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REVIEW ARTICLE

Effectiveness of adjunct therapy for the treatment of apical periodontitis: A systematic review and meta-analysis

Maarten A. Meire[1] | **Juliana D. Bronzato**[2] | **Rafael A. Bomfim**[3] | **Brenda P. F. A. Gomes**[2]

[1]Section of Endodontology, Department of Oral Health Sciences, Ghent University, Ghent, Belgium

[2]Division of Endodontics, Department of Restorative Dentistry, Piracicaba Dental School, State University of Campinas - UNICAMP, Piracicaba, Brazil

[3]Department of Community Health, School of Dentistry, Federal University of Mato Grosso do Sul, Campo Grande, Brazil

Correspondence
Maarten A. Meire, Section of Endodontology, Department of Oral Health Sciences, Ghent University, C. Heymanslaan 10/P8, B – 9000 Gent, Belgium.
Email: maarten.meire@ugent.be

Abstract

Background: Adjunct therapy refers to any intracanal procedure going beyond chemomechanical preparation with instruments and traditionally delivered irrigants (excluding interim dressings). It is not clear whether and which of these adjunct therapies have a significant impact on the outcome of root canal treatment [healing of apical periodontitis (AP) and other patient-related outcomes].

Objectives: This systematic review aimed to analyse available evidence on the effectiveness of adjunct therapy for the treatment of AP in permanent teeth, according to a population, intervention, comparison, outcome, time and study design framework formulated *a priori* by the European Society of Endodontology.

Methods: Five electronic databases (PubMed, Embase, Scopus, Cochrane and Web of Science) were searched up to October 2021 to identify clinical studies comparing adjunct therapy to no adjunct therapy in adult patients with AP. Animal studies, reviews, studies with less than 10 patients per arm and studies with a follow-up time of less than 1 year, or less than 7 days for postoperative pain, were excluded. The quality of the included studies was appraised by the appropriate tools [Risk of Bias 2 (RoB2) for randomized clinical trials (RCTs) and Newcastle–Ottawa Scale for observational studies]. Meta-analysis was performed using a random-effects model. The certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results: Fourteen studies (13 RCTs and one retrospective cohort) fulfilled the inclusion criteria for this review. They evaluated different types of adjunct therapy: antimicrobial photodynamic therapy (aPDT; three studies), diode laser canal irradiation (3), Nd:YAG laser canal irradiation (2), Er;Cr:YSGG laser canal irradiation (1), ozone therapy (2) and ultrasonically activated irrigation (UAI) (4). Radiographical healing was reported in seven studies, but meta-analysis was only possible for UAI (two studies), showing no statistically significant difference in healing after 12 months. Pain after 7 days was reported in seven studies. Meta-analysis on three studies that used aPDT and on two studies using diode laser irradiation showed no significant difference in the prevalence of pain after 7 days between the control and adjunct therapy. According to RoB2 tool, six studies had a high risk of bias, five studies had some concerns, and two studies low risk of bias. The GRADE assessment revealed a

very low strength of evidence for diode laser, and low strength of evidence for PDT, ozone and UAI studies.

Discussion: The included studies displayed significant heterogeneity in terms of type of adjunct therapy, technical details per adjunct therapy, outcome reporting and several combinations of these, limiting the potential for meta-analysis.

Conclusions: There is insufficient evidence to recommend any adjunctive therapy for the treatment of apical periodontitis.

Registration: Prospero CRD42021261869.

KEYWORDS

adjunct therapy, antimicrobial photodynamic therapy, apical periodontitis, root canal treatment, ultrasonic activation

INTRODUCTION

Apical periodontitis (AP) is an inflammatory response to microorganisms that have colonized the root canal system after pulp necrosis (Kakehashi et al., 1965; Ricucci & Siqueira Jr., 2010). Consequently, decontamination of the infected root canal space is the fundamental step towards the resolution of AP (Sjogren et al., 1990). This is obtained by chemomechanical preparation of the root canal system, combining mechanical enlargement of the canal space with irrigation with antimicrobial agents such as sodium hypochlorite (NaOCl), chlorhexidine (CHX), followed by the use of chelating agents such as ethylene-diamine tetra-acetate (EDTA), and sometimes supplemented with application of an interappointment intracanal medication. Properly performed root canal treatment is effective in the majority of cases. Clinical studies have demonstrated pooled success rates of primary root canal treatment of teeth with AP around 80% (Ng et al., 2008). This indicates that one out of five root canal-treated teeth with AP does not display the desired outcome. Studies have shown that treatment failures are mainly caused by infection: microorganisms surviving the intracanal procedures and remaining inside the root canal system or invading the pulp space after treatment (Molander et al., 1998; Rocas & Siqueira Jr., 2012; Sjögren et al., 1997).

As infection is a major cause of root canal treatment failure, efforts have been made to develop novel techniques and devices that provide additional disinfection of the root canal system. The umbrella term for this kind of technique is 'adjunct therapy'. They involve an adjunctive treatment step following traditional cleaning and shaping of the root canal system and aim at improving root canal cleaning and microbial reduction in order to increase the success rate of root canal treatment. These adjunct therapies include several different approaches.

Some adjunct therapies are based on the use of vibrating tips placed inside the canal filled with irrigant. Oscillation of the tip results in intensive movement of the liquid in the canal, aiming at improved irrigant streaming, distribution and action. When the oscillation frequency is within the ultrasonic spectrum, it is referred to as ultrasonically activated irrigation (UAI; Aveiro et al., 2020; Herrera et al., 2017; van der Sluis et al., 2007), using metallic tips at driving frequencies typically between 30 and 40 kHz (Verhaagen et al., 2012). When the oscillation frequency is within the sonic spectrum, it is referred to as sonically activated irrigation. Tips are mostly plastic, and examples include the EndoActivator operating at 33–167 Hz (Jiang et al., 2010), or the Eddy, with a driving frequency of 6 kHz (Swimberghe et al., 2018).

Other adjunct therapy approaches apply intracanal pressure differences to obtain improved cleaning by the irrigants, such as the use of apical negative pressure irrigation (Fukumoto et al., 2006; Nielsen & Craig Baumgartner, 2007; Pawar et al., 2012), RinsEndo pressure-suction technology (Hauser et al., 2007; McGill et al., 2008) or the Gentlewave system creating hydrodynamic cavitation and broad-spectrum sound waves in the irrigant throughout the root canal system (Sigurdsson et al., 2018).

Another popular form of adjunct therapy is represented by the use of light. A first approach is the use of laser light for direct canal wall irradiation (Granevik Lindström et al., 2017), where the canal walls are exposed to irradiation with laser light of a particular wavelength, typically in the absence of irrigant. Mostly, near-infrared laser light is used for this purpose, for example, 980-nm diode laser light (Morsy et al., 2018) or 1064-nm Nd:YAG laser light (Koba et al., 1999). Another form of light-based adjunct therapy is the use of laser light to activate root canal irrigants (Liapis et al., 2021), called laser-activated irrigation (LAI). In this approach, pulsed laser light is targeting the irrigant within the root canal, to improve irrigant dynamics, distribution and cleaning action (De Meyer et al., 2017). For this purpose, far-infrared laser light (2790-nm Er;Cr:YSGG laser

or 2940-nm Er:YAG laser) is typically used. Antimicrobial photodynamic therapy (aPDT) represents a yet different light-based adjunct therapy. It is the intracanal application of a photosensitizer (a compound selectively binding microbial cells), followed by irradiation by light whose wavelength matches the absorption peak of the photosensitizer, resulting in a chemical reaction that produces microbicidal elements (Garcez et al., 2008).

Distinct from any of the previous groups are the following forms of adjunct therapy: the intracanal application of gaseous ozone (Huth et al., 2009; Kist et al., 2017), or the use of rotating smooth plastic tips to activate the irrigant (Townsend & Maki, 2009).

The majority of adjunct therapeutic steps have been tested extensively *in vitro* (Caputa et al., 2019; Plotino et al., 2019; Virdee et al., 2018), and collectively, the results appear to suggest a potential added value of adjunctive therapy over conventional chemomechanical preparation (Nagendrababu et al., 2018; Virdee et al., 2018), although the level of this evidence level is fragile due to heterogeneity of the data and likelihood of bias (Caputa et al., 2019; Virdee et al., 2018).

In contrast to the considerable amount of *in vitro* studies, clinical evidence is sparse, and it is not clear if any of these adjunct therapies has a significant impact on the outcome of root canal treatment. Therefore, this systematic review aims to critically appraise all available evidence regarding the efficacy of adjunct therapy for the treatment of AP, according to a population, intervention, comparison, outcome, time and study design (PICOTS) framework formulated *a priori* by the European Society of Endodontology (Duncan et al., 2021).

The specific research question is as follows: 'In patients with AP in permanent teeth (P), what is the efficacy of any intracanal procedure going beyond chemomechanical preparation with instruments and traditionally delivered irrigants (I), in comparison with chemomechanical preparation with instruments and traditionally (syringe-needle based) delivered irrigants (C), in terms of tooth survival, radiographic and clinical (pain, tenderness, swelling and need for medication [analgesics, antibiotics]) healing of AP (O)'?

MATERIALS AND METHODS

Protocol and registration

The protocol of this systematic review was prospectively registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero) with registration number CRD42021261869. Reporting was conducted in line with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis; Moher et al., 2009; Shamseer et al., 2015).

Eligibility criteria

Eligibility criteria for study selection were the following, according to the PICOTS strategy (Methley et al., 2014):

Participants/population

General population, adult patients undergoing primary or secondary root canal treatment of a tooth with radiographic evidence of AP.

Intervention

Adjunct therapy: any type of intracanal procedure going beyond chemomechanical preparation with instruments and traditionally delivered irrigants and carried out within the same visit. It includes irrigant activation methods/devices, light-mediated disinfection (photo-activated disinfection and direct laser irradiation) and the use of ozone.

Comparison

Chemomechanical preparation with instruments and traditionally (syringe-needle based) delivered irrigants alone (excluding the use of intracanal medication).

Outcome

The most critical outcome is 'tooth survival'. Other critical outcomes are 'pain, tenderness, swelling, need for medication (analgesics, antibiotics)', 'radiographic evidence of reduction of apical lesion size (loose criteria)' and 'radiographic evidence of normal periodontal ligament space (strict criteria)'.

Secondary outcomes include the following: 'tooth function (fracture, restoration longevity), 'need for further intervention', 'adverse effects (including exacerbation, restoration integrity, allergy)', 'oral health-related quality of life (OHRQoL)' and 'presence of sinus tract'.

Study design

Randomized controlled trials, comparative clinical trials, as well as longitudinal observational studies (retrospective

and prospective comparative cohort and case–control studies) are considered to ensure that all relevant clinical information that is often not tested in experimental studies is captured.

Duration

Follow-up time of a minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which is a minimum of 7 days and maximum of 3 months and OHRQoL which is minimum of 6 months and a maximum of as long as possible.

Exclusion criteria

Trials with less than 20 (10 in each arm) patients at the end of the study. Studies applying final irrigation with a different type of irrigant (e.g. CHX instead of NaOCl) or cooled irrigant (cryogenic therapy) were excluded because those were not considered 'adjunct therapy'.

Search strategy

The search process was performed independently by two examiners (BG and MM). The electronic databases PubMed, Embase, Scopus, Cochrane and Web of Science were searched up to 1 October 2021 to identify relevant studies. Google Scholar and OpenGrey were searched for grey literature. The search was restricted to studies published in English.

The electronic search strategy was developed using specific keywords and Medical Subject Heading (MeSH) terms combined with appropriate Boolean operators. The PubMed search strategy is described in Table 1. The other database searches were based on the same strategy.

The records obtained by the electronic search were imported into a reference manager (EndNote X9) and deduplicated using the dedicated function in the software. The remaining records were introduced into an electronic web application designed for the screening procedure in systematic reviews (rayyan.qcri.org). Two reviewers (BG & MM) screened independently and in duplicate all titles and abstracts against the eligibility criteria, using liberal acceleration. The full text of the included studies was assessed for eligibility by the same two reviewers in duplicate and independently. Any disagreement was resolved by discussion with a third reviewer (JB).

Hand-searching was done by screening the reference lists of included papers and previously published reviews on the subject. In addition, the last 20 years of *International Endodontic Journal* and *Journal of Endodontics* were screened for eligible papers. If necessary, authors were contacted by email for information regarding eligibility details, data extraction or data curation.

Two independent reviewers (MM & JB) extracted in duplicate the predetermined data items from all included studies in a predefined data extraction sheet that was drafted in Excel. Data extracted included study-related information (e.g. type of study, number of patients, number of arms, number of centres and period of follow-up), baseline characteristics of the participants recruited (patient age, type of teeth and pulpal and periapical diagnosis), clinical protocol information (chemomechanical canal procedures), adjunct therapy information (type and details as instrument size or wavelength or chemical substance) and outcomes (number of events per group and number of missing patients). In case of missing information, the corresponding authors of the studies were contacted using the mail address provided in the paper.

Quality assessment

Two reviewers (BG & MM) assessed independently and in duplicate the risk of bias (RoB) of individual studies using version 2 of the Cochrane risk of bias tool (RoB 2) for randomized trials (Sterne et al., 2019) and the Newcastle–Ottawa Scale for observational studies. In the case of RoB 2, a template was used to assess five different domains for each study, and in case of multiple outcomes, RoB was determined for every outcome. The overall risk of bias was determined as follows: when all domains were judged to be low risk, a trial was given a low risk of bias; a score of some concerns was given when one of the domains was determined to raise some concern; when a clinical trial had at least one domain with a high risk of bias, it was categorized as having a high risk of bias (Sterne et al., 2019). In case of disagreement, a discussion with a third reviewer (JB) was performed to reach a consensus.

Statistical analysis

The studies that met the inclusion criteria on the same type of endodontic adjunct therapy were selected for meta-analysis (minimum of two studies per adjunct therapy), which was carried out using Review Manager software (RevMan version 5.4, The Cochrane Collaboration, 2020). The Mantel–Haenszel type method of Greenland and Robins (1985) was used to estimate the pooled risk difference (RD) for all strata, assuming a random-effects model and with a confidence interval (CI) 95% for the

TABLE 1 PubMed search strategy

Name of database (interface): MEDLINE via PubMed		
Concept	**Line number**	**Search strategy**
Concept 1: orthograde root canal treatment	1	'root canal therapy' [mesh] OR 'root canal therapy' [tw] OR 'root canal treatment' [tw] OR 'endodontic treatment' [tw] OR 'endodontic therapy' [tw]
Concept 2: teeth with apical periodontitis	2	'periapical periodontitis' [mesh] OR 'periapical periodontitis' [tw] OR 'apical periodontitis' [tw] OR 'apical lesion*' [tw] OR 'periapical lesion*' [tw] OR 'periradicular periodontitis' [tw] OR 'apical radiolucenc*' [tw]
Concept 3: irrigant activation, light-mediated disinfection	3	'irrigant activation' [tw] OR 'irrigant agitation' [tw] OR 'final irrigation' [tw] OR 'supplementary irrigation' [tw] OR 'activated irrigation' [tw] OR 'photo activation' [tw] OR 'light activation' [tw] OR 'photodynamic therapy' [tw] OR 'photo activated' [tw] OR PDT [tw] OR UAI [tw] OR PUI [tw] OR SAI [tw] OR Eddy [tw] OR Endoactivator [tw] OR Vibringe [tw] OR Irrisafe [tw] OR ultrasonic* [tw] OR sonic* [tw] OR LAI [tw] OR PIPS [tw] OR laser [tw] OR 'apical negative pressure' [tw] OR Endovac [tw] OR Rinsendo [tw] OR Gentlewave [tw] OR 'XP-endo' [tw] OR ozon* [tw] OR 'manual-dynamic' [tw] OR 'manual dynamic' [tw] OR brush [tw]
Filter/search block: Randomized controlled trial, controlled clinical trial, observational	4	randomized controlled trial [pt] OR multicentre study [pt] OR controlled clinical trial [pt] OR clinical study [pt] OR clinical trial [pt] OR clinical trials as topic [mh] OR 'prospective stud*' [tw] OR random* [tw] OR trial* [tw] OR blind* [tw] OR allocat* [tw] OR 'multicenter study' [tw] OR 'multicentre study' [tw] OR rct [tw] OR 'clinical study' [tw] OR 'Case-Control' [tw] OR 'Case control' [tw] OR cohort [tw] OR longitudinal [tw] OR prospective [tw] OR retrospective [tw]
Combination of concepts	5	1 AND 2 AND 3 AND 4

pooled RD. A chi-square statistic test is given with the associated probability of the pooled relative risk being equal to one. Results are reported as a forest plot and presented as a pooled estimate RD with 95% CI. The inconsistency of results across studies is summarized in the I^2 statistic, which is the percentage of variation across studies that are due to heterogeneity rather than chance (Greenland & Robins, 1985). Publication bias analysis was not performed since there were less than five studies in each meta-analysis.

Quality of evidence collection

Quality of evidence and strength of recommendation was assessed by two authors (JB & BG) using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) guidelines (Guyatt et al., 2011), using the GRADEpro Guideline Development Tool software (McMaster University and Evidence Prime, 2022; available from gradepro.org). This assessment is based on study design, risk of bias, inconsistency (heterogeneity), indirectness (PICO), imprecision (number of events, CI and sample size) and publication bias. Scores 'not serious', 'serious' and 'very serious' were applied for each criterion. If the score 'serious' and 'very serious' was applied, there was a downgrade in one and two levels, respectively. The level of certainty amongst the evidence identified was characterized as high, moderate, low or very low (Guyatt et al., 2011). GRADE was performed for the outcomes supported by a meta-analysis (pain at 7 days after photodynamic therapy and 980-nm diode laser, radiographical healing after ozone therapy and UAI).

RESULTS

Study selection

Six hundred twenty-one (622) records were identified from the electronic databases and another ninety-three (93) through manual search. A total of 714 records were entered in EndNote, and after removing the duplicates, 394 records were entered into Rayyan. After screening titles and abstracts, 86 records we considered relevant, of which 80 full texts could be retrieved to assess eligibility. After full-text assessment, the corresponding authors of five studies were contacted by email for additional information or data, of which two provided the required information for inclusion or exclusion of the studies in the systematic review and meta-analyses. A total of 64 articles were excluded (Table S1). The main reasons for exclusion were the wrong outcome (e.g. only microbiological data or insufficiently long follow-up time) or the wrong intervention (e.g. no adjunct therapy; Table 2). Finally, 15 records met the inclusion criteria, representing 14 studies. Pietrzycka and

TABLE 2 Excluded studies with reasons

Reason for exclusion	Number of articles	Author(s), year
Wrong population	5	Abielhassan et al. (2021), Conejero et al. (2021), Dagher et al. (2019), Jesus et al. (2019), Mandras et al. (2020)
Wrong outcome	32	Ahangari et al. (2017), Amaral et al. (2020), Asnaashari et al. (2017), Aveiro et al. (2020), Ballal et al. (2020), Beus et al. (2012), Bharti et al. (2021), Braitt et al. (2013), Carvalho et al. (2020), Chen et al. (2016), Cohenca et al. (2013), de Miranda and Colombo (2018), Garcez et al. (2010), Granevik Lindström et al. (2017), Gueorgieva and Gergova (2021), Herrera et al. (2017), Huffaker et al. (2010), Janković et al. (2013), Jurič et al. (2014), Malkhassian et al. (2009), Martins et al. (2013), Moreira et al. (2021), Nakamura et al. (2018), Paiva et al. (2012), Paiva et al. (2013), Pawar et al. (2012), Rabello et al. (2017), Rodrigues et al. (2015), Saleh and Mammani (2020), Yoo et al. (2014), Yoshinari et al. (2019), Zorita-García et al. (2019)
Wrong intervention	18	Arslan et al. (2017), Azim et al. (2016), Calişkan and Sen (1996), Chávez de Paz et al. (2005), Cheung and Chan (2003), Chugal et al. (2001), Doğanay Yıldız and Arslan (2018), Doğanay Yıldız et al. (2019), Kebke et al. (2021), Lee et al. (2012), Llena et al. (2020), Loftus et al. (2005), Ng et al. (2004), Ng et al. (2011a), Ørstavik et al. (2004), Poornima et al. (2021), Restrepo-Restrepo et al. (2019), Siddique et al. (2020)
No control group	3	Asnaashari et al. (2016), Bonsor et al. (2006), Karakov et al. (2018)
Sample too small	4	Coelho et al. (2019), da Silva et al. (2018), Orozco et al. (2019), Vilas-Boas et al. (2021)
Wrong study design	2	Ng et al. (2011b), Smadi (2017)

Pawlicka (2011, 2013) published two works, both reporting the same data regarding the control group and adjunctive therapy group; therefore, only one (2011) was analysed. Ten authors were contacted for additional information or data. Most of them did not reply, and some replied with relevant information. Pietrzycka and Pawlicka (2011) and Souza et al. (2021) contributed with their entire dataset, enabling statistical analysis of their results. Figure 1 shows the flow diagram of the study.

Study characteristics

Tables 3 and 4 show the characteristics of the included studies. All of them were published within the last decade, except for Koba et al. (1999). Thirteen of the 14 studies were randomized controlled trials (RCT); one was a retrospective cohort study (Masilionyte & Gutknecht, 2018). The RCT by Pietrzycka and Pawlicka (2011) included teeth both with and without apical radiolucencies. As the authors provided their original dataset, data on teeth with apical radiolucencies could be retrieved and used for further analysis.

The majority of RCTs were parallel, 2-arm studies with a control group and an adjunct therapy group, except for Verma et al. (2020), which was a 3-arm studies comparing 2 adjunct therapies, and Souza et al. (2021), which was a 4-arm study but using only one type of adjunct therapy. Fourteen studies were qualitatively analysed, and out of them, 11 were quantitatively analysed through

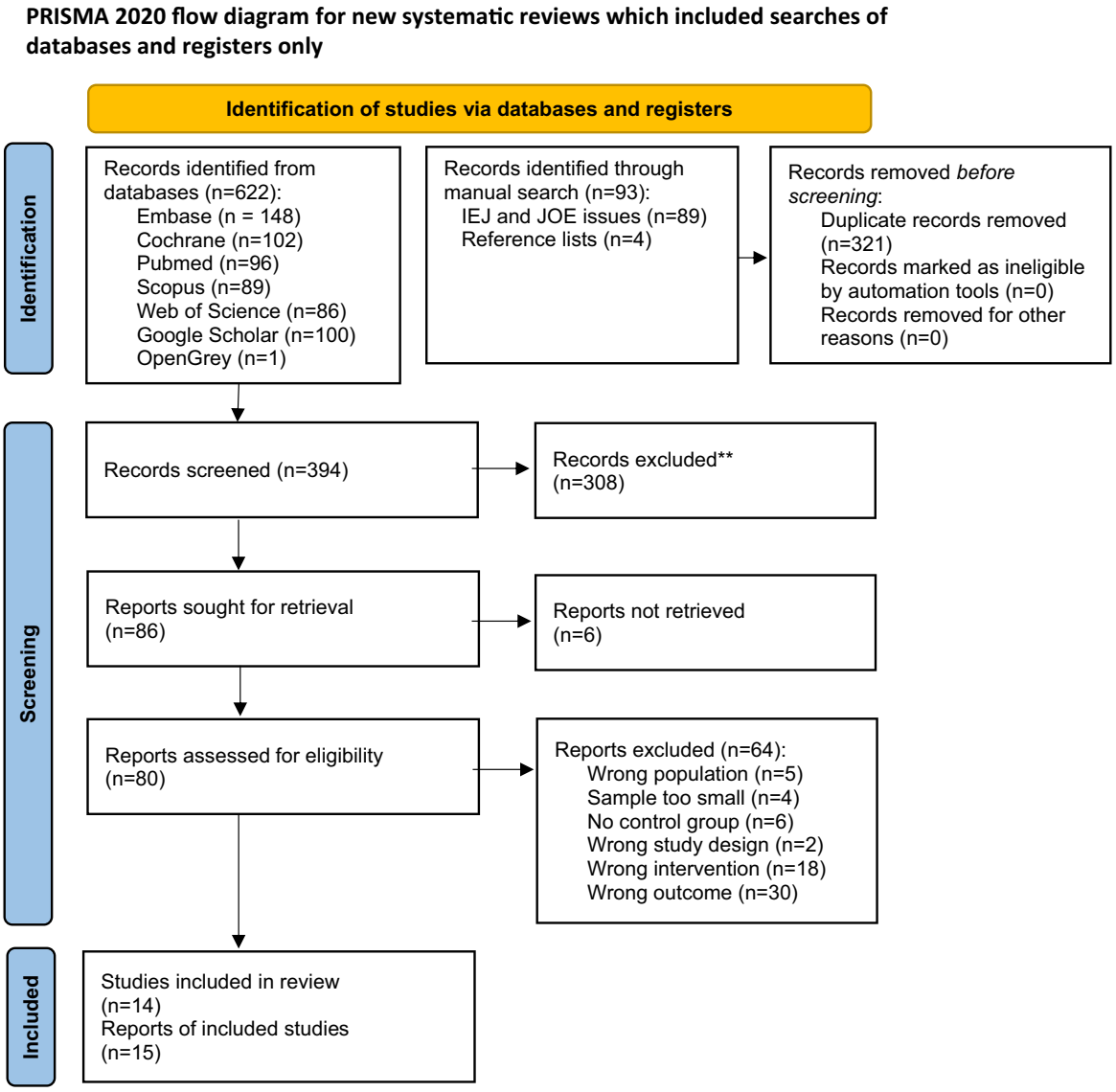

FIGURE 1 PRISMA flowchart of the search and selection strategy

meta-analysis. The included studies differed in the type of outcome reported and frequently also in the way this outcome was reported. These studies were classified according to the different forms of adjunct therapy and outcome as follows:

a. UAI: Two studies reported pain as outcome (Middha et al., 2017; Tang et al., 2015). Tang et al. (2015) also reported periapical lesion reduction through periapical radiographs. Two studies used periapical lesion reduction as determined by cone-beam computed tomography (CBCT) as an outcome (Liang et al., 2013; Verma et al., 2020). With regard to the activation technique adopted, Middha et al. (2017) used continuous ultrasonic irrigation, whilst the others used intermittent ultrasonic activation.
b. Ozone therapy (OZT): Two studies (Kist et al., 2017; Pietrzycka & Pawlicka, 2011) reported radiographic healing as determined by periapical radiographs.
c. Diode laser (DL): Three studies. Morsy et al. (2018) and Kaplan et al. (2021) used pain as outcome (Kaplan et al., 2021; Morsy et al., 2018). Masilionyte and Gutknecht (2018) used periapical lesion reduction as outcome.
d. Nd:YAG laser (Nd:YAG): Two studies. Koba et al. (1999), irradiating in a dry canal, used pain and periapical lesion reduction (periapical RX) as outcomes. Verma et al. (2020), using Nd:YAG in a liquid-filled canal, used periapical lesion reduction based on CBCT.
e. Er;Cr:YSGG laser: One study (Martins et al., 2014) used periapical lesion reduction using periapical radiographs as an outcome—NB in this study the Er;Cr:YSGG laser was used both in liquid-filled as in dried canals.

TABLE 3 General characteristics of the included studies in this review

Study	Country	Study design	Type of adjunct therapy	Industrial funding	Setting (primary or secondary root canal treatment)	Number of patients	Mean age (SD)	Tooth type	Apical diagnosis	Outcome
Barciela et al. (2019)	Brazil	RCT (2-arm)	aPDT	No	Primary	40	NI	Single-rooted	AAP	Pain at 7 days
Guimarães et al. (2021)	Brazil	RCT (2-arm)	aPDT (supplemented with LLLT)	No	Primary	70	41.8 (±1.37)	Anterior and premolar	AAP	Pain at 7 days, tenderness at 7 days
Kaplan et al. (2021)	Turkey	RCT (2-arm)	980-nm diode laser irradiation	No	Primary	60	Control: 32.07 (±10.54); laser: 34.43 (±11.04)	Single-rooted	AAP	Pain at 7 days
Kist et al. (2017)	Germany	RCT (2-arm)	Ozone therapy	No	Primary	57	51.9 (±18.4)	All	SAP or AAP	Apical healing
Koba et al. (1999)	Japan	RCT (2-arm)	Nd:YAG laser irradiation	No	Primary	38	Aged 26 to 59	Incisor, premolar, and molar	AAP	Tenderness at 7 days
Liang et al. (2013)	China	RCT (2-arm)	Ultrasonic irrigant activation (intermittent)	No	Primary	105	Median (range): 37 (18–76)	Incisor, canine, and single-rooted premolar	NI	Apical healing
Masilionyte et al. (2018)	Germany	Retrospective cohort (2-arm)	940-nm diode laser irradiation	No	Primary and secondary	46	53.7 (±19.1)	Anterior, premolar, and molar	AAP, SAP, CAA, AAA	Apical healing
Martins et al. (2014)	Portugal	RCT (2-arm)	Er,Cr:YSGG laser irradiation	No	Primary	43	46 (range: 12–76)	Single-rooted and premolar	NI	Apical healing
Middha et al. (2017)	India	RCT (2-arm)	Ultrasonic irrigant activation (continuous)	No	Primary	70	27.2 (range, 18–45)	Lower molar	Patients with and without pain	Pain at 7 days
Morsy et al. (2018)	Egypt	RCT (2-arm)	980-nm diode laser irradiation	No	Primary	56	Control: 26.25 (±5.47) diode: 25.28 (±5.11)	Upper anterior	No pain	Pain at 7 days
Souza et al. (2021)	Brazil	RCT (4-arm)	aPDT	No	Primary	40	34.55 (range 15 to 63)	Lower first and second molar	AAP	Pain at 7 days
Tang et al. (2015)	China	RCT (3-arm)	Ultrasonic irrigant activation (intermittent)	No	Primary	300	61.3	All	AAP	Pain at 7 days
Verma et al. (2020)	India	RCT (3-arm)	Ultrasonic irrigant activation (intermittent); Nd:YAG laser irradiation	No	Primary	69	Range 18–60	Incisor and single-rooted premolar	NI	Apical healing
Pietrzycka et al. (2011)	Poland	RCT	Ozone therapy	No	Primary and secondary	152	Slightly above 40 years (range 13–69)	All	NI	Apical healing

Abbreviations: aPDT, antimicrobial photodynamic therapy; LLLT, low-level laser therapy; NA, not applicable; NI, not informed.

TABLE 4 Details of the endodontic treatment and the adjunct therapy applied in each study included in this review

Study	Number of visits (intracanal medication)	Method of instrumentation (MAF)	Working length (WL)	Irrigant used (final flush)	Obturation	Type of operator (number)	Type adjunct therapy	Details adjunct therapy
Barciela et al. (2019)	1	Reciproc (R40)	0 at apex locator	2.5% NaOCl (17% EDTA)	gutta-percha, AH plus sealer, McSpadden condensers	Endodontist (1)	aPDT	methylene blue (Chimiolux 5, DMC, São Carlos, Brazil) placed in canal with 30G needle. 5-min pre-irradiation time. 660-nm laser light applied for 90 s (320 J/cm^2)
Guimarães et al. (2021)	1	Reciproc (NI)	0 at apex locator	NaOCl (17% EDTA and saline solution)	gutta-percha, MTA Fillapex sealer, lateral condensation	Endodontist (1)	aPDT (supplemented with LLLT)	methylene blue (0.01%), 5 min pre-irradiation; 660-nm InGaAIP laser (Laser Duo; MMOptics); 90 s irradiation with optical fibre, 100 mW of output power, fluence of 300 J/cm^2, irradiance of 3.33 W/cm^2, performing helicoidal movements from apical to the cervical
Kaplan et al. (2021)	2 ($Ca[OH]_2$ paste)	Protaper Next (size 40, 0.06 taper)	NI	2.5% NaOCl (17% EDTA and distilled water)	gutta-percha, AH plus sealer, cold lateral condensation	NI (1)	980-nm diode laser irradiation	980-nm diode laser (Medency Primo 10 W Diode Laser, Vicenza, Italy) coupled with a 200-μm optical fibre, output power of 1.2 W, pulsed mode (frequency of 50 Hz, pulse duration: 20 μs), irradiation for 4 × 10 s, average power density = 3822 W/cm^2. Helicoidal movements with fibre tip from apical to cervical (speed of 2 mm/s)
Kist et al. (2017)	At least 2 (UltraCal XS)	Mtwo (ISO 40)	NI	Sterile 0.9% NaCl (17% EDTA)	Gutta-percha, AH plus sealer, cold lateral condensation	Experienced dentist (2)	Ozone therapy	Ozone gas 32 g m(−3) was applied for 120 s with the specific endo-cannula of the HealOzone Compact X4 device (Curozone GmbH, Wiesbaden, Germany)
Koba et al. (1999)	1	Peeso reamers and K files (one size beyond the file that produced clean dentine shavings)	1 mm short of the 0 at apex locator	Alternate irrigation with 5% NaOCl and 3% H_2O_2	Gutta-percha, Canals N sealer, lateral condensation	NI (NI)	Nd:YAG laser irradiation	1064-nm pulsed Nd:YAG laser (d-Lase 300, American Dental Laser, Birmingham, MI, USA), 320 μm optical fibre, power of 1 W and frequency of 15 Hz (66 mJ/pulse, 150 ps pulse duration) for 1 s

(Continues)

TABLE 4 (Continued)

Study	Number of visits (intracanal medication)	Method of instrumentation (MAF)	Working length (WL)	Irrigant used (final flush)	Obturation	Type of operator (number)	Type adjunct therapy	Details adjunct therapy
Liang et al. (2013)	1	FKG rotary and S-Apex (size 40)	0.5 mm short of the 0 at apex locator	5.25% NaOCl (15% EDTA)	Gutta-percha, AH Plus sealer, warm vertical condensation	Experienced dentist (4)	Ultrasonic irrigant activation (intermittent)	#20 IrriSafe file (Satelec Acteon) 2 mm short to its binding point or WL, driven by P5 Newtron (Satelec Acteon, Merignac, France) at setting 'Yellow 8' dry mode. 10s activation after every instrument, and finally 3 × 10 s
Masilionyte et al. (2018)	2–3 (min 1, max 8) ($Ca[OH]_2$ paste in control group; empty in laser group)	ProTaper Universal (minimum ISO 30)	NI	Control group: NaOCl 2.5% (2% citric acid) laser group: distilled water; in six cases also 0.5% NaOCl (17% EDTA)	Gutta-percha, AH plus sealer, cold lateral or warm vertical condensation; MTA in some cases	Dentist (2)	940-nm diode laser irradiation	940-nm diode laser (epic10, BIOLASE Tech, Irvine, USA) with 200-μm fibre tip, output power 1–1,3 W, continuous emission,4 × 2 mm/s per canal, circular movement from apex to crown
Martins et al. (2014)	2 (sterile cotton pellet soaked in Cresophene first visit and then with $Ca[OH]_2$)	Manual K files (minimum ISO 35)	1 mm short of the biological apex	Control group: 3% NaOCl; laser group: sterile saline	Gutta-percha, handmade zinc-oxide eugenol sealer, cold lateral condensation	Undergraduate students (many)	Er,Cr:YSGG laser irradiation	2780-nm Er,Cr:YSGG laser (Waterlase MD; Biolase Technology, Inc, San Clement, CA) with a 270 μm diameter radial firing tip 1st visit: panel settings: 0.75 W, 20 Hz, 37.5 mJ per pulse, 14.0 J/cm^2 energy density, 140 μs pulse duration (two times with the main canal filled with distilled water and the following two with the canal dry) 2nd visit, idem, but: 1.25 W, 20 Hz, 62.5 mJ per pulse, 23.6 J/cm^2, 140 μs pulse duration
Middha et al. (2017)	2 ($Ca[OH]_2$ paste)	Gates glidden and K files (three sizes larger than the first apical binding file at the WL)	flashing bar was between 'APEX' and '1'	5.25% NaOCl (17% EDTA)	NI	NI (1)	ultrasonic irrigant activation (continuous)	ProUltra PiezoFlow ultrasonic irrigation needle (Dentsply) attached to Satelec P5 (Acteon, Mount Laurel, NJ, USA) unit at power setting of 5. The stopper on the PiezoFlow needle was set 1 mm short of binding in the canals, but no more than 75% of the working length. A syringe containing 15 ml of 5.25% NaOCl was attached to the Piezoflow activation needle. During activation, the needle was moved up and down passively in the canal

TABLE 4 (Continued)

Study	Number of visits (intracanal medication)	Method of instrumentation (MAF)	Working length (WL)	Irrigant used (final flush)	Obturation	Type of operator (number)	Type adjunct therapy	Details adjunct therapy
Morsy et al. (2018)	2 (no)	ProTaper Universal (F4)	NI	2.5% NaOCl (17% EDTA)	gutta-percha, ADSEAL resin-based root canal sealer, modified single cone technique	Endodontist (1)	980-nm diode laser irradiation	Irradiation with 980-nm diode laser coupled with optical fibre 200 μm (Lite medics, Italy), 1.2 W power, in pulsed mode. 4 × 5 s irradiation. The tip was positioned 1 mm short of the apex, helicoidal movements from apical to the cervical at a speed of approximately 2 mm/s
Souza et al. (2021)	1	WaveOne Gold (ISO 25)	0 at apex locator or 1 mm beyond	2% CHX gel + distilled water (17% EDTA)	gutta-percha, AH Plus sealer, cold lateral condensation	NI (1)	aPDT	0.01% methylene blue (0.1 mg/ml, Chimio Lux DMC, Sao Carlos, SP, Brazil), 5 min pre-irradiation time. Irradiation for 90 s with 660–690-nm laser (Therapy XT® DMC) 100 mW power and continuous emission, using intracanal fibre (DMC) with diameter of 600 μm attached 3 mm short of the working length whilst in a static position, energy density of 320 J/cm^2
Tang et al. (2015)	1	Mtwo (NR)	NI	2.5% NaOCl	Gutta-percha, AH Plus sealer, cold lateral condensation	Endodontist (2)	Ultrasonic irrigant activation (intermittent)	K file (same as MAF or one size less) driven by a multifunctional ultrasound therapy machine. The length of the K file inserted into the canal was 2 mm less than the working length; the staying time was 60s, and the file did not touch the canal wall
Verma et al. (2020)	1	Protaper Next (X3)	NI	3% NaOCl (17% EDTA)	Gutta-percha, AH Plus selaer, cold lateral condensation	NI (1)	Ultrasonic irrigant activation (intermittent); Nd:YAG laser irradiation	#20 IrriSafe (Satelec Acteon) 2 mm short of WL; driven by P-Max Newtron (Satelec Acteon), 4 × 20 s Nd:YAG Laser (FIDELIS (AT), 1.5 W, 15 Hz for 4 × 5 s). The optic fibre was kept 5 mm short of the WL, kept steady during activation
Pietrzycka et al. (2011)	1	Manual with K files (minimum ISO 35)	NI	5.25% NaOCl (15% EDTA and 0.9% NaCl)	Gutta-percha, AH Plus sealer, lateral condensation	Postgraduate student (NI)	Ozone therapy	The dental chamber was ozonated for 40 s (KaVo HealOzone)

Abbreviations: aPDT, antimicrobial photodynamic therapy; NA, not applicable; NI, not informed.

f. aPDT: Three studies, reporting pain as outcome (Barciela et al., 2019; Guimarães et al., 2021; Souza et al., 2021).

Verma et al. (2020) contributed with two different adjunct therapies, the Nd:YAG laser and the UAI. The sample size in the studies varied between 40 and 300 teeth. The tooth type varied in the studies from single-rooted teeth, incisors and premolars, mandibular molars and all tooth types. In the majority of the studies, NaOCl was the main irrigant during instrumentation. Kist et al. (2017) used a physiological saline irrigant, and Koba et al. (1999) alternated NaOCl and hydrogen peroxide. Masilionyte and Gutknecht (2018) and Martins et al. (2014) used NaOCl in the control group and distilled water or saline in the laser group. In the study by Souza et al. (2021), 2% CHX gel was used during instrumentation.

Risk of bias

The risk of bias assessment for individual studies is presented in Figures 2 and 3.

Figure 2 shows the risk of bias using the RoB2 tool of randomized controlled trial studies included in this review. Overall, six studies had a high risk of bias, five studies had some concerns, and two studies low risk of bias. Deviation from the intended intervention was a criterion without any high risk of bias score from any study. The most frequent reasons threatening the validity of the studies were the significant number of patients that were lost to follow-up, potentially inadequate outcome measurement and potential selection of multiple eligible outcome measurements in some studies.

Figure 3 shows the risk of bias using Newcastle/Ottawa tool of the retrospective cohort study included in this review, which scored one star in the comparability criteria and scored the maximum stars in the selection and outcome criteria.

Table 3 shows that none of the included studies have received industrial funding.

Primary outcomes

Tooth survival

The primary outcome 'tooth survival' was reported in none of the studies.

Apical healing

Eight studies (Kist et al., 2017; Koba et al., 1999; Liang et al., 2013; Martins et al., 2014; Masilionyte & Gutknecht, 2018; Pietrzycka & Pawlicka, 2011; Tang

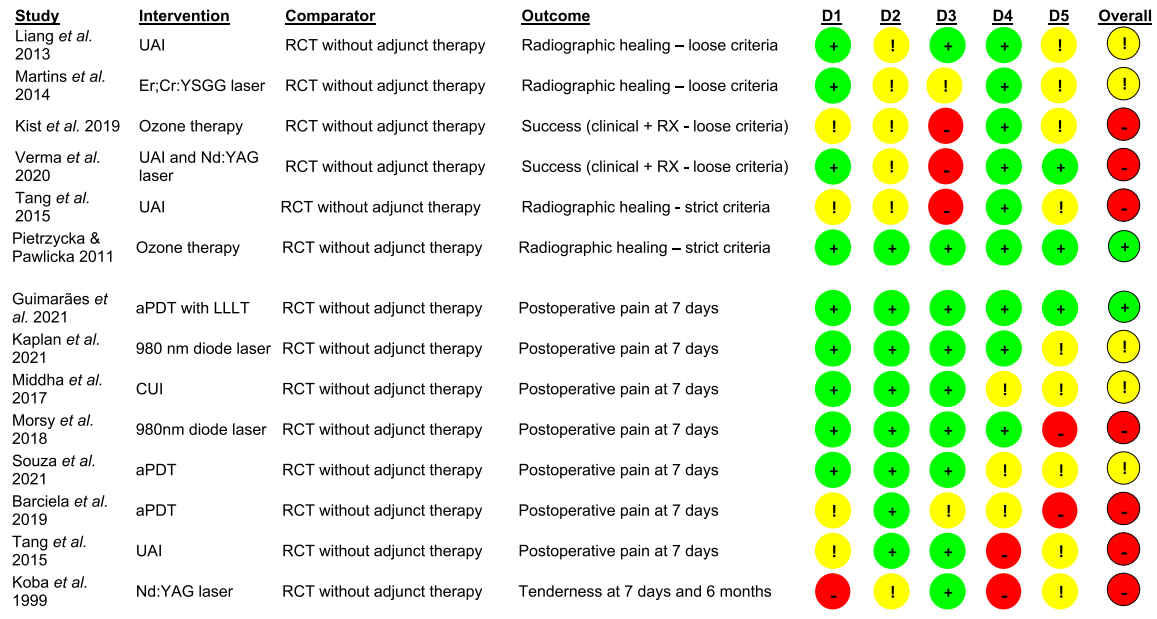

FIGURE 2 Risk of bias using RoB2 tool of randomized controlled trial studies included in this review, categorized according to outcome

FIGURE 3 Risk of bias using Newcastle/Ottawa tool of a retrospective cohort study included in this review

et al., 2015; Verma et al., 2020) reported apical healing. However, due to considerable heterogeneity in the type of adjunct therapy and determination of healing (combined clinical-radiographical success and radiographical success using strict vs. loose criteria), meta-analysis was only possible for the following two items.

Liang et al. (2013) and Verma et al. (2020) investigated CBCT-based reduction in the periapical lesion after UAI. Meta-analysis showed that after 12 months, the lesion reduction in the UAI group was 12% higher than in the control group, but this difference was not statistically significant ($p = .09$; Figure 4). The heterogeneity ($I^2 = 35\%$) was low, indicating low variance across studies.

Kist et al. (2017) and Pietrzycka and Pawlicka (2011) investigated the radiographic-based reduction of the periapical lesion after the use of gaseous ozone. Meta-analysis showed that after 12 months, there was no significant difference in lesion regression between the two groups ($p = .97$; Figure 5). The heterogeneity ($I^2 = 0\%$) was low, indicating low variance across studies.

Pain (from 7 days postoperatively)

Seven studies (Barciela et al., 2019; Guimarães et al., 2021; Kaplan et al., 2021; Middha et al., 2017; Morsy et al., 2018; Souza et al., 2021; Tang et al., 2015) reported pain at 7 days. Meta-analysis on the two studies (Middha et al., 2017; Tang et al., 2015) using UAI was not possible as the raw data in the study by Middha et al. (2017) could not be obtained.

No significant difference in the prevalence of pain 7-day post-treatment was demonstrated after meta-analysis on the two studies comparing diode laser irradiation with no adjunct therapy (RD of 0.07, 95% CI: −0.27, 0.13). Figure 6 shows the corresponding forest plot.

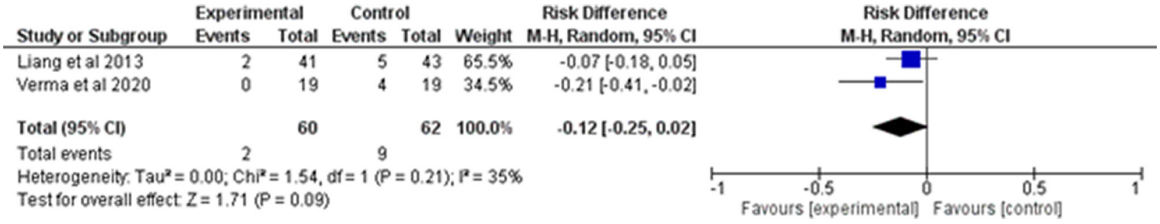

FIGURE 4 Forest plot of the RD in radiographic healing (loose criteria) at 12 months for studies ($n = 2$) using adjunctive UAI (intervention) compared with conventional chemomechanical preparation alone (control). The squares represent the effect estimated by RDs, and the lines represent the respective 95% CIs. The square boxes' size is proportional to each study's weight in the meta-analysis. The black diamond represents the combined RDs and corresponding 95% CIs

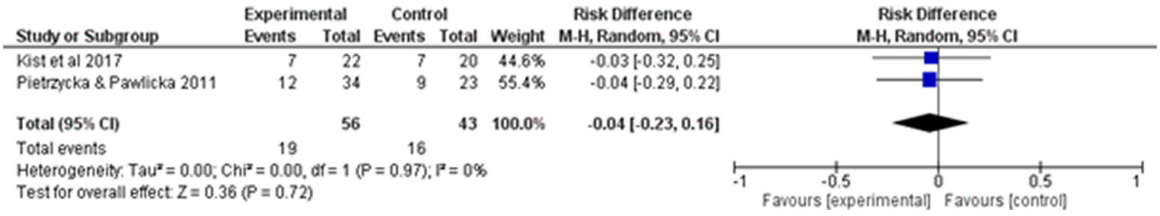

FIGURE 5 Forest plot of the RD in radiographic healing (loose criteria) at 12 months for studies ($n = 2$) using ozone (intervention) compared with conventional chemomechanical preparation alone (control). The squares represent the effect estimated by RDs, and the lines represent the respective 95% CIs. The square boxes' size is proportional to each study's weight in the meta-analysis. The black diamond represents the combined RDs and corresponding 95% CIs

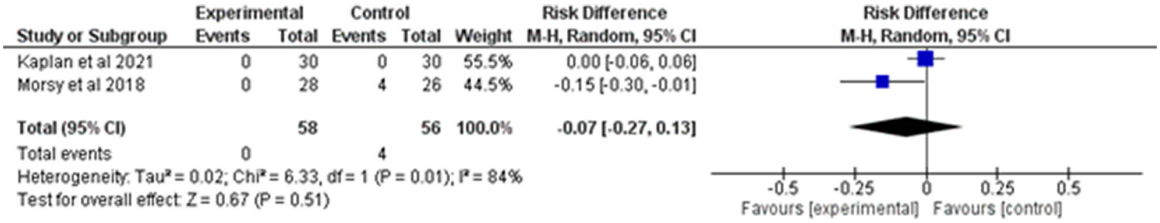

FIGURE 6 Forest plot for the RD in postoperative pain after 7 days for studies ($n = 2$) using 980-nm diode laser (intervention) compared with conventional chemomechanical preparation alone (control). The squares represent the effect estimated by RDs, and the lines represent the respective 95% CIs. The square boxes' size is proportional to each study's weight in the meta-analysis. The black diamond represents the combined RDs and corresponding 95% CIs

The heterogeneity ($I^2 = 84\%$) was high due to the percentage of variation across studies.

Meta-analysis on three studies that used aPDT showed no significant difference in postoperative pain at 7 days between the control and aPDT group (RD of −0.03, 95% CI: −0.11, 0.06, $p = .64$). Figure 7 shows the corresponding forest plot. The heterogeneity ($I^2 = 0\%$) was low, indicating low variance across studies.

Regarding analgesic intake data, Guimarães et al. (2021), Kaplan et al. (2021) and Souza et al. (2021) reported no analgesic intake 7-day post-treatment. Morsy et al. (2018) have excluded patients who reported the intake of an analgesic during the study period. Other studies have not reported how many patients need the use of analgesics or have not replied to our email.

Secondary outcomes

Secondary outcomes were not reported in any of the studies.

GRADE

The overall quality of evidence as assessed by GRADE was identified as very low for 980-nm diode laser studies, and it was classified as low for UAI, ozone and aPDT studies (Table 5). Principal reasons include serious risk of bias in the trials and imprecision due to the limited number of events and samples in the trials. Explanations are presented in Table 5.

DISCUSSION

This systematic review sought to reveal the best available evidence regarding the effectiveness of the different types of adjunctive therapy in the treatment of AP. Even though a great number of studies working with adjunct therapy were primarily selected, due to the strict inclusion criteria, including a minimum of patients per arm and a certain duration (follow-up time), the number of papers finally included after the systematic search was small, with 15 reports (reporting on a wide variety of adjunct therapies) meeting the inclusion criteria.

In addition, the heterogeneity amongst these studies was substantial. The first source of heterogeneity was the type of adjunct therapy with studies investigating activation of irrigants by ultrasonically driven instruments, diode laser, pulsed erbium laser, intracanal laser irradiation and the use of ozone therapy. A second important source of heterogeneity was found in the reporting of the outcomes, which varied from radiographical healing according to strict versus loose criteria, based on 2D versus 3D assessment, combined clinical-radiographical success and postoperative pain, amongst others. There were also differences amongst studies regarding the type of included teeth; the risk of bias; type of the main irrigant used during chemomechanical preparation; details of the adjunct therapy in terms of products, settings and time of application; evaluation time, amongst others. Therefore, with so many variables, there were limited available data for meta-analysis, evidenced by the fact that most analyses were based on only two studies (except for postoperative pain after 7 days where three studies could be included).

Unfortunately, none of the included studies reported formally about tooth survival, which was the principle outcome outlined in the review protocol (Duncan et al., 2021). With regard to healing of AP, the data obtained in the present systematic literature search found no significant benefit of any of the different types of adjunct therapy. For UAI, the combined data from the two included studies demonstrated a trend towards higher radiographical healing rate when ultrasonic irrigant activation was employed, although this difference was not statistically significant.

Concerning the other critical outcomes such as pain, tenderness, swelling and need for medication (analgesics and antibiotics), the only information that could be

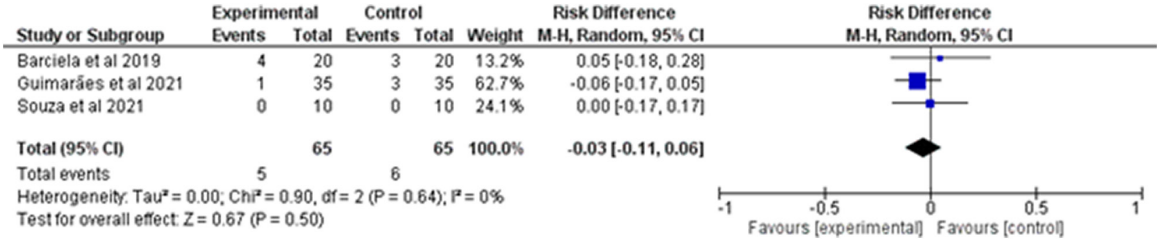

FIGURE 7 Forest plot of the RD in postoperative pain after 7 days for studies ($n = 3$) using aPDT (intervention) compared with conventional chemomechanical preparation alone (control). The squares represent the effect estimated by RDs, and the lines represent the respective 95% CIs. The square boxes' size is proportional to each study's weight in the meta-analysis. The black diamond represents the combined RDs and corresponding 95% CIs

TABLE 5 Certainty of evidence assessment using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach

Certainty assessment								
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Risk difference**	**Certainty**
PDT—pain after 7 days								
3	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Undetected[c]	−0.03 (95% CI, −0.11-0.06)	⨁⨁◯◯ Low
Ozone—lesion reduction after 12 months								
2	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Undetected[c]	−0.04 (95% CI, −0.23-0.16)	⨁⨁◯◯ Low
Diode laser—pain after 7 days								
2	RCT	Very serious[d]	Serious[e]	Not serious	Serious[b]	Undetected[c]	−0.07 (95%CI, −0.27-0.13)	⨁◯◯◯ Very low
UAI—lesion reduction after 12 months								
2	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Undetected[c]	−0.12 (95%CI, −0.25-0.02)	⨁⨁◯◯ Low

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; UAI, ultrasonically activated irrigation.

[a]Some limitations for multiple criteria.

[b]Limited number of events and samples.

[c]Not enough trials to judge.

[d]Critical limitation for one criterion.

[e]Statistical significance for I^2.

collected pertained to pain 7 days after treatment, with seven studies contributing data (Barciela et al., 2019; Guimarães et al., 2021; Kaplan et al., 2021; Middha et al., 2017; Morsy et al., 2018; Souza et al., 2021; Tang et al., 2015). Analgesic intake 7-day post-treatment was reported only by three studies (Guimarães et al., 2021; Kaplan et al., 2021; Souza et al., 2021). Individual studies mentioned pain after 30 days, tenderness to percussion after 7 or 30 days, or 6 months, but these data did not allow any conclusions.

Meta-analysis of the studies on postoperative pain indicated no significant influence of aPDT and diode laser irradiation on the prevalence of pain 7 days postoperatively. The postoperative pain prevalence at this time-point, however, was generally very low in both groups. Overall, no significant impact of any of the different types of adjunct therapy on pain, tenderness, swelling and need for medication could be demonstrated.

More importantly, nevertheless, is that the number of primary trials contributing data was low, and too low in most instances to perform the meta-analysis. Thus, the main conclusion of this systematic review is that there is a lack of substantial high-quality data to draw robust conclusions about the effectiveness of adjunct therapy in the treatment of AP. Therefore, more trials addressing this topic of adjunct therapy are required. These trials should ideally be executed to conform the highest standards of trial methodology and trial reporting. In this respect, 'preferred reporting items for study designs in endodontology' guidelines have been published (PRIDE, www.pride-endodonticguidelines.org) to help authors improve the design and quality of their (clinical) research. These guidelines have been endorsed by the major endodontic journals, including International Endodontic Journal. A specific point of attention is the reporting of the endodontic outcome. In many instances, the comparison of studies was difficult as outcome measures were different. It would be beneficial to report for example clinical as well as radiographical outcomes, and radiographical data based on loose as well as strict criteria, or to make available the entire dataset in a repository to allow different analyses.

Ultrasonically activated irrigation, ozone therapy, diode laser, Nd:YAG laser, Er;Cr:YSGG laser irradiation and aPDT were the adjunct techniques evaluated in the present study.

Regarding UAI, two distinct clinical techniques have been described, namely continuous or intermittent ultrasonic activation (CUA and IUA). Continuous ultrasonic irrigation provides an uninterrupted supply of fresh irrigation solution in the root canal. In the intermittent ultrasonic irrigation, the irrigant is injected into the root canal with a syringe; the irrigant solution is ultrasonically activated and flushed with a syringe after that with several repetitions of this activation cycle. Therefore, the amount of irrigant activated in IUA is smaller than that in CUA.

Despite differences in clinical application of UAI (insertion depth, movement of the tip) and different forms of UAI (Tang et al., 2015, using IUA; and Middha et al., 2017 using CUA), both studies had very low pain levels at 1 week after treatment.

Liang et al. (2013) also studied the effect of ultrasound as an adjunct therapy in single-rooted teeth. In their work, NaOCl solution was used to rinse the canal between each instrument, and after every other instrument, the irrigant was also activated by ultrasound for 10 s. The authors reported the status of the periapical lesion after 10–19 months using CBCT. They concluded that root canal treatment with and without additional activation of the irrigant contributed equally to periapical healing. Verma et al. (2020) evaluated the combined clinical and radiographic success rate of endodontic treatment of incisors and single-rooted premolars using UAI compared with conventional syringe irrigation. The authors reported the status of the periapical lesion after 12 months using CBCT. They found significantly higher successful treatment outcomes in the ultrasonic activation group than in the control group without activation.

When combining the radiographical data from the study by Verma et al. (2020), with those from the study by Liang et al. (2013), the results of the meta-analysis indicated that adjunctive ultrasonic irrigant activation to conventional endodontic therapy failed to yield statistically significant improvements with respect to CBCT-based radiographical healing of AP after 12 months. The certainty of evidence for this conclusion as determined by Grade was however low, as the studies suffered from serious risk of bias and imprecision (Table 5). These findings are in accordance with previous literature reviews on the subject. Caputa et al. (2019), systematically reviewing the literature on ultrasonic irrigant activation, found only one eligible clinical study (Liang et al., 2013) and concluded that ultrasonic activation did not improve the healing rate of AP. Moreira et al. (2019), reviewing the literature on root canal disinfection *in vivo*, demonstrated no significant difference in microbial load reduction between passive ultrasonic and conventional irrigation.

Ozone is a strong antioxidant, promoting disinfection by breaking the microbial cell membrane. Its application in dentistry, including endodontics, has therefore gained attention. It exists in three presentation forms: ozonated water, ozone mixed with oil mostly olive oil and gaseous ozone (Sen & Sen, 2020). Two works used ozone as an adjunct therapy to the endodontic treatment (Kist et al., 2017; Pietrzycka & Pawlicka, 2011) reporting regression of periapical lesions as an outcome. Differences in clinical application of ozone therapy between both studies

were noted in terms of the device to produce ozone, the application time, etc., but the results of the meta-analysis showed that both adjunctive ozone therapy and conventional endodontic therapy resulted in similar radiographical healing rates after 12 months.

A first group of commonly used lasers in endodontics are the ones with wavelengths within the near-infrared spectrum (between 760 and 1400 nm), including the Nd: YAG laser (1064 nm) and several diode lasers (810, 940 and 980 nm). These are typically used in a dry canal, aiming at disinfection and reduction of postoperative pain (Saydjari et al., 2016). A second group of lasers used in endodontics consists of lasers in the mid-infrared spectrum (between 1400 and 3000 nm), including the Er:YAG (2940 nm) and Er;Cr;YSGG (2780 nm) laser. These wavelengths have been reported to have good antimicrobial effects (Meire et al., 2012; Noiri et al., 2008), but they are typically used to activate irrigants (LAI; Divito et al., 2012), due to the extremely strong absorption of these wavelengths in water, producing cavitational effects and irrigant dynamics (Blanken et al., 2009).

In this SR, only two studies using 980-nm diode laser (Kaplan et al., 2021; Morsy et al., 2014) and monitoring the presence of pain as outcome were statistically analysed. The results showed that no significant difference was found in the occurrence of postoperative pain at 7 days between the control and diode laser group.

Masilionyte and Gutknecht (2018), in a retrospective cohort study investigating apical healing after adjunctive 940-nm diode laser use, reported faster initiation of healing in the diode laser group. However, no significant differences from conventional treatment were demonstrated after longer observation times.

Koba et al. (1999) studied the use of adjunctive Nd:YAG laser. They reported that the occurrence of spontaneous pain after 1 day in the laser-treated group (18.2%) was less than in the control group (50.0%), but the difference was insignificant. Seven-day post-treatment, all teeth were asymptomatic.

Martins et al. (2014) used Er,Cr:YSGG laser as adjunctive therapy. Their study protocol included both laser irradiation in a dry canal and laser irradiation in the canal containing saline solution. After 12 months of follow-up, there were no significant differences between the control and experimental groups regarding the reduction in periapical lesion.

Antimicrobial photodynamic therapy has been suggested as a good option to maximize root canal disinfection, with the potential to disinfect the canals predictably in one visit. However, a protocol of aPDT to be used as an effective antibacterial supplement to chemomechanical therapy remains to be established. There are many variables to be taken into account when developing aPDT protocol, including light parameters, photosensitizer and light delivery techniques (Alves-Silva et al., 2021; Singh et al., 2015).

Usually, patients are asked to record their perception of pain using a visual analogic scale (VAS). The clinical outcome (reduction of pain) of the three studies that used aPDT (Barciela et al., 2019; Guimarães et al., 2021; Souza et al., 2021) showed that at 7-day post-treatment no difference was found amongst the groups.

It may be noted that several included studies also reported clinical outcomes after 24-, 48-, and 72-h post-treatment; whilst others were excluded as they reported only shorter follow-up periods. Therefore, information on shorter follow-up periods would be incomplete and potentially biased in the present study setup, therefore not being reported. Whilst short-term pain may not be relevant to long-term tooth retention, shorter follow-up periods may be important to the patient and therefore worth investigating in the future.

Regarding the RoB, studies reporting on the radiographical healing of AP which were judged 'some concerns' did so due to insufficient blinding of participants and caregivers and the lack of a pre-specified analysis plan (Liang et al., 2013; Martins et al., 2014). For the studies reporting radiographical healing of AP which were judged with high risk of bias, this was because there were too many participants with missing outcome data (Kist et al., 2019; Tang et al., 2015, Verma et al., 2020). When considering the trials with pain at 7 days as the main outcome, only one study was labelled low RoB (Guimarães et al., 2021). Barciela et al. (2019) and Morsy et al. (2018) reporting pain at 7 days received the high RoB label because data analysis was not in accordance with a pre-specified data analysis plan or the potential of multiple eligible outcome measurements (VAS scores were measured but pain categories were reported in Morsy et al., 2018; VAS scale data are reported in Barciela et al., 2019 but the methodology [statistical analysis] refers to an ordinal scale). Tang et al. (2015) judged high RoB because of questionable outcome measurement (telephone calls to self-assess pain levels) and lack of information on outcome assessor blinding. Koba et al. (1999) judged high risk of bias because no information regarding randomization or allocation concealment was reported, as well as lack of information on outcome assessor blinding. Studies on pain judged as 'some concerns' either had a retrospective protocol registration (Kaplan et al., 2021; Middha et al., 2017) or no pre-specified plan (Souza et al., 2021) Attempts to contact the authors to obtain missing information were not successful.

The risk of bias influenced the results of the GRADE assessment. The studies obtained a 'serious' or 'very serious' score in the risk of bias criteria, lead to a downgrade in the GRADE assessment. Also, the high heterogeneity ($I^2 = 84\%$) in the meta-analysis of 980-nm diode laser contributed to its inconsistency score in the GRADE

assessment. The reasons for the heterogeneity between studies were explained earlier in the discussion section. Another subject that affected the low score in the GRADE assessment of the studies was the small sample size of the studies, which ranged from 10 to 43 per group.

Based on RoB and GRADE results, we recommend using a larger sample size for future studies; provide as much detail as possible of the clinical cases investigated; and use a protocol for endodontic treatment where different studies can be compared.

The clinical trials selected for this SR did not find evidence of an additional effect of the adjuvant therapies evaluated over conventional chemomechanical preparation of the root canal system in the treatment of AP. One might conclude that these treatment steps are redundant. However, the present findings in the first place demonstrate the lack of good quality evidence assessing the efficacy of these adjuvant therapies. More detailed RCTs with a larger sample size and sufficiently long follow-up are needed so that the role of adjuvant therapy can be robustly assessed.

CONCLUSION

Based on the results of this systematic review, no additional effect of any of the investigated types of adjunctive therapy over conventional endodontic therapy in terms of AP healing and pain 7 days after treatment could be demonstrated. Evidence on the outcome 'tooth retention' was absent. The available evidence was limited by the low number of controlled studies and the heterogeneity of the studies. The absence of evidence on the efficacy of adjuvant therapy in the treatment of AP does not necessarily invalidate the effect of adjunctive therapy, but it does underscore the need for future high-quality studies to better establish the role of adjunctive therapy in endodontic outcomes.

AUTHOR CONTRIBUTIONS

B.P.F.A. Gomes, J.D. Bronzato and M.A. Meire involved in conception and design and acquisition of data. R.A. Bomfim involved in data analysis. B.P.F.A. Gomes, J.D. Bronzato, M.A. Meire and R.A. Bomfim involved in interpretation of data, reviewing, editing and final approval. B.P.F.A. Gomes and M.A. Meire involved in first draft preparation.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICAL APPROVAL

This paper did not involve human or animal subjects.

ORCID

Maarten A. Meire https://orcid.org/0000-0001-6661-3772
Juliana D. Bronzato https://orcid.org/0000-0002-8249-7916
Rafael A. Bomfim https://orcid.org/0000-0002-6478-8664
Brenda P. F. A. Gomes https://orcid.org/0000-0002-8449-0646

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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