, Habib FA, Monteiro JS, Paraguassú GM, Araújo TM, Cangussú MC, et al (2010) Tooth movement after infrared laser phototherapy: clinical study in rodents. Photomed Laser Surg 28:79-83.
32. Pallotta RC, Bjordal JM, Frigo L, Leal Junior EC, Teixeira S, Marcos RL, et al (2012) Infrared (810-nm) low-level laser therapy on rat experimental knee inflammation. Lasers Med Sci 27:71-8.
33. de Freitas LF, Hamblin MR (2016) Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Sel Top Quantum Electron 22(3):7000417.
34. AlGhamdi KM, Kumar A, Moussa NA (2012) Low-level laser therapy: a useful technique for enhancing the proliferation of various cultured cells. Lasers Med Sci 27:237-49.
35. Comparin D, Moreira EJL, Souza EM, De-Deus G, Arias A, Silva EJNL (2017) Postoperative pain after endodontic retreatment using rotary or reciprocating instruments: a randomized clinical trial. J Endod 43:1084-8.
36. Garcia-Font M, Durán-Sindreu F, Morelló S, Irazusta S, Abella F, Roig M, et al (2018) Postoperative pain after removal of gutta-percha from root canals in endodontic retreatment using rotary or reciprocating instruments: a prospective clinical study. Clin Oral Investig 22:2623-31.
37. Sadaf D, Ahmad MZ (2014) Factors associated with postoperative pain in endodontic therapy. Int J Biomed Sci 10:243–7.
38. Rechenberg DK, Galicia JC, Peters OA (2016) Biological Markers for Pulpal Inflammation: A Systematic Review. PLoS One 11:e0167289.
39. Arslan H, Köseoğlu S, Doğanay Yildiz E, Arabaci T, Savran L, Yildiz DA, et al (2018) Effect of intracanal diode laser application and low-level laser therapy on CGRP change. Braz. Oral Res 32:e125.
40. Alí A, Olivieri JG, Duran-Sindreu F, Abella F, Roig M, García-Font M (2016) Influence of preoperative pain intensity on postoperative pain after root canal treatment: a prospective clinical study. J Dent 45:39–42.

41. Glennon JP, Ng YL, Setchell DJ, Gulabivala K (2004) Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. Int Endod J 37:29–37.
42. Sathorn C, Parashos P, Messer H (2008) The prevalence of postoperative pain and flare-up in single-and multiple-visit endodontic treatment: a systematic review. Int Endod J 412:91–9.
43. Bordea IR, Hanna R, Chiniforush N, Grădinaru E, Câmpian RS, Sîrbu A, et al (2020) Evaluation of the outcome of various laser therapy applications in root canal disinfection: a systematic review. Photodiagnosis Photodyn Ther 29:101611.
44. Stuart CH, Schwartz SA, Beeson TJ, Owatz CB (2006) Enterococcus faecalis: its role in root canal treatment failure and current concepts in retreatment. J Endod 32:93-8.
45. Alves Vde O. Endodontic flare-ups: a prospective study (2010) Oral Surg Oral Med Oral Pathol Oral Radiol Endod 110:68-72.
46. Holstein A, Hargreaves KM, Niederman R (2002) Evaluation of NSAIDs for treating post-endodontic pain. Endod Top 3:3–13.
47. Carroll JD, Milward MR, Cooper PR, Hadis M, Palin WM (2014) Developments in low level light therapy (LLLT) for dentistry. Dent Mater 30:465-75.
48. AlFawaz YF, Alonaizan FA (2019) Efficacy of phototherapy in the adhesive bonding of different dental posts to root dentin: A systematic review. Photodiagnosis Photodyn Ther 27:111-6.
49. Bjordal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RA (2006) Low-level laser therapy in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. Photomed Laser Surg 24:158-68.
50. Huang YY, Sharma SK, Carroll J, Hamblin MR (2011) Biphasic dose response in low level light therapy - an update. Dose Response 9:602-18.
51. Eyuboglu TF, Olcay K, Özcan M (2017) A clinical study on single-visit root canal retreatments on consecutive 173 patients: frequency of periapical complications and clinical success rate. Clin Oral Invest 21:1761–8.
52. Olcay K, Eyüboglu TF, Özcan M (2019) Clinical outcomes of non surgical multiple visit root canal retreatment: a retrospective cohort study. Odontology 107:536-45.

Table 1. Reasons for the articles exclusion articles.

Reasons	References
Prospective study; absence of phototherapy intervention	Garcia-Font *et al*. [36] and Gotler *et al.* [3]
Retrospective study; absence of phototherapy intervention	Eyuboglu et *al*. [51] and Olcay et *al*. [52]

Table 2. General characteristics of the studies selected for this systematic review.

Author/ year (Country of study)	Study Design	Groups (n); M/F	Mean age (Age range)	Tooth root	Pre-op status	Status PAI	Outcomes evaluated	Outcome variable	Number of patients need medication	Follow-up	Results	Conclusion
Fazlyab et al. 2021 (Iran)	RCT	Laser: n=18 G2: Placebo: n=18 (16/20)	43.5	Multi	Symptomatic	Present Score periapical index 2-3	Postoperative pain	VAS Scale	Laser : 0 Pacebo: 0	4h,8h, 12h, 24h, 48h, 72h and 7 days	No significant difference was detected at 8, 12 and 24 h (p > .05), but the 4-h pain intensity was significantly lower in the laser group (p = .016)	The use of low-level laser therapy reduced the intensity of post-treatment pain only at 4 h after single-visit root canal retreatment of mandibular molars.
Genc Sen et *al.* 2019 (Turkey)	RCT	Laser: n=37; 19/18 Placebo: n= 36; 15/21	Laser: 36 Placebo: 31	Uni	Asymptomatic	Present Periapical lesion: 2–2 mm minimum size	Postoperative pain and postoperative pain on percussion	NRS Scale	Laser: Over 3 days: 0.11 (0.52) Placebo: Over 3 days: 1.11 (2.14) Medication: Ibuprofen 400 mg every 6h	24,48 and 72h	The pain scores in the first 2 d after treatment were significantly lower for the laser group than for the placebo (p=0.036 and 0.016, respectively); the significance disappeared on the third day (p=0.056).	The root canal disinfection with diode laser subsequent to chemomechanical procedures can efficiently reduce pain and provide comfort to the patient after endodontic retreatment.
Arslan et *al.* 2017 (Turkey)	RCT	Laser: n= 16; 8/8 Placebo: n= 17; 13/4	Laser: 32.62 ± 9.27 Placebo: 25.76 ± 8.14	Multi	Symptomatic	Present Score periapical index 2-3	Postoperative pain and postoperative pain on palpation and percussion	VAS Scale	Laser: 1 Placebo: 9 Medication: N.R	1day - 7days	The laser group reported less pain compared with the placebo group in the first 4 d (P<0.05). No statistically significant differences after 5d and 7 d	Low level laser may reduce postoperative pain after endodontic retreatment of mandibular molars.

											(P>0.05). No significant differences in terms of postoperative pain on percussion (P>0.05).	
Asnaashari et *al.* 2017 (Iran)	RCT	Laser: n= 41; N.R Placebo: n= 20; N.R	Laser: NR Placebo: N.R	Multi	Asymptomatic and Symptomatic	N.R	Postoperative pain, Consumption of analgesics after treatment	VAS Scale	Laser: 4 Placebo: 4 Medication: N.R	4, 8, 12, 24 and 48 h	No significant differences between groups.	Low level laser irradiation did not decrease pain associated with endodontic retreatment, however more studies are required.
Yoo et *al.* 2014 (Korea)	RCT	Laser: n= 20; 9/11 Placebo: n= 20; 7/13	Laser: 44.3 ± 9.1; Placebo: 46.4 ± 11.3	Uni And Multi: Anterior: 8/6; Posterior: 12/14	Symptomatic	Present Periapical Lesion, Score: N. R	Postoperative pain, postoperative pain on percussion and neuropeptide levels	VAS Scale	Laser: 0 Placebo: 0 Medication: Ibuprofen/ arginine	3 days	The laser irradiation was significantly more effective in reducing pain on percussion (P = .003) and in decreasing substance P (P = .002), CGRP (P = .049), and MMP-8 (P = .002) concentrations.	Favorable effects of the fiberoptic delivered Nd: YAG laser on the pain and inflammation modulation, suggesting a causal basis for use in nonsurgical endodontics.

Table 3. Laser parameters of included studies.

Author/year	Type of laser	Wavelength, Nanometres	Energy fluence (J/cm^2)	Power output (mW)	Power density (W/cm^2)	Duration of irradiation (seconds)	Optic fibre diameter (mm)	Site
Fazlyab et al. 2021	Diode laser	980	NR	500	6,89	15s	10	Soft tissues covering the mesial and distal apices of the tooth
Genc Sen et *al.* 2019	Diode Laser	940	NR	1000	NR	NR	0.2	From the apical to the most coronal part of the root canal.
Arslan et *al.* 2017	Diode Laser	970 ± 15	NR	500	2,86	30s	0.2	Mesial and distal root apexes
Asnaashari et *al.* 2017	Diode Laser	808	70 J/cm^2	100	NR	80s	0.6	At the level of the apices, buccal and lingual mucosa
Yoo et *al.* 2014	Neodymium:yttriumaluminum-garnet (Nd:YAG)	1440	200 J/cm^2	NR	NR	10s	0.3	The apical 3-mm level of the root canals

Table 4. Quality of evidence.

Quality assessment								
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty	Explanations
5	randomized trials	serious[a]	serious[b,c]	not serious	serious[d]	all plausible residual confounding would reduce the demonstrated effect.	⊕⊕◯◯ LOW	[a]Five studies were judged as "unclear" risk of bias. [b]Mean of pain in laser group were lower, compared to control group, in the studies. [c]Studies presented high methodological differences. [d]Total number of people evaluated was 243.

Figure 1. PRISMA Flowchart of study selection, presenting the number of studies identified, screened, eligible, and included in the review.

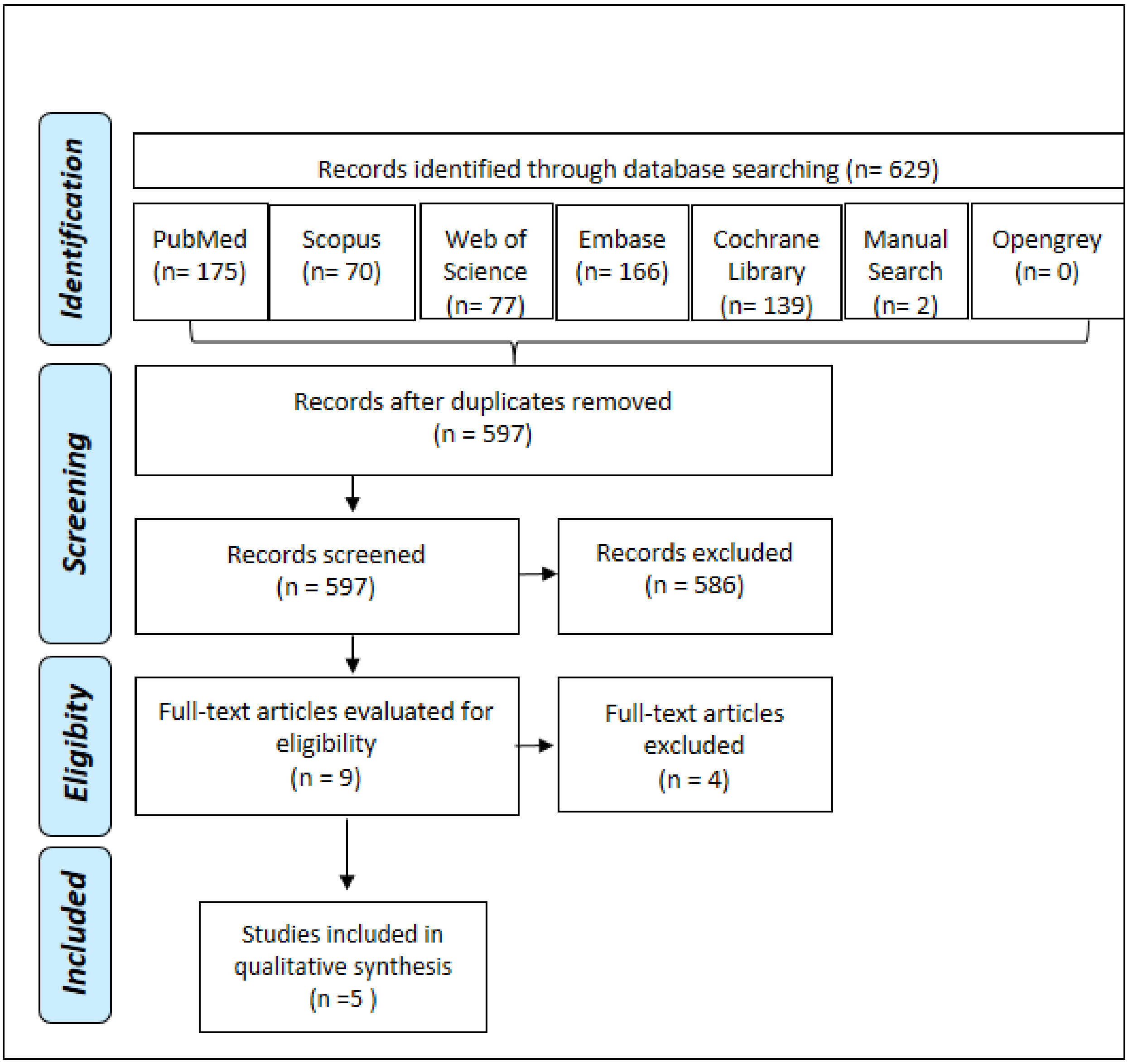
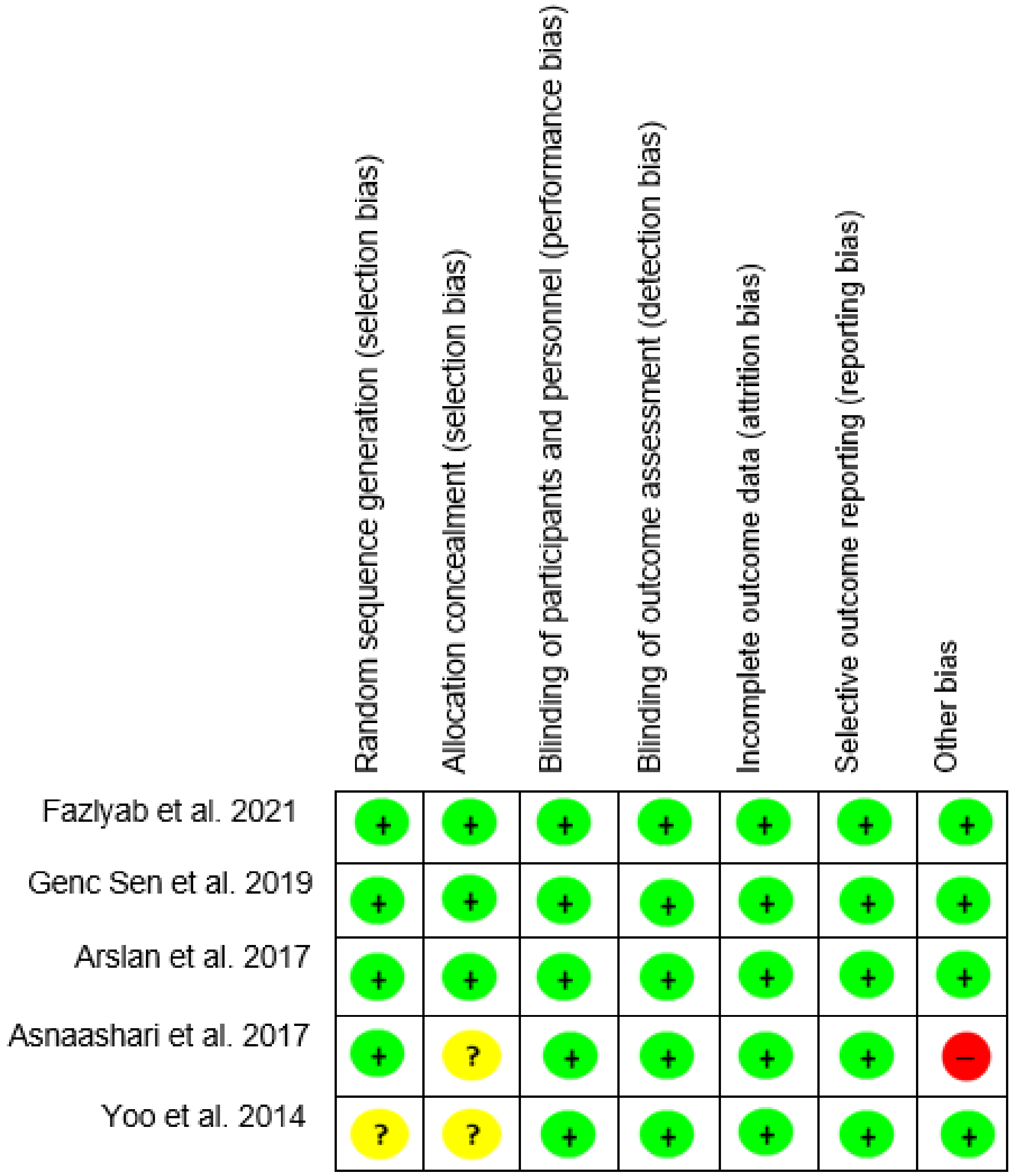


Figure 2. Bias risk of randomized clinical studies - Cochrane Scale.



Appendix A

Search Strategy
#1 (Tooth, Nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Endodontic retreatment) OR (Root channel retreatment) OR (Root canal retreatment)
#2 Phototherapy OR Phototherapies OR (Therapy, Photoradiation) OR (Photoradiation Therapies) OR (Therapies, Photoradiation) OR (Light Therapy) OR (Light Therapies) OR (Therapies, Light) OR (Therapy, Light) OR (Photoradiation Therapy) OR Laser
#3 ((Pain, Postoperative) OR (Post-surgical Pain) OR (Pain, Post-surgical) OR (Post surgical Pain) OR (Pain, Post-operative) OR (Pain, Post operative) OR (Postsurgical Pain) OR (Pain, Postsurgical) OR (Post-operative Pain) OR (Post operative Pain) OR (Post-operative Pains) OR (Postoperative Pain) OR (Postoperative Pain, Chronic) OR (Pain, Chronic Postoperative) OR (Chronic Postoperative Pain) OR (Chronic Post-surgical Pain) OR (Chronic Post surgical Pain) OR (Pain, Chronic Post-surgical) OR (Post-surgical Pain, Chronic) OR (Chronic Postsurgical Pain) OR (Chronic Postsurgical Pains) OR (Pain, Chronic Postsurgical) OR (Postsurgical Pain, Chronic) OR (Persistent Postsurgical Pain) OR (Pain, Persistent Postsurgical) OR (Postsurgical Pain, Persistent) OR (Post-operative Pain, Chronic) OR (Pain, Chronic Post-operative) OR (Post operative Pain, Chronic) OR (Chronic Post-operative Pain) OR (Chronic Post operative Pain) OR (Postoperative Pain, Acute) OR (Pain, Acute Postoperative) OR (Acute Postoperative Pain) OR (Acute Post-operative Pain) OR (Acute Post operative Pain) OR (Post-operative Pain, Acute) OR (Pain, Acute Post-operative) OR (Post operative Pain, Acute)
#1 AND #2 AND #3

Artigo 2

3. Antimicrobial photodynamic therapy in endodontic reintervention: a systematic review and meta-analysis

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3.1 ABSTRACT

Background: To evaluate the effectiveness of the use of antimicrobial photodynamic therapy (aPDT) in root canals disinfection in cases of endodontic retreatments.

Methods: This Systematic Review was registered in PROSPERO (CRD42021260013) and followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Searches were performed in the electronic databases PubMeb, Scopus, Web of Science, Embase, Web of Science, Clinical Trials and Cochrane Library. Methodological quality and risk of bias were assessed by the Cochrane Risk of Bias tool for randomized clinical trials (RCT) and by the Newcastle-Ottawa (NOS) qualifier for non-RCT (prospective) studies. Meta-analysis was performed using R software, version 3.6.3 with the "META" package assistant by the RStudio platform. The odds ratio (OR) measure of effect was calculated and the random effect model was applied with a 95% confidence interval, and heterogeneity tested by the I^2 index. The certainty of evidence was rated using GRADE.

Results: Regarding the 1513 studies screened, 10 met the eligibility criteria and were included, and 8 used in the quantitative synthesis. Meta-analysis showed that all of studies data presented a significant difference before and after of antimicrobial photodynamic therapy in the microbial load reduction in secondary endondontic infections (OR 0.15 [0.07; 0.32], p<0.0001). Overall, the studies had a low risk of bias and, the analysis of evidence by GRADE assessment was rated as moderate.

Conclusion: It is suggested that aPDT is a beneficial and promising tool, showing efficacy in reducing the microbial load in cases of endodontic retreatment.

Keywords: Root canal treatment - Retreatment; Photochemotherapy; Antimicrobial activity; Systematic review; Meta-analysis.

3.2 INTRODUCTION

Root canal systems (RCS) decontamination and microorganisms (MO) eradication are an essential step in endodontic treatment and is directly related to the therapy success, since MO and its toxins present an important function in pulp and periapical pathologies development [1]. Some microbial species are able of forming biofilms, colonizing areas of difficult access and elimination, which can impair tissue repair and contribute to the endodontic therapy failure [2].

The complete elimination of MO from RCS is considered a complex and challenging goal [3]. The most widespread procedures aiming to eliminateintracanal infection include mechanical instrumentation for cleaning and shaping the RCS, use of irrigating solutions with antimicrobial action, such as chlorhexidine and sodium hypochlorite, and application of intracanal medication, such as calcium hydroxide [4]. Although these techniques are able to reduce the MO amount in the RCS, they cannot provide its total eradication [5]. This is related to the fact that irrigation instruments and solutions are often unable to act in deep areas of RCS due to anatomical complexity, in addition to the fact that some bacteria develop resistance to these methods [6].

According to Siqueira [2001] the microbial species associated with primary endodontic infections are generally mixed biofilms with a predominance of gram-negative anaerobic bacteria (G-) and in secondary endodontic infections microbial species are associated with gram-positive bacteria (G+) [3]. Among the G+ bacteria, *Enterococcus faecalis* is a facultative anaerobic MO and one of the most prevalent species found in retreatment cases [7]. This MO has the ability to form biofilm [8], surviving in severe conditions with minimal amounts of nutrients and to tolerate ocilations of pH, temperature and O_2 concentration within the root canal, thus being resistant to antimicrobial agents, including calcium hydroxide medication [9,10].

Due to the MO presence in RCS being one of the main causes of endodontic failure, some complementary methods have been investigated to eliminate MO and neutralize their toxic products [11]. Among these additional methods, antimicrobial photodynamic therapy (aPDT) is an antimicrobial strategy that is based on the chemical interaction between a non-toxic photosensitizer (PS) and a low-intensity laser with a specific wavelength [12]. This interaction with the oxygen of the environment generates reactive oxygen species (ROS) causing damage to the membrane and intracellular molecules of the MO [11,12]. The aPDT presents promising characteristics in terms of MO amount reduction in RCS, and has the advantage of not causing microbial resistance [12, 13].

However, despite some studies evaluating aPDT in microbial reduction in endodontic retreatment cases [6, 14], evidence regarding to its effectiveness is still scarce, and there is no consensus in Literature as to its correct indication. Thus, considering that cases of endodontic failure are recurrent, that microbial strains in retreatment are more resistant than in primary infection, and given the absence of Systematic Reviews of clinical studies that assess the effect of aPDT in secondary infections, the purpose of this Systematic Review was to answer this clinical question and investigate whether aPDT is effective in reducing microbial species in cases of root canal retreatments.

3.3 MATERIALS AND METHODS

3.3.1 Protocol and registry

This systematic review was conducted following guidelines for systematic reviews and meta-analyses in accordance with PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses, in accordance with the Cochrane Handbook guidelines [15] and International Prospective Register of Systematic Reviews (PROSPERO) registration number: CRD42021260013.

3.3.2 Eligibility criteria

The studies met the following inclusion criteria: (a) clinical trials that evaluated the antimicrobial efficacy of aPDT in root canal retreatment, regardless of the type of photosensitizer used, type of laser, exposure time and power density; (b) studies with initial antimicrobial collection and post-application of aPDT; (c) patients without systemic diseases. Studies that did not meet the inclusion criteria were excluded. A specific question was asked based on the population, intervention, comparison, outcome and design criteria (PICO): “Is the use of antimicrobial photodynamic therapy effective in the disinfection of root canals during endodontic reintervention?”, according to the PICO strategy described below:

(P) Population: Patients in need of endodontic reintervention;

(I) Intervention: Endodontic reinterventions using aPDT;

(C) Comparison: Endodontic reinterventions not associated with aPDT

(O) Outcome: Antimicrobial activity.

In vitro studies, retrospective studies, editorial letters, case series, case reports, literature review articles and studies based on research or expert opinion were excluded. The present systematic review and the search strategy were developed only with articles published in English language and with no publication time restrictions.

3.3.3 Database sources and search strategy

An electronic search was performed on the following databases: PubMeb, Scopus, Web of Science, Embase, Web of Science, Clinical Trials and Cochrane Library. A specialized librarian guided the entire electronic search strategy. Hand search was also performed to identify manuscripts that might not have been retrieved by the electronic search for articles published in the following journals: Photodiagnosis and Photodynamic Therapy, Journal of Photochemistry and Photobiology. B Biology, Lasers in Medical Science, Journal of Endodontics, International Endodontic Journal, Clinical Oral Investigations, Brazilian Oral Research.

To find unpublished or ongoing studies, the registry of clinical trials was investigated on the website ClinicalTrials.gov (www.clinicaltrials.gov), without restriction as to date or language of publication. Additionally, the grey literature (produced at governmental, academic, entrepreneurial and industrial levels, in printed or electronic format, yet not controlled by commercial publishers) was searched using the grey literature database OpenGrey (http://www.opengrey.eu/http://www.opengrey.eu/).

Two independent authors (LPN and GPN) conducted the electronic search (Appendix A) for articles indexed until December 1, 2021.

3.3.*4 Study selection and data collection*

Initially, all collected studies were imported into an online reference manager (EndNote Web; Thomson Reuters Inc., Philadelphia, PA, USA), where duplicate researches were removed. Articles were selected by title and abstract according to pre-established eligibility criteria. After selecting the appropriate studies, the two authors (LPN and GPN) independently reviewed the full texts if they were considered potentially eligible or if there was insufficient information in the titles and abstracts. When the disagreement could not be resolved, a third investigator (GSA) was consulted. Authors were contacted as necessary for details on study design and clarification of data.

One of the authors collected relevant data from the articles and a second author reviewed all the information collected. The variables collected from the articles were: Author/year, Study design, Sample size, Tooth root, Periapical Index (PAI), Groups (n), Age, Bacteria, Evaluation method and Main Outcomes. In addition, aPDT application parameters were also collected, such as: light source, type and concentration of photosensitizer, optical fiber, laser wavelength (nm), energy (J), energy fluency (J/cm^2), output power (mW), power density (mW/cm^2) and duration of irradiation.

3.3.*5 Additional analysis*

The kappa score was used to calculate the inter-reader agreement during the inclusion process for publication-evaluated databases. Any disagreements were resolved by discussion and consensus of all authors.

3.3.6 *Evaluation of the risk of bias*

The methodological quality and risk of bias of the included studies were analyzed by two independent reviewers (LPN and GPN). The quality of the included randomized clinical trials (RCT) studies was assessed using the Cochrane Risk of Bias tool (http://handbook.cochrane.org), which checks for selection bias (random sequence generation and allocation), performance and detection bias (blinding of patients and outcome evaluation), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other possible biases (bias from other sources). The quality of the assessment of selected non-RCT (prospective) studies was verified using the Newcastle-Ottawa (NOS) scale. The NOS scale is based on 3 main components: selection, comparability, and outcome for cohort studies. According to this quality scale, a maximum of 9 stars can be assigned to a study, representing the highest quality. Five or fewer stars pose a high risk of polarization, while 6 or more stars pose a low risk of polarization. Thus, selection can provide four stars, two stars can be assigned for compatibility, and three stars can be assigned for exposure [16].

3.3.7 *Level of evidence: assessment classification, development and evaluation of recommendations (GRADE)*

To assess the certainty of evidence across studies, the GRADE tool [17] was applied using microbiological data. Included articles were evaluated for study design, risk of bias, inconsistency, indirection, and imprecision. The certainty of evidence (certainty in effect estimates) was determined for the outcome using the Assessment, Development and Evaluation of the Rating of Recommendations (GRADE) approach. The evaluations were carried out by two researchers independently (GPN and LPN) and then compared.

3.3.8 *Summary measurements*

The meta-analysis was performed using R software, version 3.6.3 with the “META” package assistant by the RStudio platform. Eight studies were able to be included in the meta-analysis [6, 14, 18, 19, 20, 21, 22, 23]. Two articles were not included in the meta-analysis due to missing data [24, 25]. The measure of effect was used odds ratio (OR). Additionally, the "Peto" metho was used to carry out the meta-analysis. The random-effect model was applied with a 95% confidence interval (CI). Heterogeneity was tested using the I^2 index, and an I^2 index ≥ 50% was considered substantial or high. To check publication bias, the trim-and-fill method was used.

3.4 RESULTS

3.4.1. Literature search

The initial search in the databases identified 1513 studies, including 361 from PubMed/MEDLINE, 438 from Scopus, 264 from Embase, 295 from the Web of Science, 151 from the Cochrane Library and 4 in manual searches. After removing the duplicates, a total of 686 studies remained for evaluation of titles and abstracts. After evaluating the titles and abstracts, 673 studies were excluded, thus 13 articles were selected for evaluation of the full text and application of the Eligibility Criteria. After reading the full texts of these articles, 3 were excluded (Figure 1). Thus, 10 studies were included in the systematic review for qualitative analysis, with 7 prospective studies [6, 14, 18, 19, 23, 24, 25] and 3 randomized clinical trials [20, 21, 22]. Figure 1 represents the study selection flowchart. The kappa agreement between investigators for the articles included showed an excellent level of agreement (k = 0.93).

3.4.2 Characteristics of the studies

Table 2 shows the general characteristics of the studies included in this systematic review. The number of participants involved in the studies ranged from 20 to 60 patients, resulting in a total of 288 patients evaluated. The articles originated from different countries, such as Iran [16, 19, 20, 21, 25], Brazil [18, 24], Croatia [6], Russia [23] and India [22].

All articles evaluated teeth in need of endodontic reintervention and with the presence of periradicular lesion. Regarding the number of treated teeth roots, six studies were performed with single-rooted teeth [6, 18, 19, 20, 22, 25], one study with multirooted teeth [21], one study evaluated both root morphologies [24], and two studies did not report this information [14, 23]. Regarding the 10 studies evaluated, only one dealt with surgical endodontic reintervention [24].

3.4.3 *Lasers paramenters and photosensitizer*

The laser parameters and photosensitizer types used are described in Table 3. The most used laser was the diode type [14, 18, 19, 20, 23, 24, 25]], with a wavelength ranging from 635 to 810 nm, with the exception of some studies that used Fotosan LED with approximately 630 nm of wavelength [21, 22] and Helbo laser with a wavelength of 660 nm [6]. The power of the laser devices ranged from 40 mW to 1000 mW, the optical fiber diameter from 200 to 750 µm and the duration of application ranged from 10s to 360s.

Regarding the sensitizing agents used, four studies used methylene blue [14, 19, 20, 24], one study evaluated polyethylenimine chlorin (e6) [18], other studies evaluated toluidine blue [21, 22, 25], Elofit - chlorin (e6) [23] and phenothiazine chloride [6]. In addition to varying the type, most of the studies also showed differences in relation to the photosensitizers concentration used.

3.4.4 Microbiological Results

Colony Forming Units (CFU) counting was the method used in all included studies to analyze the antimicrobial effect of aPDT. Five studies reported the MO investigated [6, 18, 20, 22, 25]. The study carried out by Pourhajibagher et al. [2017] evaluated 13 microbial species [*Enterococcus faecalis, C. albicans, Veillonella parvula, Propionibacterium acne, P. gingivalis, Aggregatibacter actinomycetemcomitans, A. naeslundii, L. rhamnosus, L. casei, Streptococcus sanguinis, S. saivarius, L. acidophilus. S. mitis*], being the study that evaluated a larger number of MO compared to the another studies included in this systematic review. Four studies investigated the *Enterococcus faecalis* MO [6, 20, 22, 25], and observed that this microbial species was the most prevalent in root canals before disinfection with aPDT. The other studies did not report the microbial species investigated [14, 24, 19, 21, 23].

Overall, all articles reported a significant reduction in the microbial load after using aPDT, showing the effectiveness of this therapy in MO reduction in retreatment cases. However, in two included studies, although the reduction in microbial load provided by aPDT was effective, it did not prove to be superior, being similar to the treatment proposed in the control group [14, 20].

It is relevant to take account that none of the studies reported any adverse effects regarding the use of aPDT, and any conventional therapy did not showsuperior efficacy to its use.

3.4.5.Risk of bias in included studies

The assessment of risk of bias in selected studies is shown in Figure 2 and Table 3. In general, the Cochrane risk-of-bias tool for the RCTs [20, 21, 22] was low bias risk. Regarding the selection bias, one study [21] did not report sufficient information for allocation concealment, being considered as “unclear risk of bias”. For detection bias, the studies performed by Ahangari et al. [2017] and Bharti et al. [2021] did not specify how it was blinded the outcome assessment.

The quality assessment for cohort studies was conducted by using NOS. All included studies were classified with a low risk of bias. The evaluated studies showed 7 [19, 23, 24, 25] and 8 stars [6, 14, 18]. The absence of stars for the studies was related to a lack of terms for the nonexposed cohort (directly related to study design) and additional factor in comparability. Besides the standardized methods, the absence of systemic diseases and the use of statistical methods to reduce the confounding factors may reduce the risk of bias of the included studies.

3.4.6 *Synthesis of meta-analysis and level of evidence*

The meta-analysis performed showed that all of studies data presented a significant difference before and after of aPDT in microbial load reduction in secondary endondontic infections: OR 0.15 [0.07; 0.32], $p < 0.0001$, with a substantial level of heterogeneity ($I^2 > 50\%$) (Figure 3A). Additionally, the trim-and-fill test did not identify any article with possible publication bias and presented substantial level of heterogeneity ($I^2 = 63\%$ remained (Figure 3B). Certainty of the evidence was classified as moderate (Table 4). Inconsistency item was categorized as serious because of the clinical heterogeneity of the studies included and the meta-analysis.

3.5 DISCUSSION

One of the main causes of endodontic therapy failure is the inadequate disinfection of the persistence of MO present in the SRC [26]. When these remaining MO have pathogenicity, reach a sufficient amount and manage to reach the periradicular tissues to induce or maintain the periradicular infection, occurring the endodontic treatment failure [26]. The anatomical complexity of the dental elements, poorly performed biomechanical preparation and the presence of resistant MO are some factors that hinder the elimination of bacteria only through the use of conventional chemical and mechanical techniques [21, 27], making the use of additional and coadjuvant methods such as aPDT indispensable in achieving treatment success [28].

The present study was based on the hypothesis that aPDT is an effective method to reduce microbial species in endodontic reintervention cases. Ten articles were included in the systematic review, and all of them showed that the use of aPDT managed to reduce the microbial amount, and none of the evaluated therapies (control groups) was superior to its use. In 8 studies, microbial reduction was significantly greater in the aPDT group when compared to the control groups, suggesting that aPDT may be a favorable method for microbial reduction in cases of endodontic retreatments

[6, 18, 19, 21, 22, 23, 24, 25]. In the other two studies included, the MO reduction was similar compared to the control groups [14, 20].

The effectiveness of aPDT in eliminating MO can be explained by the mechanism in which the light emitted by laser devices activates the photosensitizers which, in presence of oxygen, generates the reactive oxygen species and singlet oxygen that induce a phototoxic and oxidative reaction killing a wide range of pathogens and disrupting biofilms [11, 12, 29]. Studies report that there are some factors that must be taken into account to obtain more satisfactory results in the use of aPDT, such as the PS type and its concentration, light source radiation and its wavelength, output power, irradiation time, and other factors that can interfere with the final result. [28, 30, 4, 31].

In this sense, regarding to the light sources used, most of the included studies used laser devices [6, 14, 18, 19, 20, 23, 24, 25], and only two studies used LED light [21, 22]. The literature describes three main types of light sources that can be used for aPDT: laser, LED and halogen lamps [32, 33]. The laser has been effective in microbial reduction, but it has the limitation of having a high cost, and depending on the time and dose of irradiation, it can cause an increase in temperature and possible damage to tissues [33]. LED, in turn, has a lower cost and has the advantage of not causing an increase in temperature; however, it has a restricted wavelength spectrum [33, 34]. On the other hand, halogen lamps are devices that can be combined with any PS, as they have the characteristic of being spectrally filtered, however, it can also lead to temperature increases and tissue damage [33, 34].

The studies carried out by Asnaashari et al. [2016] and Ahangari et al. [2017] did not observe a significantly superior effect of the aPDT groups compared to the method evaluated in the control groups. In these studies, the methylene blue dye, which consists of a hydrophilic, positively charged compound with low molecular weight [11], was used as a photosensitizer. Literature reports that this dye is easy to enter into membranes of gram-positive and gram-negative bacteria, being able to promote an irreversible oxidation in MO, as long as it is activated by a light source with a specific wavelength of 660 nm, which consists of its maximum absorption dose [4, 11, 35, 36]. However, it is necessary to emphasize that these studies used diode lasers with inappropriate wavelength for activation of the PS used, using an incorrect wavelength, longer than recommended (810 nm), which may have influenced the results and absence of statistical difference between the groups.

Despite non-statistically significant difference between the groups, the study performed by Ahangari et al. [2017] compared the aPDT group with the control group where the indwelling dressing with calcium hydroxide was used. Although the use of aPDT did not promote statistically superior effect when compared to the evaluated control therapy, it is important to emphasize that the use of the indwelling dressing with calcium hydroxide it is necessary when endodontic reinterventions are performed in more than one clinical session, due to the need of changing/removing the intracanal medication [37]. In this sense, the use of aPDT has an advantage over this therapy, since aPDT has similar satisfactory effects on microbial reduction, in just a single clinical step [14, 20], providing more convenience to the patient and a better workflow for the professional.

In addition to all the aforementioned advantages, the use of aPDT has a very important beneficial characteristic when we think about endodontic reintervention cases, which is the ability to promote adequate disinfection without triggering microbial resistance mechanisms [38]. The most prevalent MO found in cases of secondary endodontic treatment is *Enteroccocus faecalis*, which is a difficult species to be eliminated, as it can survive in extreme conditions, with nutrient deprivation, with standing pH variations, and presenting resistance to antimicrobial agents, including calcium hydroxide medication, being an important factor in the pathogenesis of recurrent periradicular diseases [9, 10, 39]. Four of the included studies evaluated the effectiveness of using aPDT in eliminating *Enteroccocus faecalis* and three of them showed that this method was more effective when compared to conventional therapy, reducing up to 95% of the amount of this MO [6, 24, 25].

Two studies could not be included in the meta-analysis due to the high heterogeneity of data [24, 25]. This high heterogeneity can be explained by a limitation and absence of standardized protocols regarding the performance of aPDT and difference in study models. As an example of methodological variation, we can mention in relation to the types of light sources, type and concentration of PSs, in addition to different wavelengths and power density. In addition, all studies included in this review have a common limitation, which is the use of sterile paper tips to collect microbial samples. Although this method is classic and there is no other superior sampling method, it is not able to map the MO present throughout the root, as it cannot reach areas of difficult access, such as isthmus region, lateral and /or secondary canals, dentinal tubules and branches, being restricted to the main canal [40, 41]. This fact may have hidden the observation of greater beneficial effects provided by the use of aPDT, as well as it may have disguised the actual achievement of the absolute elimination of MO, since aPDT is expected to act in these difficult-to-access areas, promoting a more effective microbial eradication than conventional methods [42]

Therefore, it is extremely important to carry out more robust clinical studies in order to obtain studies with standardized protocols and study designs regarding the use of aPDT, to evaluate its use and elucidate the results found in this systematic review and meta-analysis study.

Within the limitations of this study, the evidence suggests that aPDT is a beneficial and promising therapy, showing efficacy in reducing microbial load in cases of endodontic reintervention. Due to the relatively low number of studies and heterogeneity of data, further randomized clinical trials are recommended to provide better understanding and support of the findings obtained in this review.

3.6 REFERENCES

[1] Trindade, A. C., De Figueiredo, J. A., Steier, L., & Weber, J. B. (2015). Photodynamic therapy in endodontics: a literature review. Photomedicine and laser surgery, 33(3), 175–182. https://doi.org/10.1089/pho.2014.3776.

[2] Cavalli, D., Toia, C. C., Flores Orozco, E. I., Khoury, R. D., Cardoso, F., Alves, M. C., Carvalho, C., & Valera, M. C. (2017). Effectiveness in the Removal of Endotoxins and Microbiological Profile in Primary Endodontic Infections Using 3 Different Instrumentation Systems: A Randomized Clinical Study. *Journal of endodontics*, *43*(8), 1237–1245. https://doi.org/10.1016/j.joen.2017.03.032.

[3] Siqueira J. F., Jr (2001). Aetiology of root canal treatment failure: why well-treated teeth can fail. *International endodontic journal*, *34*(1), 1–10. https://doi.org/10.1046/j.1365-2591.2001.00396.x.

[4] Strazzi-Sahyon, H. B., Oliveira, A., Carvalho, A. P., Figueiredo, R. B., Cintra, L., Gomes-Filho, J. E., Dos Santos, P. H., & Sivieri-Araujo, G. (2021). Influence of photodynamic therapy and intracanal medication on Martens hardness, elastic modulus and bond strength of glass-fiber posts to endodontically treated root dentin. *Photodiagnosis and photodynamic therapy*, *36*, 102571. https://doi.org/10.1016/j.pdpdt.2021.102571.

[5] Plotino, G., Cortese, T., Grande, N. M., Leonardi, D. P., Di Giorgio, G., Testarelli, L., & Gambarini, G. (2016). New Technologies to Improve Root Canal Disinfection. *Brazilian dental journal*, *27*(1), 3–8. https://doi.org/10.1590/0103-6440201600726.
[6] Jurič, I. B., Plečko, V., Pandurić, D. G., & Anić, I. (2014). The antimicrobial effectiveness of photodynamic therapy used as an addition to the conventional endodontic re-treatment: a clinical study. *Photodiagnosis and photodynamic therapy*, *11*(4), 549–555. https://doi.org/10.1016/j.pdpdt.2014.10.004.
[7] Chen, L., Li, X., Zhou, X., Zeng, J., Ren, Z., Lei, L., Kang, D., Zhang, K., Zou, J., & Li, Y. (2018). Inhibition of Enterococcus faecalis Growth and Biofilm Formation by Molecule Targeting Cyclic di-AMP Synthetase Activity. *Journal of endodontics*, *44*(9), 1381–1388.e2. https://doi.org/10.1016/j.joen.2018.05.008.
[8] Stuart, C. H., Schwartz, S. A., Beeson, T. J., & Owatz, C. B. (2006). Enterococcus faecalis: its role in root canal treatment failure and current concepts in retreatment. *Journal of endodontics*, *32*(2), 93–98. https://doi.org/10.1016/j.joen.2005.10.049.
[9] Saatchi, M., Shokraneh, A., Navaei, H., Maracy, M. R., & Shojaei, H. (2014). Antibacterial effect of calcium hydroxide combined with chlorhexidine on Enterococcus faecalis: a systematic review and meta-analysis. *Journal of applied oral science : revista FOB*, *22*(5), 356–365. https://doi.org/10.1590/1678-775720140032.
[10] Zancan, R. F., Calefi, P., Borges, M., Lopes, M., de Andrade, F. B., Vivan, R. R., & Duarte, M. (2019). Antimicrobial activity of intracanal medications against both Enterococcus faecalis and Candida albicans biofilm. *Microscopy research and technique*, *82*(5), 494–500. https://doi.org/10.1002/jemt.23192.
[11] Strazzi Sahyon, H. B., Pereira da Silva, P., Silva de Oliveira, M., Angelo Cintra, L. T., Gomes-Filho, J. E., Henrique Dos Santos, P., & Sivieri-Araujo, G. (2018). Effect of photodynamic therapy on the mechanical properties and bond strength of glass-fiber posts to endodontically treated intraradicular dentin. *The Journal of prosthetic dentistry*, *120*(2), 317.e1–317.e7. https://doi.org/10.1016/j.prosdent.2018.05.009.
[12] Soares, L., Crugeira, P., Nunes, I., Santos, A. S., Cangussú, M., de Almeida, P. F., Pinheiro, A., & Habib, F. (2019). Oral microbiological control by photodynamic action in orthodontic patients. *Photodiagnosis and photodynamic therapy*, *28*, 221–225. https://doi.org/10.1016/j.pdpdt.2019.08.002.
[13] Nunes, L. P., Chalub, L. O., Strazzi-Sahyon, H. B., Dos Santos, P. H., Cintra, L., & Sivieri-Araujo, G. (2021). Photodynamic therapy as a potential oral disinfection protocol during COVID-19 outbreak. *Photodiagnosis and photodynamic therapy*, *33*, 102187. https://doi.org/10.1016/j.pdpdt.2021.102187.
[14] Asnaashari, M., Godiny, M., Azari-Marhabi, S., Tabatabaei, F. S., & Barati, M. (2016). Comparison of the Antibacterial Effect of 810 nm Diode Laser and Photodynamic Therapy in Reducing the Microbial Flora of Root Canal in Endodontic Retreatment in Patients With Periradicular Lesions. *Journal of lasers in medical sciences*, *7*(2), 99–104. https://doi.org/10.15171/jlms.2016.17.
[15] Higgins, J.P.T., Green, S. (2011) Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011). The Cochrane Collaboration. Available at: www.handbook.cochrane.org.
[16] Wells, G., Shea, B., O'Connel,l D., et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis (2011) [Accessed 16 August 2021].

[17] Ryan, R. & Hill, S, (2019) How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group https://cccrg.cochrane.org/author-resources Version 30 March 2019. Accessed 17 August 2021.
[18] Garcez, A. S., Nuñez, S. C., Hamblim, M. R., Suzuki, H., & Ribeiro, M. S. (2010). Photodynamic therapy associated with conventional endodontic treatment in patients with antibiotic-resistant microflora: a preliminary report. *Journal of endodontics*, *36*(9), 1463–1466. https://doi.org/10.1016/j.joen.2010.06.001.
[19] Asnaashari, M., Homayuni, H., & Paymanpour, P. (2016). The Antibacterial Effect of Additional Photodynamic Therapy in Failed Endodontically Treated Teeth: A Pilot Study. *Journal of lasers in medical sciences*, *7*(4), 238–242. https://doi.org/10.15171/jlms.2016.42.
[20] Ahangari, Z., Mojtahed Bidabadi, M., Asnaashari, M., Rahmati, A., & Tabatabaei, F. S. (2017). Comparison of the Antimicrobial Efficacy of Calcium Hydroxide and Photodynamic Therapy Against *Enterococcus faecalis* and *Candida albicans* in Teeth With Periapical Lesions; An In Vivo Study. *Journal of lasers in medical sciences*, *8*(2), 72–78. https://doi.org/10.15171/jlms.2017.13.
[21] Asnaashari, M., Ashraf, H., Rahmati, A., & Amini, N. (2017). A comparison between effect of photodynamic therapy by LED and calcium hydroxide therapy for root canal disinfection against Enterococcus faecalis: A randomized controlled trial. *Photodiagnosis and photodynamic therapy*, *17*, 226–232. https://doi.org/10.1016/j.pdpdt.2016.12.009.
[22] Bharti, R., Tikku, A. P., Chandra, A., & Gupta, P. (2021). Antimicrobial Effectiveness of Photodynamic Therapy, 5% Sodium Hypochlorite and 2% Chlorhexidine Gluconate in Root Canal Treated Teeth: A Clinical Study. *Journal of Advanced Oral Research*, *12*(2), 193–199. https://doi.org/10.1177/23202068211018984.
[23] Manukyan, I.A. & Risovanniy, S.I. (2021). Efficacy of the root canal system disinfection by photodynamic therapywith a low-intensity diode laser and photosensitizer “elofit”. *International Research Journal*, 5 (107): 99-102. doi: 10.18454/IRJ.2227-6017.
[24] Garcez, A. S., Arantes-Neto, J. G., Sellera, D. P., & Fregnani, E. R. (2015). Effects of antimicrobial photodynamic therapy and surgical endodontic treatment on the bacterial load reduction and periapical lesion healing. Three years follow up. *Photodiagnosis and photodynamic therapy*, *12*(4), 575–580. https://doi.org/10.1016/j.pdpdt.2015.06.002.
[25] Pourhajibagher, M., Ghorbanzadeh, R., Parker, S., Chiniforush, N., & Bahador, A. (2017). The evaluation of cultivable microbiota profile in patients with secondary endodontic infection before and after photo-activated disinfection. *Photodiagnosis and photodynamic therapy*, *18*, 198–203. https://doi.org/10.1016/j.pdpdt.2017.02.013.
[26] Siqueira, J. F., Jr, & Rôças, I. N. (2008). Clinical implications and microbiology of bacterial persistence after treatment procedures. *Journal of endodontics*, *34*(11), 1291–1301.e3. https://doi.org/10.1016/j.joen.2008.07.028.
[27] Souza, L. C., Brito, P. R., de Oliveira, J. C., Alves, F. R., Moreira, E. J., Sampaio-Filho, H. R., Rôças, I. N., & Siqueira, J. F., Jr (2010). Photodynamic therapy with two different photosensitizers as a supplement to instrumentation/irrigation procedures in promoting intracanal reduction of Enterococcus faecalis. *Journal of endodontics*, *36*(2), 292–296. https://doi.org/10.1016/j.joen.2009.09.041.
[28] Sivieri-Araujo, G., Strazzi-Sahyon, H. B., Jacomassi, D. P., Dos Santos, P. H., Cintra, L., Kurachi, C., & Bagnato, V. S. (2021). Effects of methylene blue and curcumin photosensitizers on the color stability of endodontically treated intraradicular

dentin. *Photodiagnosis and photodynamic therapy*, *37*, 102650. Advance online publication. https://doi.org/10.1016/j.pdpdt.2021.102650.
[29] Strazzi Sahyon, H. B., Silva, P., Oliveira, M. S., Cintra, L., Dezan-Júnior, E., Gomes-Filho, J. E., Jacinto, R. C., Dos Santos, P. H., & Sivieri-Araujo, G. (2019). Influence of curcumin photosensitizer in photodynamic therapy on the mechanical properties and push-out bond strength of glass-fiber posts to intraradicular dentin. *Photodiagnosis and photodynamic therapy*, *25*, 376–381. https://doi.org/10.1016/j.pdpdt.2019.01.025.
[30] Chiniforush, N., Pourhajibagher, M., Shahabi, S., Kosarieh, E., & Bahador, A. (2016). Can Antimicrobial Photodynamic Therapy (aPDT) Enhance the Endodontic Treatment?. *Journal of lasers in medical sciences*, *7*(2), 76–85. https://doi.org/10.15171/jlms.2016.14.
[31] Strazzi-Sahyon, H. B., da Silva, P. P., Nakao, J. M., da Silva, P. Z., Nunes, L. P., Seron, M. A., Cintra, L., Dos Santos, P. H., & Sivieri-Araujo, G. (2021). Influence of two photodynamic therapy sessions and different photosensitizers on the bond strength of glass-fiber posts in different regions of intraradicular dentin. *Photodiagnosis and photodynamic therapy*, *33*, 102193. https://doi.org/10.1016/j.pdpdt.2021.102193.
[32] Nagata, J. Y., Hioka, N., Kimura, E., Batistela, V. R., Terada, R. S., Graciano, A. X., Baesso, M. L., & Hayacibara, M. F. (2012). Antibacterial photodynamic therapy for dental caries: evaluation of the photosensitizers used and light source properties. *Photodiagnosis and photodynamic therapy*, *9*(2), 122–131. https://doi.org/10.1016/j.pdpdt.2011.11.006.
[33] Zago, L., de Annunzio, S. R., de Oliveira, K. T., Barbugli, P. A., Valdes, B. R., Feres, M., & Fontana, C. R. (2020). Antimicrobial photodynamic therapy against metronidazole-resistant dental plaque bactéria. *Journal of photochemistry and photobiology. B, Biology*, *209*, 111903. https://doi.org/10.1016/j.jphotobiol.2020.111903.
[34] Silva, P. C., De Fátima Zanirato Lizarelli, R., Moriyama, L. T., De Toledo Porto Neto, S., & Bagnato, V. S. (2005). Temperature analysis during bonding of brackets using LED or halogen light base units. *Photomedicine and laser surgery*, *23*(1), 41–46. https://doi.org/10.1089/pho.2005.23.41.
[35] Chiniforush, N., Pourhajibagher, M., Shahabi, S., & Bahador, A. (2015). Clinical Approach of High Technology Techniques for Control and Elimination of Endodontic Microbiota. *Journal of lasers in medical sciences*, *6*(4), 139–150. https://doi.org/10.15171/jlms.2015.09.
[36] Pourhajibagher, M., Kazemian, H., Chiniforush, N., Hosseini, N., Pourakbari, B., Azizollahi, A., Rezaei, F., & Bahador, A. (2018). Exploring different photosensitizers to optimize elimination of planktonic and biofilm forms of Enterococcus faecalis from infected root canal during antimicrobial photodynamic therapy. *Photodiagnosis and photodynamic therapy*, *24*, 206–211. https://doi.org/10.1016/j.pdpdt.2018.09.014.
[37] Nunes, G. P., Delbem, A., Gomes, J., Lemos, C., & Pellizzer, E. P. (2021). Postoperative pain in endodontic retreatment of one visit versus multiple visits: a systematic review and meta-analysis of randomized controlled trials. *Clinical oral investigations*, *25*(2), 455–468. https://doi.org/10.1007/s00784-020-03767-7.
[38] Zoccolillo, M. L., Rogers, S. C., & Mang, T. S. (2016). Antimicrobial photodynamic therapy of S. mutans biofilms attached to relevant dental materials. *Lasers in surgery and medicine*, *48*(10), 995–1005. https://doi.org/10.1002/lsm.22534.
[39] Siqueira, J. F., Jr, & Rôças, I. N. (2004). Polymerase chain reaction-based analysis of microorganisms associated with failed endodontic treatment. *Oral surgery, oral*

medicine, oral pathology, oral radiology, and endodontics, *97*(1), 85–94. https://doi.org/10.1016/s1079-2104(03)00353-6.
[40] Gonçalves, L. S., Rodrigues, R. C., Andrade Junior, C. V., Soares, R. G., & Vettore, M. V. (2016). The Effect of Sodium Hypochlorite and Chlorhexidine as Irrigant Solutions for Root Canal Disinfection: A Systematic Review of Clinical Trials. *Journal of endodontics*, *42*(4), 527–532. https://doi.org/10.1016/j.joen.2015.12.021.
[41] Ruksakiet, K., Hanák, L., Farkas, N., Hegyi, P., Sadaeng, W., Czumbel, L. M., Sang-Ngoen, T., Garami, A., Mikó, A., Varga, G., & Lohinai, Z. (2020). Antimicrobial Efficacy of Chlorhexidine and Sodium Hypochlorite in Root Canal Disinfection: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Journal of endodontics*, *46*(8), 1032–1041.e7. https://doi.org/10.1016/j.joen.2020.05.002.
[42] Qi, M., Chi, M., Sun, X., Xie, X., Weir, M. D., Oates, T. W., Zhou, Y., Wang, L., Bai, Y., & Xu, H. H. (2019). Novel nanomaterial-based antibacterial photodynamic therapies to combat oral bacterial biofilms and infectious diseases. *International journal of nanomedicine*, *14*, 6937–6956. https://doi.org/10.2147/IJN.S212807.

Table 1. General data of the studies selected for this systematic review.

Author/Year (Country)	Study design	Sample size	Tooth root	Status PAI	Groups	Age	Bacteria	Evaluation method	Main outcomes
Garcez *et al.*, 2010 (Brazil)	Clinical Study	21	Uni	Present Periapical lesion Size: N.R.	Group 1: Before endodontic therapy Group 2: After conventional endodontic therapy Group 3: After conventional endodontic therapy + aPDT	17 to 52 years	*Enterococcus sp, Prevotella sp, Actinomyces sp, Peptostreptococcus sp, Streptococcus sp, Fusobacterium sp, Porphyromonas sp, Enterobacter sp, and Propionibacterium sp.*	CFU	The use of aPDT as an adjuvant to conventional endodontic treatment leads to a significant further reduction of bacterial load and is effective against multi-drug resistant bacteria.
Juric *et al.*, 2014 (Croatia)	Clinical Study	21	Uni	Present Periapical lesion Size: N.R.	Group 1: Endodontic retreatment with 2.5% NaOCl and 17% EDTA Group 2: aPDT Group 3: Conventional endodontic therapy + aPDT	20 to 45 years	*Enterococcus faecalis, Peptostreptococcus, Streptococcus intermedius Actinomyces naeslundii, Propionibacterium acnes Bifidobactrium sp. Propionibacterium propionicum Actinomyces odontolyticus, Porphyromonas, Veillonella parvula, Prevotella intermedia and Pseudomonas aeruginosa*	CFU	The combination of endodontic treatment and aPDT was statistically more effective than endodontic treatment alone.
Garcez et al., 2015 (Brazil)	Clinical Study	28	Uni e multi	Present Periapical lesion Size: N.R.	Group 1: Conventional treatment using ultrasonic retrotip Group 2: Conventional treatment using ultrasonic retrotip + aPDT	17 to 52 years	N.R.	CFU	The microbiological samples showed an significant reduction with aPDT. aPDT highly improves the microbial reduction compared to the traditional technique.
Asnaashari et al., 2016 (Iran)	Clinical Study	20	N.R.	Present Periapical lesion Size: N.R.	Group 1: aPDT Group 2: Diode laser only	N.R.	N.R.	CFU	CFU/mL amounts showed statistically significant reduction in both groups.

Asnaashari et al., 2016b (Iran)	Clinical Study	30	Uni	Present Periapical lesion Size: 2-5mm	Group 1: Initial Group 2: After chemomechanical preparation Group 3: After chemomechanical preparation + additional PDT	N.R.	N.R.	CFU	The addition of aPDT to procedures significantly enhanced the number of bacteria-free samples compared with groups 1 and 2.
Ahangari et al., 2017 (Iran)	Randomized Clinical Trial	20	Uni	Present Periapical lesion Size: N.R.	Group 1: aPDT Group 2: $Ca(OH)_2$ therapy	N.R.	*Enterococcus faecalis, Candida. albicans*.	CFU	Group 1 presented similar CFU/mL reduction compared with group 2.
Asnaashari et al., 2017 (Iran)	Randomized Clinical Trial	20	Multi	Present Periapical lesion Size: N.R.	Group 1: aPDT Group 2: $Ca(OH)_2$ therapy	N.R.	N.R.	CFU	The number of CFU/mL was lower in group 1 compared with group 2.
Pourhajibagher et al., 2017 (Iran)	Clinical Study	14	Uni	N.R.	Group 1: After chemomechanical preparation Group 2: After chemomechanical preparation + additional aPDT	N.R.	*Enterococcus faecalis, Candida. albicans, Veillonella parvula, Propionibacterium acne, P. gingivalis, Aggregatibacter actinomycetemcomitans, A. naeslundii, L. rhamnosus, L. casei, Streptococcus sanguinis, Streptococcus saivarius, L. acidophilus, Streptococcus. mitis.*	CFU	The number of bacterial species was significantly reduced in specimens collected after PDT.
Bharti et al., 2021 (India)	Randomized Clinical Trial	54	Uni	Periapical lesion Index 3	Group 1: Disinfection with 5% Sodium Hypochlorite Group 2: Disinfection with 2% Chlorehexidine Group 3: Disinfection with aPDT	20 to 70 years	*Enterococcus faecalis*	CFU	Suggests that aPDT can achieve better infection control in the apical region of canal, and is more effective than NaOCl and CHO.
Manukyan & Risovanniy, 2021 (Rússia)	Clinical Study	60	N.R.	Present Periapical lesion Size: N.R.	Group 1: Standard endodontic treatment, with "Hypochloran-3"	30 to 50 years	N.R.	CFU	The disinfection of the canals of the teeth in the gourp 2, the content of microorganisms is 38.7% less (p = 0.0001), in

					Group 2: Standard endodontic treatment, with "Hypochloran-3" + aPDT				comparison with disinfection with the group 1.

Abbreviation: N.R. = Not Reported; $Ca(OH)_2$ = Calcium hydroxide; CFU = Colony Forming Units; NaOCl = Sodium hypoclorite; CHO = Chlorhexidine

Table 2. Laser and photosensitizer parameters.

Author/Year	Light source	PS/ concentration	Fiber (µm)	Wavelength (nm)	Energy (J)	Energy fluence (J/cm^2)	Power (mW)	Power density (mW/cm^2)	Irradiation time (s)
Garcez *et al.*, 2010	Diode laser	Polyethylenimine (PEI) and chlorin(e6) - PBS solution (60 mmol/L) (60s incubação)	200	660	9.6	N.R.	40	N.R.	240 s
Juric *et al.*, 2014	Helbo Laser	Phenothiazinium chloride (10 mg ml^{-1})	450	660	6	N.R.	100	N.R.	60 d
Garcez *et al.*, 2015	Diode laser	Methylene blue (60 µм — 3 min of pre-irradiation time)	200	660	15	N.R.	40	N.R.	360 s
Asnaashari *et al.*, 2016	Diode laser	Methylene blue (0.5 mL of 0.01%) 5 min	200	810	N.R.	N.R.	200	N.R.	40 s
Asnaashari *et al.*, 2016b	Diode laser	Methylene blue (50 mg/mL)	300	665	9.6	N.R.	1000	N.R.	240 s
Ahangari *et al*., 2017	Diode laser	Methylene blue (50 µg/mL)	200	810	N.R.	N.R.	200	N.R.	10 s
Asnaashari *et al*., 2017	Fotosan LED	Toluidine blue (0.5 mL of 0.1 mg/mL)	N.R.	630	N.R.	0.0012-0.0044	N.R.	2-4	60 s
Pourhajibagher et al., 2017	Diode laser	Toluidine blue (25 µg/mL)	750	635	N.R.	N.R.	220	N.R.	30 s
Bharti et al., 2021	Fotosan LED	Toluidine blue (100 µg/mL)	500	628	N.R.	N.R.	N.R.	N.R.	60 s
Manukyan & Risovanniy, 2021	Diode laser	Elofit - chlorin(e6)	N.R.	662	N.R.	N.R.	200-400	N.R.	40 s

Table 3. Risk of Bias of the Prospective Studies– NewCastle Ottawa.

Study	Selection				Comparability		Outcome			Total
	Exposed Cohort	Non exposided cohort	Ascertainment of exposure	Outcome of interest not present at start	Main factor	Additional factor	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Manukyan et *al.*, 2021	☆	0	☆	☆	☆	0	☆	☆	☆	7
Pourhajibagher et al., 2017	☆	0	☆	☆	☆	0	☆	☆	☆	7
Asnaashari et *al*., 2016a	☆	0	☆	☆	☆	☆	☆	☆	☆	8
Asnaashari et *al*., 2016b	☆	0	☆	☆	☆	0	☆	☆	☆	7
Garcez et al., 2015	☆	0	☆	☆	☆	0	☆	☆	☆	7
Juric et *al*., 2014	☆	0	☆	☆	☆	☆	☆	☆	☆	8
Garcez et *al*., 2010	☆	0	☆	☆	☆	☆	☆	☆	☆	8

Table 4. Evidence profile: Complementary effect of antimicrobial photodynamic therapy in the disinfection of root canals undergoing to retreatment.

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[aPDT]	[Control]	Absolute (95% CI)	
10	clinical trials	not serious	serious	not serious	not serious	none	189	189	OR 0.15 SD higher (0.07 lower to 0.32 lower)	⊕⊕⊕◯ MODERATE

CI: Confidence interva; SD: Standard Deviation; **OR:** odds rati

Figure 1. PRISMA 2020 Flow diagram of study selection, presenting the number of studies identified, screened, eligible, and included in the review.

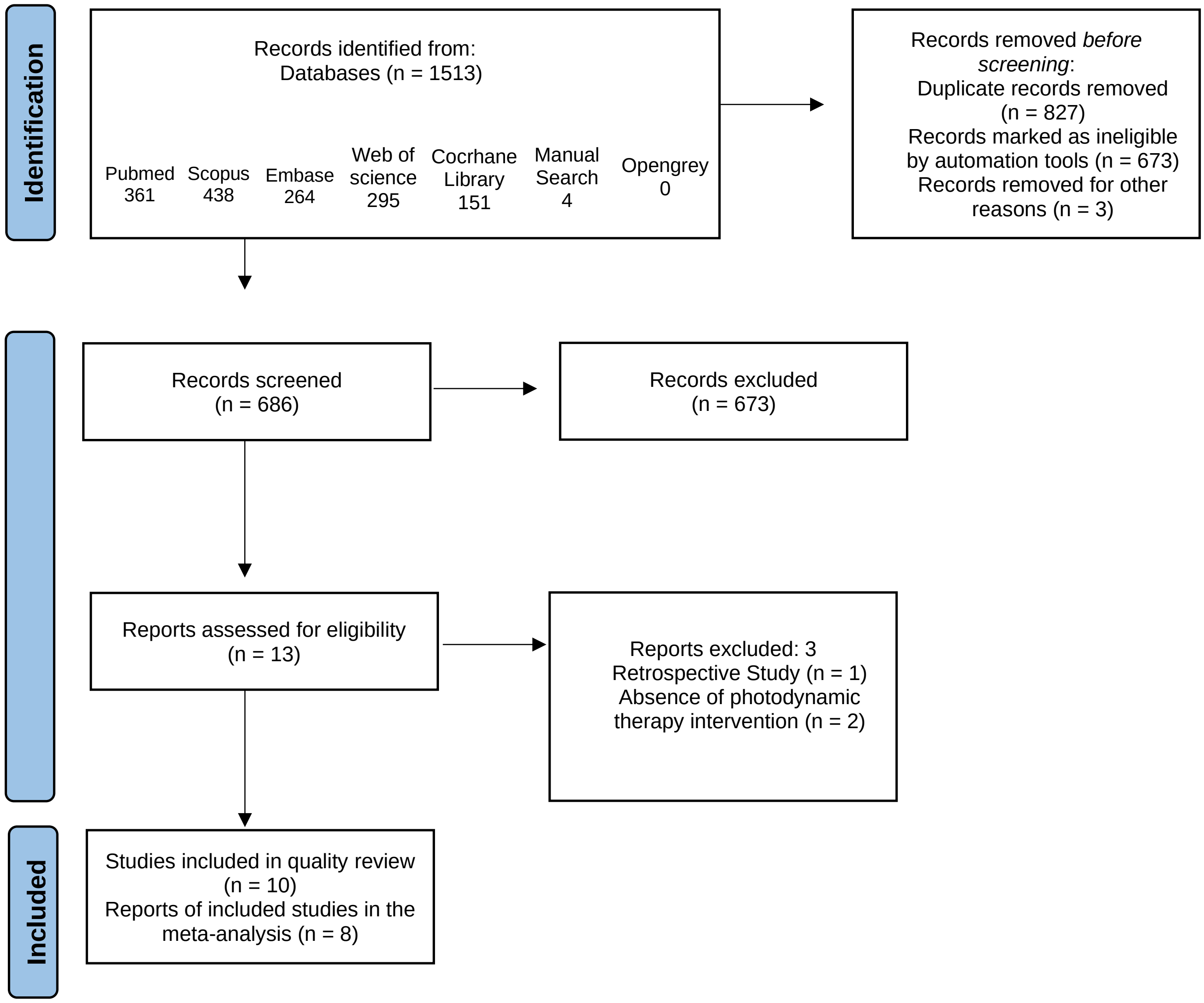
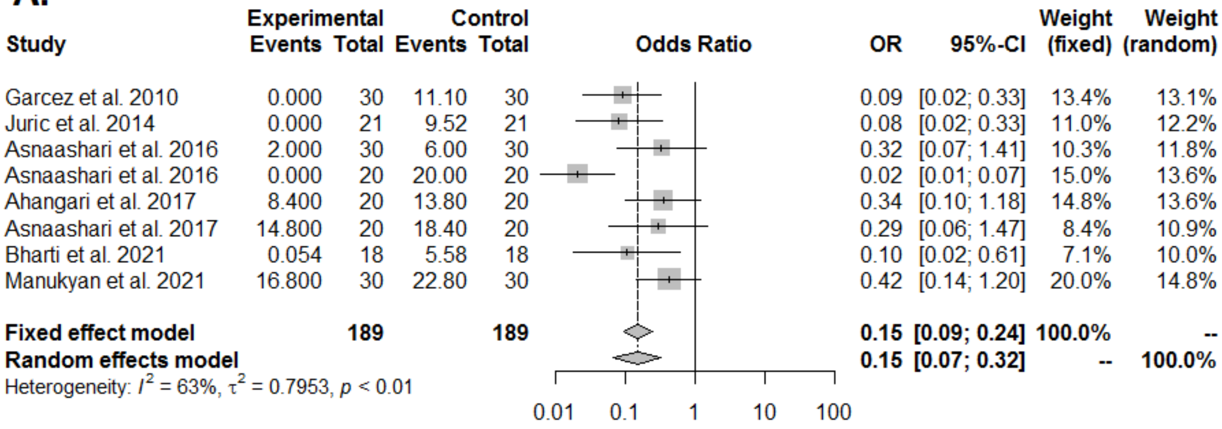


Figure 2. Bias Risk of Randomized Clinical Studies - Cochrane Scale

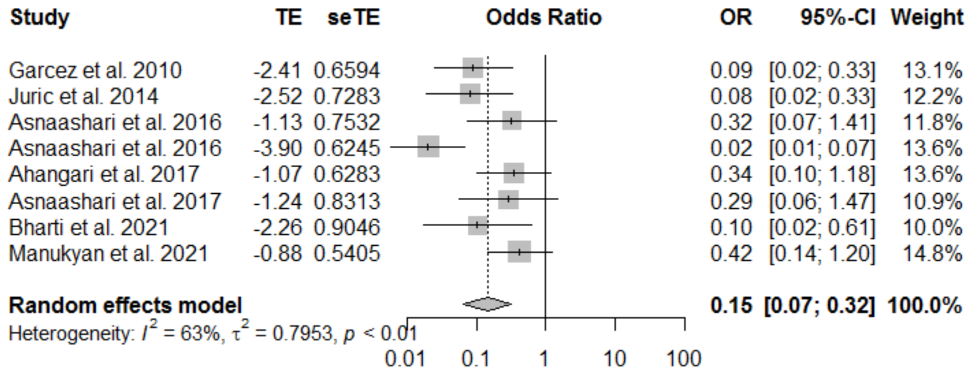
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other bias
Bharti et al. 2021	+	?	+	+	+	+	+
Asnaashari et al. 2017	+	+	+	?	+	+	+
Ahangari et al. 2017	+	?	+	+	+	+	+

Figure 3. Quantitative results. A: Meta-analysis results illustrated in a forest plot; B: Analysis of publication bias and meta-analysis (trim-and-fill). Experimental: Use of antimicrobial photodynamic therapy (aPDT); Control: conventional endodontic retreatment

A.



B.



Appendix A

Search Strategy
#1 (Retreatment OR Reoperation OR Retreatments OR (endodontic retreatment) OR (root canal reinterventions) OR (root canal retreatment) #2 (photochemotherapy OR (photodynamic therapy) OR (photo-activated disinfection) OR Photochemotherapies OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial photodynamic therapy) OR aPDT #3 (Anti-Bacterial Agents) OR (Anti-Bacterial Agents) OR (Antimicrobial activity) #1 AND #2 AND #3

4. CONCLUSÃO GERAL

Em suma, a abordagem do uso da fototerapia tem se mostrado eficaz na redução da dor pós-operatória e na desinfecção dos canais radiculares, podendo ser uma terapia indicada nos casos de reintervenção endodôntica.

5. REFERÊNCIAS DA INTRODUÇÃO GERAL

[1] Olcay K, Eyüboglu TF, Özcan M. Clinical outcomes of non-surgical multiple-visit root canal retreatment: a retrospective cohort study. Odontology. 2019 Oct;107(4):536-545. doi: 10.1007/s10266-019-00426-6.
[2] Salehrabi R, Rotstein I. Endodontic treatment outcomes in a large patient population in the USA: an epidemiological study. J Endod. 2004;30:846–50.
[3] Olcay K, Ataoglu H, Belli S. Evaluation of Related Factors in the Failure of Endodontically Treated Teeth: A Cross-sectional Study. J Endod. 2018 Jan;44(1):38-45. doi: 10.1016/j.joen.2017.08.029.
[4] He J, White RK, White CA, Schweitzer JL, Woodmansey KF. Clinical and Patient-centered Outcomes of Nonsurgical Root Canal Retreatment in First Molars Using Contemporary Techniques. J Endod. 2017 Feb;43(2):231-237. doi: 10.1016/j.joen.2016.10.029.
[5] Ng YL, Mann V, Gulabivala K. Outcome of secondary root canal treatment: a systematic review of the literature. Int Endod J. 2008 Dec;41(12):1026-46. doi: 10.1111/j.1365-2591.2008.01484.x.
[6] Asnaashari M, Ashraf H, Daghayeghi AH, Mojahedi SM, Azari-Marhabi S. Management of Post Endodontic Retreatment Pain With Low Level Laser Therapy. J Lasers Med Sci. 2017;8(3):128-131.
[7] Vendramini Y, Salles A, Portella FF, Brew MC, Steier L, de Figueiredo JAP, Bavaresco CS. Antimicrobial effect of photodynamic therapy on intracanal biofilm: A systematic review of in vitro studies. Photodiagnosis Photodyn Ther. 2020 Dec;32:102025. doi: 10.1016/j.pdpdt.2020.102025.
[8] Cavalli D, Toia CC, Flores Orozco EI, Khoury RD, Cardoso FGDR, Alves MC, Carvalho CAT, Valera MC. Effectiveness in the Removal of Endotoxins and Microbiological Profile in Primary Endodontic Infections Using 3 Different Instrumentation Systems: A Randomized Clinical Study. J Endod. 2017 Aug;43(8):1237-1245. doi: 10.1016/j.joen.2017.03.032.
[9] Gao Y, Jiang X, Lin D, Chen Y, Tong Z. The Starvation Resistance and Biofilm Formation of Enterococcus faecalis in Coexistence with Candida albicans, Streptococcus gordonii, Actinomyces viscosus, or Lactobacillus acidophilus. J Endod. 2016 Aug;42(8):1233-8. doi: 10.1016/j.joen.2016.05.002.
[10] Silva EJNL, Rover G, Belladonna FG, Herrera DR, De-Deus G, da Silva Fidalgo TK. Effectiveness of passive ultrasonic irrigation on periapical healing and root canal disinfection: a systematic review. Br Dent J. 2019 Aug;227(3):228-234. doi: 10.1038/s41415-019-0532-z.
[11] Korkut E, Torlak E, Gezgin O, Özer H, Şener Y. Antibacterial and Smear Layer Removal Efficacy of Er:YAG Laser Irradiation by Photon-Induced Photoacoustic Streaming in Primary Molar Root Canals: A Preliminary Study. Photomed Laser Surg. 2018 Sep;36(9):480-486. doi: 10.1089/pho.2017.4369.
[12] Jurič IB, Plečko V, Pandurić DG, Anić I. The antimicrobial effectiveness of photodynamic therapy used as an addition to the conventional endodontic re-treatment: a clinical study. Photodiagnosis Photodyn Ther. 2014 Dec;11(4):549-55. doi: 10.1016/j.pdpdt.2014.10.004.
[13] Bordea IR, Hanna R, Chiniforush N, Grădinaru E, Câmpian RS, Sîrbu A, Amaroli A, Benedicenti S. Evaluation of the outcome of various laser therapy applications in root canal disinfection: A systematic review. Photodiagnosis Photodyn Ther. 2020 Mar;29:101611. doi: 10.1016/j.pdpdt.2019.101611.

[14] Yoo YJ, Shon WJ, Baek SH, Kang MK, Kim HC, Lee W. Effect of 1440-nanometer neodymium:yttrium-aluminum-garnet laser irradiation on pain and neuropeptide reduction: a randomized prospective clinical trial. J Endod. 2014 Jan;40(1):28-32.
[15] Lopes LPB, Herkrath FJ, Vianna ECB, Gualberto Júnior EC, Marques AAF, Sponchiado Júnior EC. Effect of photobiomodulation therapy on postoperative pain after endodontic treatment: a randomized, controlled, clinical study. Clin Oral Investig. 2019;23(1):285-292.

Anexos

ANEXO A

Normas para submissão dos artigos confeccionados.

Artigo 1: **Clinical Oral Investigations**

Link para as normas:

https://www.springer.com/journal/784/submission-guidelines

Artigo 2: **Photodiagnosis and Photodynamic Therapy**

Link para as normas:

https://www.elsevier.com/journals/photodiagnosis-and-photodynamic-therapy/1572-1000/guide-for-authors