UNIVERSIDADE ESTADUAL DE CAMPINAS
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IMPACTO DA IRRIGAÇÃO ULTRASSÔNICA PASSIVA NO ÍNDICE DE SUCESSO DOS TRATAMENTOS ENDODÔNTICOS NÃO CIRÚRGICOS: REVISÃO SISTEMÁTICA COM META-ANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS

IMPACT OF PASSIVE ULTRASONIC IRRIGATION ON THE OUTCOME OF NON-SURGICAL ROOT CANAL TREATMENT: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestre em Clínica Odontológica, na Área de Endodontia.

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Orientador: Prof. Dr. Caio Cezar Randi Ferraz.

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RESUMO

O uso da agitação ultrassônica das substâncias químicas auxiliares vem demonstrando boa eficácia na descontaminação do sistema de canais radiculares. O objetivo do presente estudo foi avaliar se o uso da irrigação ultrassônica passiva (PUI) tem impacto na taxa de sucesso do tratamento endodôntico não cirúrgico. Foi realizada busca eletrônica de artigos publicados até janeiro de 2022 nas bases de dados MedLine (via PubMed), Scopus, Web of Science, Embase, LILACS e Cochrane Library. Além disso, foram realizadas buscas na “literatura cinza” (por exemplo, OpenGrey, OpenThesis e Google Scholar). Como variáveis dicotômicas, utilizou-se como efeito estimado o Risco Relativo (RR), com intervalo de confiança (IC) de 95%. A certeza da evidência foi avaliada usando a abordagem de Classificação de Recomendações, Avaliação, Desenvolvimento e Avaliação (GRADE - grading of reccomendation assessment, development and evaluation). De 997 artigos selecionados, três estudos preencheram todos os critérios de inclusão para a meta-análise. Com base nesses três estudos incluídos, os resultados mostraram que o uso de PUI são mais favoráveis quando comparados à irrigação convencional com seringa (ICS) nos resultados de reparo periapical (RR: 1,10; IC 95%: 1,01;1,21, I^2=0%). A análise da sequência de tentativas (trial sequence analysis) foi realizada usando 5% de erro tipo I e 20% de erro tipo II, usando um modelo de efeitos aleatórios. Esta análise demonstrou que as evidências obtidas na meta-análise podem ser consideradas "inconclusivas". A certeza da evidência avaliada pela abordagem GRADE foi considerada moderada devido à imprecisão. As evidências disponíveis na literatura indicam vários benefícios no uso da PUI que podem levar a um resultado mais favorável no tratamento do canal radicular. No entanto, o presente estudo demonstra que mais trabalhos clínicos randomizados de alto impacto com maior tamanho amostral e períodos de proservação mais longos são necessários para entender completamente o impacto da PUI no sucesso dos tratamentos endodônticos. Apesar de inconclusivos, os achados mostraram que o uso de PUI tem um potencial impacto positivo na taxa sucesso do tratamento endodôntico primário não cirúrgico quando comparado à ICS.

Palavras-chave: Ultrassom. Irrigação. Endodontia. Revisão sistemática.

ABSTRACT

The use of ultrasonic methods for agitating the auxiliary chemical solutions has shown good efficacy in decontaminating the root canal system. The objective of the present study was to evaluate whether the use of Passive Ultrasonic Irrigation (PUI) has an impact on the success rate of non-surgical root canal treatment. An electronic search was performed up to January 2022 in the MedLine (via PubMed), Scopus, Web of Science, Embase, LILACS and Cochrane Library databases. Also, searches were performed on the grey literature (e.g., OpenGrey, OpenThesis, and Google Scholar). As dichotomous variables, the Relative Risk (RR) was used as an estimated effect, with a confidence interval (CI) of 95%. The certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. From 997 records screened, three studies fulfilled all inclusion criteria for the meta-analysis. Based on three included trials, the results showed that the use of PUI is more successful when compared to conventional syringe irrigation (CSI) on the periapical healing outcome (RR: 1.10; 95%CI: 1.01;1.21, I^2=0%). The trial sequence analysis was performed using 5% type I error and 20% type II error, using a random effects model. This analysis showed that the evidence obtained in the meta-analysis can be considered "inconclusive". The certainty of evidence assessed by the GRADE approach was considered moderate due to imprecision. The available literature supports the use of PUI shows several benefits that could potentially lead to a more favorable outcome in root canal treatment. Nevertheless, the present study shows that more high-impact randomized controlled trials (RCTs) with a larger sample size, longer follow-up periods, and following RCTs quality reporting guidelines are necessary to fully understand the impact of PUI on the periapical healing outcome. Besides it is inconclusive, the findings showed that the use of PUI has a potential positive impact on the periapical healing rate of nonsurgical primary root canal treatment when compared with CSI.

Keywords: Ultrasonics, Irrigation. Endodontics. Systematic review.

SUMÁRIO

1 INTRODUÇÃO

A periodontite apical crônica é uma doença inflamatória que afeta os tecidos periapicais em resposta a uma infecção bacteriana (Nair, 2004). O tratamento endodôntico não cirúrgico é a primeira opção para tratar esta doença, o qual apresenta uma taxa de sucesso entre 82% (redução completa da lesão periapical) e 92,6% (redução do tamanho da lesão periapical existente) (Burns et al., 2022; Ng et al., 2011a) e uma taxa de sobrevida dentária de até 95% (Ng et al., 2011b), quando devidamente realizado e o dente adequadamente restaurado.

Vários agentes irrigantes podem ser utilizados como substâncias químicas auxiliares (SQA) durante o tratamento endodôntico, por exemplo, hipoclorito de sódio (NaClO) (Mohammadi, 2008), digluconato de clorexidina (CLX) (Gomes et al., 2013), ácido etilenodiaminotetracético (EDTA), e vários outros agentes (3). A literatura vem avaliando se a ativação mecânica destas substâncias pode melhorar suas propriedades químicas e otimizar a desinfecção no sistema de canais radiculares (Herrera et al., 2017; Aveiro et al., 2020; Abu Hasna et al., 2021).

Os métodos de ativação das SQA podem auxiliar no tratamento endodôntico não cirúrgico, uma vez que o preparo químico-mecânico (PQM) convencional deixa áreas intocadas no interior do sistema de canais radiculares, independentemente do instrumento ou da cinemática utilizada (Zuolo et al., 2018). Para esta questão, foram desenvolvidos vários dispositivos que ativam a SQA (URBAN et al., 2017), tais como o XP-Endo Finisher (FKG Dentaire, La Chaux-de-Fonds, Suíça) (Azarpazhooh et al., 2022), Easy Clean (Easy Equipamentos Odontológicos, Belo Horizonte, MG, Brasil) (Kato et al., 2016), EndoVac (Discus Dental, Culver City, CA, EUA) (Desai e Himel, 2009), EndoActivator (Dentsply Maillefer, Ballaigues, Suíça) (Uroz-Torres et al., 2010), ativação a laser (Kimura et al., 2000; Wang et al., 2017) e ativação ultrassônica (Crozeta et al., 2020; Van Der Sluis et al., 2007).

A ativação ultrassônica das SQA, denominada como irrigação ultrassônica passiva (IUP), é realizada com pontas ultrassônicas específicas, que oscilam livremente no sistema de canais radiculares promovendo pressão negativa que transmite a energia acústica a SQA, causando o efeito da cavitação do fluido (Abu

Hasna et al., 2021; Van Der Sluis et al., 2007). Este efeito cria bolhas que oscilam à medida que as ondas ultrassônicas são projetadas. Conforme essas ondas ultrassônicas continuam, as bolhas crescem e se tornam altamente instáveis, eventualmente colidindo e implodindo. Esta implosão produz uma energia chamada de fluxo acústico (Van Der Sluis et al., 2007). Desta forma, a IUP é apresentada como importante método auxiliar na limpeza do sistema de canais radiculares e, quando comparada à irrigação convencional por seringa (ICS), é mais eficaz na remoção de restos de tecidos orgânicos, bactérias e detritos dentinários (Abu Hasna et al., 2021). Este fator é possível, devido ao fluxo acústico que permite que essas SQA alcancem regiões mais complexas do sistema de canais radiculares, inclusive através de curvaturas, istmo, sulcos e canais laterais, melhorando a limpeza geral durante o tratamento e retratamento endodôntico não cirúrgico, aumentando o potencial de desinfecção e limpeza de todo o sistema de canais radiculares (De Oliveira et al., 2022; Van Der Sluis et al., 2007).

Entretanto, todos os possíveis benefícios promovidos pela IUP são embasados em estudos in vitro, e a literatura ainda é escassa em estudos clínicos que avaliem, com o mais alto nível de evidência, os resultados relacionados a ela. Uma revisão sistemática anterior sobre este tópico incluiu apenas um ensaio clínico randomizado (ECR), tornando-se impossível fornecer uma certeza de evidência suficiente (Silva et al., 2019); desde então, novos estudos clínicos foram publicados. Portanto, o objetivo desta revisão sistemática é sintetizar as evidências clínicas e responder se a IUP pode ter impacto na cura periapical de tratamentos endodônticos não cirúrgicos.

2 ARTIGO: IMPACT OF PASSIVE ULTRASONIC IRRIGATION ON THE OUTCOME OF NON-SURGICAL ROOT CANAL TREATMENT: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Impact of passive ultrasonic irrigation on the outcome of non-surgical root canal treatment: a systematic review with meta-analysis of randomized clinical trials

Abstract

Background: The use of ultrasonic methods for agitating the auxiliary chemical solutions has proven to be very effective in decontaminating root canal system. **Objectives:** To evaluate whether the use of Passive Ultrasonic Irrigation (PUI) has an impact on the success rate of non-surgical root canal treatment. **Method:** The electronic search was performed up to January 2022 in the MedLine (via PubMed), Scopus, Web of Science, Embase, LILACS and Cochrane Library databases. Also, searches were performed on the grey literature (e.g., OpenGrey, OpenThesis, and Google Scholar). As dichotomous variables, the Relative Risk (RR) was used as an estimated effect, with a confidence interval (CI) of 95%. The certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. **Results:** Based on three included trials, the results showed that the use of PUI is more successful when compared to conventional syringe irrigation (CSI) on the periapical healing outcome (RR: 1.10; 95%CI: 1.01;1.21, I^2=0%). The trial sequence analysis was performed using 5% type I error and 20% type II error, using a random effects model. This analysis showed that the evidence obtained in the meta-analysis can be considered "inconclusive". The certainty of evidence assessed by the GRADE approach was considered moderate due to imprecision. Moreover, the available evidence supports the use of PUI shows several benefits that could potentially lead to a more favorable outcome in root canal treatment. **Conclusions:** It is clear that more high-impact RCTs with a larger sample size, longer follow-up periods, and following RCTs quality reporting guidelines are needed to fully understand the impact of PUI on the periapical healing outcome. However, the findings showed that the use of PUI has a potential positive impact on the periapical healing rate of nonsurgical primary root canal treatment when compared with CSI.

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Registration: PROSPERO database (CRD42021290894)

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

Keywords: Ultrasonics, Irrigation, Endodontics, Systematic review

1 Introduction

Chronic apical periodontitis is an inflammatory disease affecting the periapical tissues in response to bacterial infection (1). Nonsurgical root canal treatment is the first choice to treat this disease, presenting a success rate between 82% (complete resolution of periapical lesion) and 92.6% (reduction in the size of existing periapical lesion) (2,3) and a dental survival rate of up to 95% (4), when properly performed and the tooth is restored.

Several irrigant agents can be used as auxiliary chemical substances (ACS) during endodontic treatment, e.g. sodium hypochlorite (NaClO) (5), chlorhexidine digluconate (CHX) (6), ethylenediaminetetraacetic acid (EDTA), and several other agents (7). Scientific evidence has discussed that activation of these substances may enhance their chemical properties and improve disinfection in the root canal system (8–10).

Activation methods of these ACS are of great importance in nonsurgical root canal treatment since the conventional chemo-mechanical preparation (CMP) usually leaves untouched root canal areas, regardless of the instrument or kinematics used (11). For this issue, several devices designed for activation of the ACS were developed (12), such as the XP-Endo Finisher (FKG Dentaire, La Chaux-de-Fonds, Switzerland) (13), Easy Clean (Easy Equipamentos Odontologicos, Belo Horizonte, MG, Brazil) (14), EndoVac (Discus Dental, Culver City, CA, USA) (15), EndoActivator (Dentsply Maillefer, Ballaigues, Switzerland) (16), laser activation (17,18), and ultrasonic activation (19,20).

PUI is performed with specific ultrasonic tips that oscillate freely in the root canal system with the ACS promoting a negative pressure that transmits the acoustic energy to the irrigant, causing the effect of fluid cavitation(10,20). This effect creates bubbles that oscillate as the ultrasonic waves are projected. As these ultrasonic waves continue, the bubbles grow and become highly unstable, eventually colliding and imploding. This implosion produces powerful energy that is called acoustic microstreaming (20). In this way, PUI is an important adjunct method to cleaning the root canal system, and when compared to conventional syringe irrigation (CSI), it is most effective in removing organic tissue remnants, bacteria, and dentin debris (10). This factor is possible due to the acoustic microstreaming that allows these ACS to reach more complex regions of the root canal systems, including through curvatures, isthmus, grooves, and lateral canals, improving the overall cleaning during nonsurgical

root canal treatment and retreatment, increasing the potential for disinfection and cleaning of the entire root canal system (20,21).

However, all the possible benefits of performing PUI are supported by *in vitro* studies, and the literature is still scarce on studies with the highest level of evidence that evaluate clinical outcomes related to PUI. A previous systematic review on this topic only included one randomized clinical trial, which is impossible to provide sufficient certainty of evidence (22); since then, new clinical studies have been published. Hence, the purpose of this systematic review is to synthesize clinical evidence and answer whether PUI can impact the periapical healing of nonsurgical endodontic treatments.

2 Methods

2.1 Protocol Registration

The study protocol was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (23) and registered *a priori* in the PROSPERO database under protocol number: CRD42021290894. This systematic review was reported in accordance with the PRISMA 2020 (24) recommendations, and the research guiding question was formulated based on the Population (P), Intervention (I), Comparison (C), and Outcome (O) framework and defined as: “Performing PUI (I) in nonsurgical endodontic treatments (P) has a significant impact on the periapical healing (O) when compared to conventional syringe irrigation or other activation methods (C)?”.

2.2 Eligibility and exclusion criteria

Eligible studies were randomized clinical trials (RCTs) that included patients that underwent nonsurgical endodontic treatment in any tooth group, regardless of pulpal and periapical diagnosis. The CMP and root canal filling protocols employed in the treatment were not considered exclusion parameters. However, it was essential that there were intervention groups that compared PUI with other methods of activation or control groups without activation (e.g., substance renewal with conventional syringe irrigation). The included studies should report with at least 6 months of follow-up period the periapical healing rates of the treated teeth, defined as the regression or absence of the periapical lesion. For this, periapical radiographs

and/or cone-beam computed tomography should be performed and correlate the findings with the absence of clinical signs and symptoms.

Studies presenting non-standardized clinical protocols (non-standardization of file sequences, ACS, number of clinical sessions, filling material, and other possible intervention biases) were excluded. Reviews, letters, opinion articles, conference abstracts, case reports, case series, in vitro studies, animal studies, studies that did not perform the CMP step, and studies that did not have a minimum period of 6 months of follow-up to evaluate periapical healing were also excluded from this review.

2.3 Information sources and search strategy

The electronic search was performed up to January 2022 in the MedLine (via PubMed), Scopus, Web of Science, Embase, LILACS, and Cochrane Library databases, in addition to the partial search of “grey literature” (e.g., OpenGrey, OpenThesis, and Google Scholar). Additionally, a manual search in the references of potentially eligible studies was performed in an attempt to locate any studies not identified in the primary searches. Complementarily, a search was performed for eligible articles from other previously published systematic reviews evaluating the same intervention. All these steps were performed in order to minimize selection bias.

Initially, the MeSH terms (Medical Subject Headings) and their synonyms were combined using the Boolean operators OR/AND to build the search strategy for MedLine database. Then, this strategy was adapted to the other databases, respecting their syntax rules (Supplementary File 1).

Supplementary file 1. Database search strategies.

Source	Search strategy	Results
MEDLINE/PubMed	**#1** (“ultrasonic irrigation”[Title/Abstract] OR “ultrasonic activation”[Title/Abstract] OR “ultrasonic agitation”[Title/Abstract] OR “sonic irrigation”[Title/Abstract] OR “sonic activation”[Title/ Abstract] OR “sonic agitation”[Title/Abstract] OR “manual dynamic irrigation”[Title/Abstract] OR “manual dynamic activation”[Title/Abstract] OR “manual dynamic irrigation”[Title/Abstract] OR “Therapeutic Irrigation” [MeSH] OR “irrigation techniques”[Title/Abstract] OR “ irrigant activation” [Title/Abstract])	**54477**
	#2 (“Periapical Abscess”[MeSH] OR “Periapical lesion”[Title/Abstract] OR “ periradicular lesion”[Title/Abstract] OR “periapical bone destruction”[Title/Abstract] OR “periapical bone loss”[Title/ Abstract] OR “pulp necrosis”[Title/Abstract] OR “Periapical Periodontitis”[MeSH] OR “non-vital teeth” OR “Apical Periodontitis”[Title/Abstract] OR “Endodontic”[Title/Abstract])	**22169**
	#1 AND **#2**	**443**
Scopus	**#1** TITLE-ABS-KEY (“ultrasonic irrigation”) OR (TITLE-ABS-KEY (“ultrasonic activation”)) OR (TITLE-ABS-KEY (“ultrasonic agitation”)) OR (TITLE-ABS-KEY (“ sonic irrigation”)) OR (TITLE-ABS-KEY (“sonic activation”)) OR (TITLE-ABS-KEY (“sonic agitation”)) OR (TITLE-ABS-KEY (“manual dynamic irrigation”)) OR (TITLE-ABS-KEY (“manual dynamic activation”)) OR (TITLE-ABS-KEY (“Therapeutic Irrigation”)) OR (TITLE-ABS-KEY (“irrigation techniques”)) OR (TITLE-ABS-KEY (“ irrigant activation”))	**5147**
	#2 TITLE-ABS-KEY (“Periapical Abscess”) OR (TITLE-ABS-KEY (“Periapical lesion”)) OR (TITLE-ABS-KEY (“ periradicular lesion”)) OR (TITLE-ABS-KEY (“ periapical bone destruction”)) OR (TITLE-ABS-KEY (“periapical bone loss”)) OR (TITLE-ABS-KEY (“pulp necrosis”)) OR (TITLE-ABS-KEY (“Periapical Periodontitis”)) OR (TITLE-ABS-KEY (“non-vital teeth”)) OR (TITLE-ABS-KEY (“Apical Periodontitis”)) OR (TITLE-ABS-KEY (“Endodontic”))	**29283**
	#1 AND **#2**	**422**

Web of Science	**#1** TS=(“ultrasonic irrigation”) OR TS=(“ultrasonic activation”) OR TS=(“ultrasonic agitation”) OR TS=(“sonic irrigation”) OR TS=(“sonic activation”) OR TS=(“sonic agitation”) OR TS=(“manual dynamic irrigation”) OR TS=(“manual dynamic activation”) OR TS=(“Therapeutic Irrigation”) OR TS=(“irrigation techniques”) OR TS=(“ irrigant activation ”)	**2160**
	#2 TS =(“Periapical Abscess”) OR TS=(“Periapical lesion”) OR TS=(“ periradicular lesion”) OR TS=(“periapical bone destruction”) OR TS=(“periapical bone loss”) OR TS =(“pulp necrosis”) OR TS=(“Periapical Periodontitis”) OR TS=(“non-vital teeth”) OR TS=(“Apical Periodontitis”) OR TS=(“Endodontic”)	**17242**
	#1 AND **#2**	**354**
EMBASE	**#1** 'ultrasonic irrigation' OR 'ultrasonic activation' OR 'ultrasonic agitation' OR 'sonic irrigation' OR 'sonic activation' OR 'sonic agitation' OR 'manual dynamic irrigation' OR 'manual dynamic activation' OR 'therapeutic irrigation' OR ' irrigation techniques' OR ' irrigant activation'	**94975**
	#2 'Periapical Abscess' OR 'Periapical lesion' OR ' periradicular lesion' OR 'periapical bone destruction' OR 'periapical bone loss' OR `pulp necrosis` OR 'Periapical Periodontitis' OR 'non-vital teeth' OR 'Endodontic'	**28868**
	#1 AND **#2**	**655**
LILACS	(ultrasonic irrigation) OR (ultrasonic activation) OR (sonic irrigation) OR (sonic activation) OR (manual dynamic irrigation) OR (irrigation techniques) OR (irrigant activation) AND (periapical abscess OR periapical lesion OR periapical bone loss OR pulp necrosis OR periapical periodontitis OR non-vital teeth OR endodontic)	**4**
Cochrane Library	**#1** (ultrasonic irrigation): ti ,ab,kw **#2** (ultrasonic activation): ti ,ab,kw **#3** (ultrasonic agitation): ti ,ab,kw **#4** (sonic irrigation): ti ,ab,kw **#5** (sonic irrigation): ti ,ab,kw **#6** (sonic activation): ti ,ab,kw **#7** (sonic agitation): ti ,ab,kw **#8** (dynamic irrigation manual): ti ,ab,kw **#9** (dynamic activation manual): ti ,ab,kw **#10** (therapeutic irrigation): ti ,ab,kw **#11** (irrigation techniques): ti ,ab,kw **#12** (irrigant activation): ti ,ab,kw **#13** #1 or #2 or #3 or #4 or #5 or #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 **#14** (Periapical Abscess): ti,ab ,kw **#15** (Periapical lesion): ti,ab ,kw **#16** (periradicular injury): ti,ab ,kw **#17** (periapical bone destruction): ti ,ab,kw **#18** (periapical bone loss): ti ,ab,kw **#19** (pulp necrosis): ti,ab ,kw	**3**

	#20 (Periapical Periodontitis): ti,ab ,kw **#21** (non-vital teeth): ti ,ab,kw **#22** (Endodontic): ti ,ab,kw **#23** #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 **#24** #13 AND #23	
OpenGrey		**0**
OpenThesis		**0**
Google Scholar		**0**

2.4. Selection process

The studies were selected in three stages. In the first stage, the studies were identified after a comprehensive search of the databases. The results obtained were exported to the Mendeley® software (Elsevier Inc., London, United Kingdom), from which the duplicate records were removed.

Before the second step, a calibration exercise was carried out in which the reviewers discussed the eligibility criteria. In the second step, the records were exported to the Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar) (25) where the analysis of the titles and abstracts of the studies was carried out, applying the eligibility criteria mentioned above. Subsequently, eligible preliminary studies had their full texts obtained and evaluated. This entire process was carried out by two independents reviewers (LBG and LPA). The discrepancies were resolved after consulting a third reviewer (JFAA).

2.5 Data collection process

Before data extraction, to ensure consistency between examiners, a training exercise was carried out between two reviewers (LBG and WAV), in which information was extracted together from an eligible study, and a third reviewer double-checked it (TAS). Any disagreement between the examiners was resolved through discussions, and a fourth reviewer (CCRF) was consulted to achieve consensus and make the final decision.

Subsequently, the following information was extracted from eligible studies: (a) authors and year of publication; (b) country; (c) sample size of participants; (d)

activation groups and methods; (e) auxiliary chemical substance; (f) activation time; (g) tooth group; (h) age; (i) sex; (j) sample by sex; (k) follow-up method; (l) follow-up time; (m) periapical healing criteria (n) lesion regression and absence of symptoms (o) main findings (p) study type, and (q) funding sources. The corresponding author of the included study was contacted by e-mail to resolve any lack of information.

2.6 Study risk of bias assessment

Two reviewers (LBG and LPA) independently assessed the individual risk of bias in the included studies using the Cochrane Collaboration Risk of Bias Tool (RoB2) for RCTs (26). This tool consists of five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to lack of outcome data, outcome measurement bias, and reporting outcome selection bias.

The evaluation of each domain followed the algorithms proposed by the RoB2 manual. Each domain consists of signaling questions that can be answered as “yes”, “probably yes”, “probably not”, “no” or “no information”. Responses to the flagging questions reveal what happened and provide the basis for domain-level judgments about risk of bias, which can be judged as: “High risk”, “Some concerns” or “Low risk”. At the study level, the article was judged to be at low risk of bias if it was assessed as “low risk” in all domains; “some concerns” if at least one domain was rated as “some concerns”; and the study was judged at high risk of bias if it was assessed as “high risk” in at least one domain or some concerns for multiple domains. Any disagreements between reviewers were resolved through discussion and consultation with a third reviewer (WAV).

2.7 Statistical analysis

Data were summarized using the R software for Windows version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), with the aid of the meta and metafor packages. As dichotomous variables, the Relative Risk (RR) was used as an estimated effect, with a confidence interval (CI) of 95%. Inter-study variation was assessed using the tau-square statistic (τ^2), and the magnitude of heterogeneity was determined by the I^2 statistics and was classified as: low ($I^2 < 50\%$), moderate ($I^2 = 50–75\%$), or high ($I^2 > 75\%$). In order to generalize the results obtained, a meta-analysis of random effects was initially performed; if low heterogeneity was found, the meta-

analysis was supplemented with a fixed effect as a sensitivity test. As a second sensitivity test, a second meta-analysis was performed, excluding studies at high risk of bias.

The trial sequence analysis was performed using the TSA software (Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen, Denmark). The control group event rate and the intervention effect obtained by the meta-analysis were used to perform the test.

2.8 Certainty assessment

The certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The GRADEpro GDT software (GRADEpro GDT; McMaster University, Ontario, CA) was used to summarize the results. The assessment was based on five domains: (d1) risk of bias, (d2) inconsistency, (d3) indirectness, (d4) imprecision, and (d5) publication bias. The certainty of the evidence was classified as high, moderate, low, or very low (27).

3 Results

3.1 Search strategy

Figure 1 is a schematic flowchart showing the study selection process. The systematic search of all databases retrieved a total of 1881 records, from which 884 duplicates were removed. After the initial assessment by title and abstracts, 992 records were excluded for not meeting the eligibility criteria, and 5 studies were selected for full-text analysis. Two studies were excluded for having different study designs, and 3 studies were included in the qualitative and quantitative synthesis (28–30).

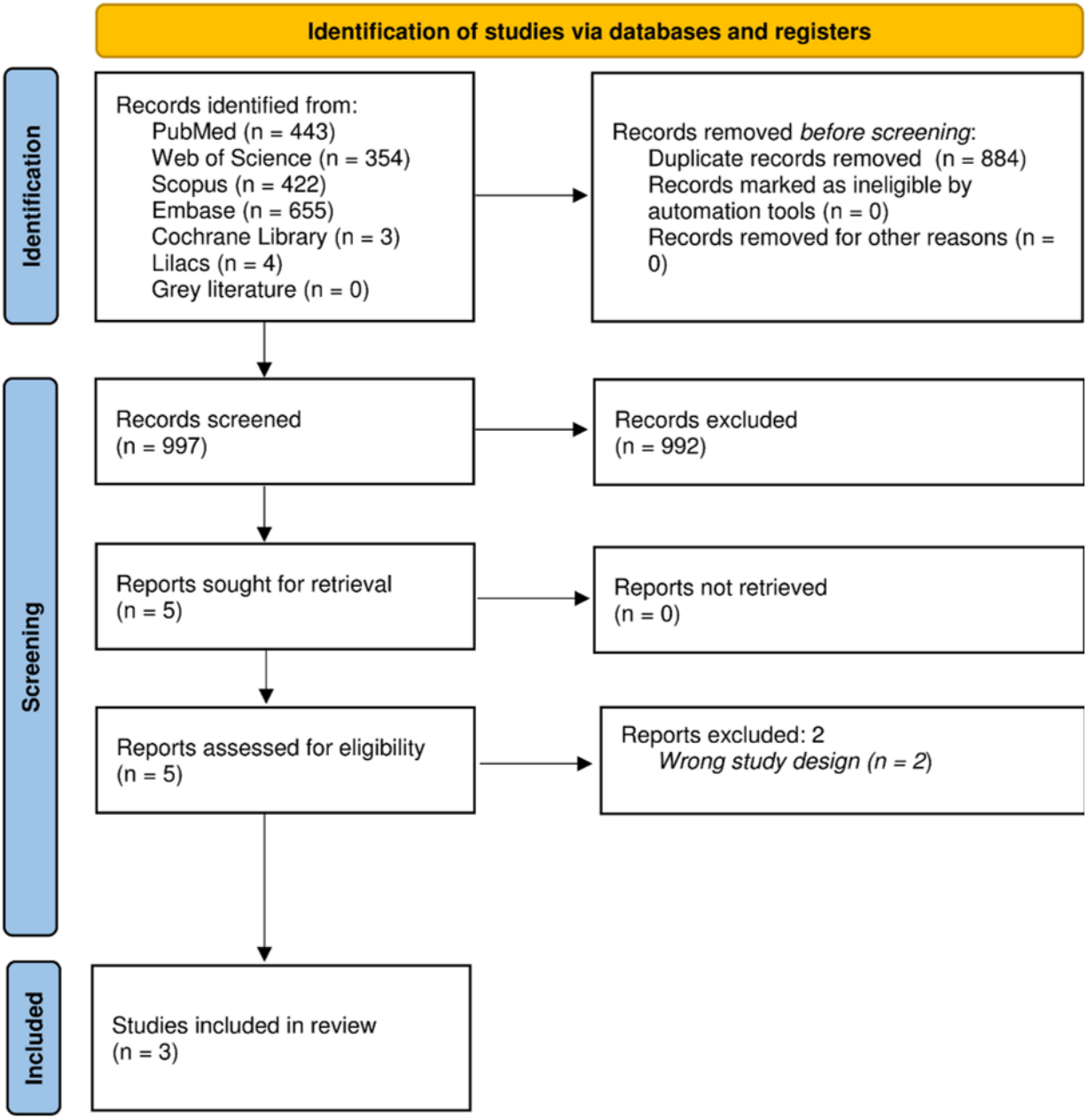


Figure 1. Search flowchart according to the PRISMA 2020 Statement.

3.2 Study characteristics

Table 1 shows demographic data, sample characteristics, and the intervention characteristics of the included studies. The trials were carried out between the years 2013 and 2020. Two studies were carried out in China (29,30) and the other in India (28). A total of 474 patients (501 teeth) were evaluated, with an age range of 18 to 72 years. All studies only included patients diagnosed with pulp necrosis and apical periodontitis. Two studies compared the periapical healing rate between CSI

versus PUI (29,30), and the other study evaluated activation with PUI versus laser-activated irrigation (LAI) or CSI (28). Activation protocols varied among the included studies, with activation times ranging from three cycles of 10 seconds to four cycles of 20 seconds each. Moreover, all studies used NaOCl as the auxiliary chemical substance to be activated, and in one study, an additional group tested a silver ion solution (29).

Two studies (28,29) carried out observation periods of up to 12 months, and in one study, the follow-up was of up to 19 months (30). Two studies (28,30) used cone-beam computed tomography scans to evaluate periapical healing, and the other study (29) assessed it through periapical radiography.

For the evaluated outcome, all studies (28–30) showed that the use of PUI had a higher percentage of periapical healing rate than CSI. Also, no difference was observed in using different concentrations of NaOCl and the use of silver ion solution (28). Moreover, one study showed a significant difference when using LAI or PUI on the periapical healing outcome when compared to CSI. Lastly, no study reported following any kind of quality guidelines for reporting RCTs. The main findings of the included trials are shown in Table 2.

Table 1. Demographic data, sample characteristics and intervention characteristics of the included trials

Sample characteristics						Intervention characteristics			
Author and country	**Number of patients**	**Age range**	**Number of teeth**	**Teeth group**	**Pulpal and periapical diagnosis**	**Intervention**	**Comparison**	**Auxiliary chemical substances**	**Activation time**
Liang et al., 2013 China	105	Not informed	84	Mandibular and maxillary single-rooted incisors, canines, and premolars	Necrotic pulp	Passive ultrasonic irrigation	Syringe irrigation	5.25% NaOCl	Three cycles of 10 seconds each
Tang et al., 2015 China	300	60 – 72	360	Any teeth	Chronic apical periodontitis	Passive ultrasonic irrigation	Syringe irrigation	5.25% NaOCl and silver ion solution	Not informed
Verma et al., 2020 India	69	18 – 60	57	Single-rooted incisors and premolars	Apical periodontitis	Passive ultrasonic irrigation, and laser-activated irrigation	Syringe irrigation	3% NaOCl	Four cycles of 20 seconds each

Table 2. Main findings of the included trials

Author	**Observation period**	**Follow-up method**	**Periapical healing rate**	**Main findings**
Liang et al., 2013	10 – 19 months	Periapical radiography and CBCT scan	PUI group: 95.12% Comparison group: 88.37%	No significant differences were found with and without additional ultrasonic activation of the irrigant on the periapical healing rate.
Tang et al., 2015	7 days, 6 months, and 1 year	Clinical evaluation and periapical radiography	PUI group with NaOCl: 85% PUI group with Silver Ions: 88.52% Comparison group: 77.97%	No significant differences were found in the PUI groups with both NaOCl and silver ions solution compared to conventional syringe irrigation.
Verma et al., 2020	7 days and 1 year	Clinical evaluation and CBCT scan	PUI group: 100% LAI group: 100% Comparison group: 78.4%	Passive ultrasonic irrigation and laser-activated irrigation can significantly increase the periapical healing rate.

3.3 Individual risk of bias assessment

One study was classified as "low risk of bias" (28), one as "some concerns" in the domains of randomization bias, deviations from intended intervention bias, and selection of the reported outcome bias (30), and the other as “high risk of bias” in the domains of deviations from intended intervention bias, missing outcome data, and measurement of the outcome bias (29). Figure 2 shows the individual assessment of each article included.

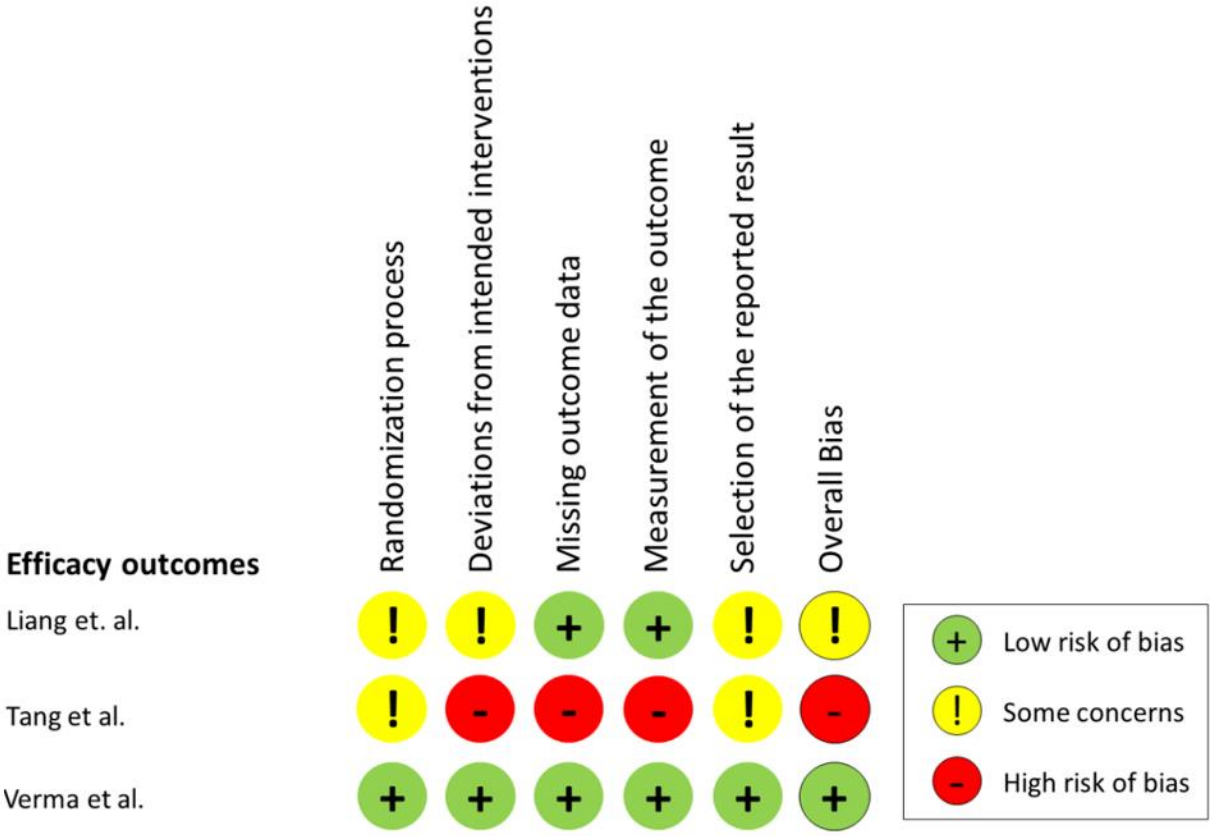


Figure 2. Findings from the risk of bias analysis

3.4 Synthesis of the results

Only one study compared PUI with alternative methods of activation (28); therefore, it was not possible to perform a meta-analysis for this outcome. In addition, a study (29) presented an activation group of NaOCl associated with silver ions solution; however, due to the lack of a control group for the association of these substances without performing activation, this group was not included in the statistical analysis.

For the meta-analysis, only groups that compared PUI with NaOCl vs. CSI groups were included. Thus, based on three studies, the results showed that the use of PUI is more successful when compared to CSI on the periapical healing outcome (RR: 1.10; 95%CI: 1.01;1.21, I^2=0%) (Figure 3). In the sensitivity test, a study with a high risk of bias was removed (29), and there was no difference in the estimate of effect from the primary meta-analysis (RR: 1.13; 95%CI: 1.01; 1.27, I^2=28%) (Supplementary Figure 1).

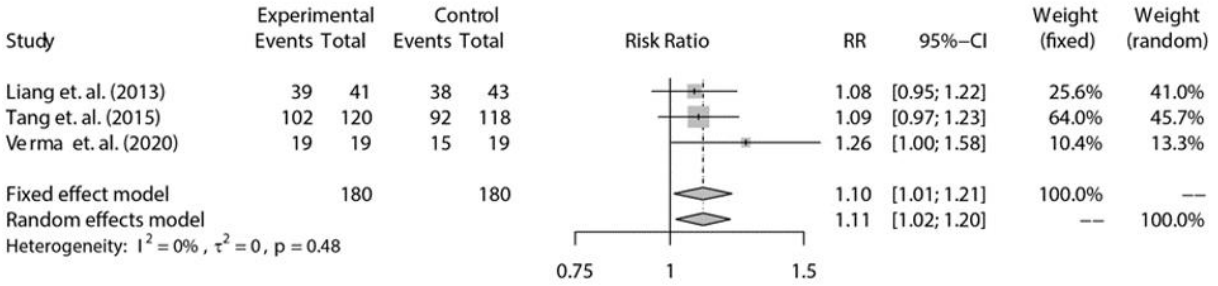
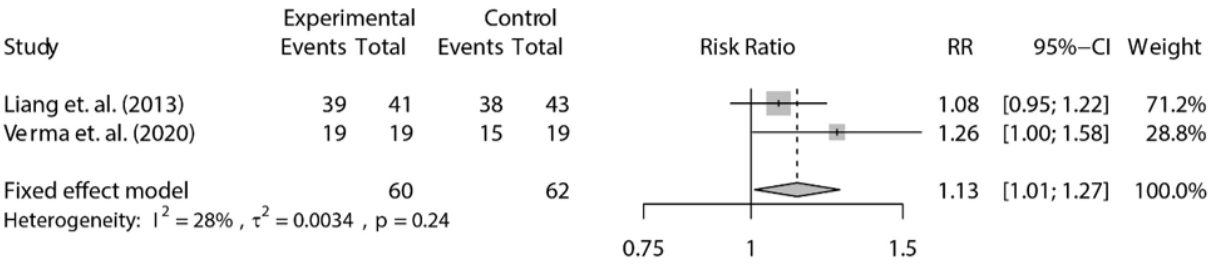


Figure 3. Group meta-analysis comparing PUI vs. CSI



Supplementary Figure 1. Group meta-analysis comparing PUI vs. CSI without the study with high risk of bias.

Figure 4 shows the trial sequence analysis. This analysis was performed using 5% type 1 error and 20% type II error, using a random effects model. The information size (n = 577) was calculated using a predicted intervention effect of RR = 1.10 (the intervention effect obtained by the primary meta-analysis) and the proportion of control events of 80.5%. The cumulative Z curve (blue line) did not cross the alpha-spending boundary (red dots line); thus, the number of patients included in the meta-analysis (n = 501) did not reach the necessary sample size. Therefore, the evidence obtained in the meta-analysis of three trials can be considered "inconclusive". The certainty of evidence assessed by the GRADE approach was considered moderate due to imprecision (Table 3).

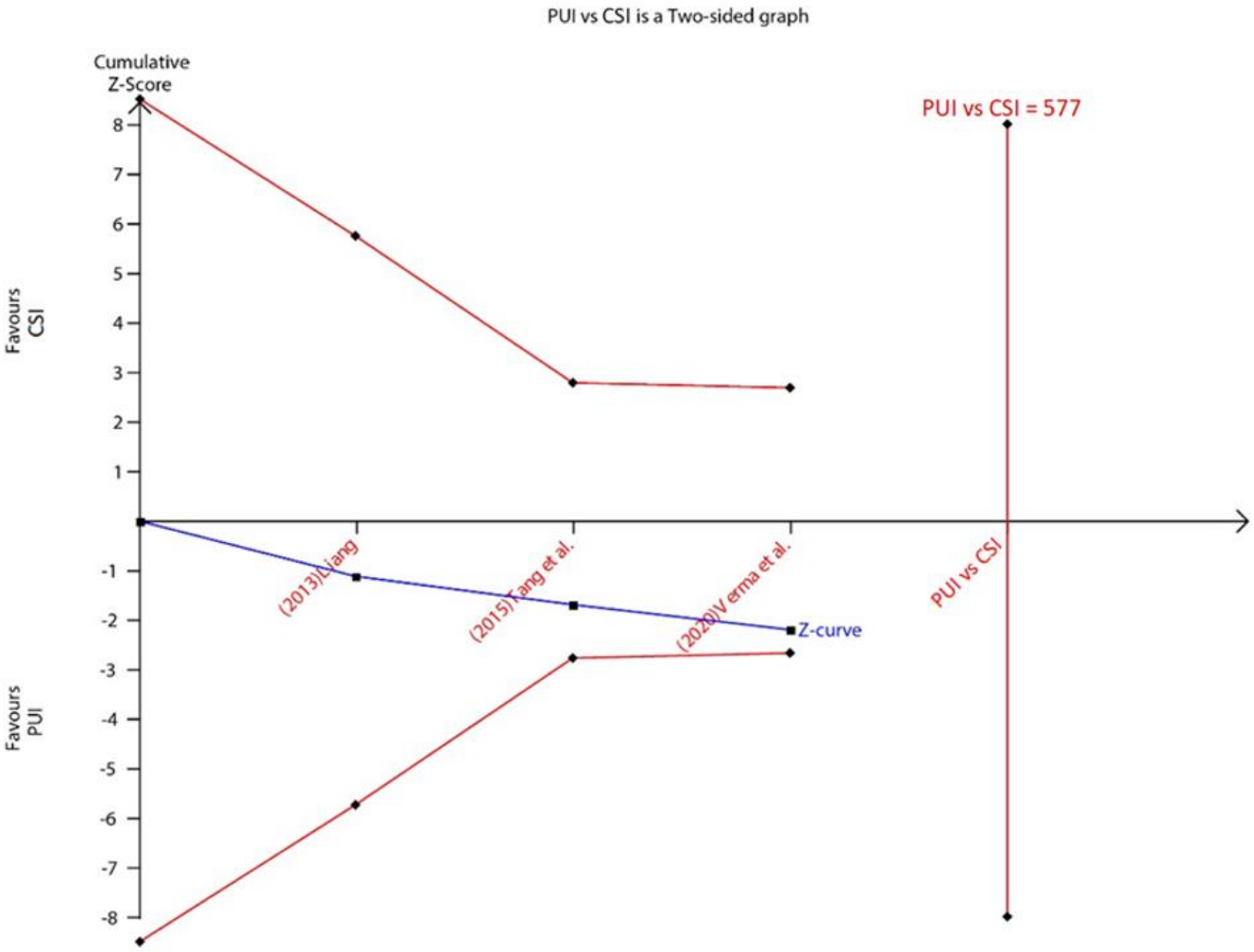


Figure 4. Trial sequence analysis assessing bone healing after using PUI or CSI.

Table 3 – Certainty of evidence based on the GRADE approach.

Certainty assessment							Number of patients			
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative effect (95% CI)**	Certainty
Bone healing (Passive ultrasonic irrigation vs. Conventional syringe irrigation)										
3	RCT	not serious[a]	not serious	not serious	serious[b]	none[c]	160/180 (88.8%)	145/180 (80.5%)	RR 1.10 (1.01 to 1.21)	⊕⊕⊕◯ MODERATE

CI, confidence interval; OR, odds ratio.
a – The sensibility test shows no difference in the effect estimate after the removal of the study with high risk of bias.
b – Based on the Trial Sequence Analysis, the meta-analysis did not reach the optimal information size – Downgraded by one level.
c - Publication bias not assessed.
Evidence levels of the GRADE workgroup
High certainty: Strongly confident the true effect is close to the effect estimate.
Moderate certainty: Moderately confident in the effect estimate: The true effect might be close to the effect estimate, but it might be substantially different.
Low certainty: Limited confidence in the effect estimate: The true effect might substantially differ from the effect estimate.
Very low certainty: Little confidence in the effect estimate: The true effect will probably substantially differ from the effect estimate.

4 Discussion

The main goal of root canal treatment is to promote effective disinfection of the root canal system, reducing the bacterial load to levels compatible with the healing of the periapical tissues (22).

PUI promotes a phenomenon called acoustic microstreaming that allows the auxiliary chemical solution to penetrate more complex regions of the root canal system, increasing the potential for decontamination. Thus, based on the findings obtained in the present meta-analysis, PUI has a higher success rate in nonsurgical primary root canal treatment when compared to non-activation methods. This result is in agreement with a clinical trial (31) that observed that PUI with 6% NaOCl reduced the levels of lipopolysaccharide and lipoteichoic acid. Moreover, the same trial observed that PUI was associated with a more significant reduction in microbial load within infected root canals. Another clinical trial (8) demonstrated that conventional CMP was effective in reducing bacteria and endotoxins but was not able to eliminate them completely; however, a significant decrease in the endotoxin levels was observed when PUI was performed with 17% EDTA. These findings corroborate that PUI may have a positive influence on the periapical healing outcome.

Many other investigations have found benefits in microbial load reduction by activating the ACS (19,20,32–34). However, they are mainly based on *in vitro* assessments, and evidence-based dental practice requires solid clinical evidence to support new techniques. The current state-of-the-art on this topic is limited, and very few RCTs (28–30) tried to answer whether PUI could improve the periapical healing rate of teeth with apical periodontitis, and in most of them, methodological flaws were observed, such as the standardization of the blind randomization of treatments to be applied to each patient, the way in which the working length was determined or the imaging exam of choice to evaluate the regression of periapical lesions. The risk of bias assessment shows that only one trial had a low risk of bias (28). These methodological flaws can be easily solved in future trials by adopting quality reporting guidelines such as CONSORT (35) or PRIRATE (36), which by structuring the reporting design, can generate more reliable findings and fewer biases. Furthermore, we can observe that the pooled sample size in the included studies (n =501) was insufficient to generate reliable results in the meta-analysis, as at least 577 teeth would be required for precise results. Also, the certainty of evidence based on the GRADE approach was considered moderate. Even though the evidence generated in this meta-

analysis is considered inconclusive, PUI has a statistically significant impact on the periapical healing rate of nonsurgical primary root canal treatment. However, further high-quality RCTs should be performed to support these findings.

In the included RCTs, the ACS activated with PUI was NaOCl, the most used irrigant worldwide. This ACS has an excellent antimicrobial action in addition to promoting organic tissue dissolution (5), but none of the RCTs sought to carry out experimental groups that evaluated other ACS, such as CHX or EDTA. These solutions present characteristics that could generate clinical differences against NaOCl. CHX gel at a 2% concentration has substantivity and broad-spectrum antimicrobial activity, which can prolong its residual antimicrobial action for up to 12 weeks (6). In addition to presenting other properties such as low cytotoxicity, rheological action, inhibition of metalloproteinases, thixotropic action, and diffusion through the dentinal tubules, among other characteristics, which could potentially impact the clinical outcome. Furthermore, EDTA activation should also be clinically assessed because it is an ACS with antimicrobial activity and is a chelating agent used in root canal treatment to promote smear-layer removal (37).

An important aspect of the included RCTs that should be considered is the method in which the CMP was performed. In one of the trials (30), the entire CMP protocol was well described, from the diagnostic image acquisition, working length determination, file sequencing, the method of ACS activation, and root filling. However, in another trial (29) the CMP protocol was not thoroughly detailed. Despite describing the file sequencing, they also informed that the CMP protocol was performed differently for each group which could be seen as a confounding bias. On the other hand, the last trial (28) described the detailed standardized CMP for all groups; however, this study reported using radiographic working length determination instead of using an electronic apex locator. This method of working length determination is well-known in the literature for having several limitations in terms of accuracy and precision since the radiographic foramen does not always coincide with the anatomical foramen, and periapical radiographs can present image distortions (38).

Patient follow-up is another issue to be considered since one of the difficulties in performing high-impact RCTs is to recall patients and assess the treatment outcome (39). The periapical healing process has a complex dynamic rate that short-frame timeline recalls are not sufficient to determine the treatment outcome, and at least 6 to 12 months are necessary to observe any progress in this outcome(13).

Also, the follow-up method is another aspect that should be considered in high-impact RCTs. Cone-bean computed tomography (CBCT) scans were used as an outcome assessment method in two of the included trials (28,30). This method is considered to have excellent accuracy in detecting apical periodontitis (40), and it should be used to determine this outcome in future trials. Even though periapical radiograph has a reasonable accuracy rate (41), it is a two-dimensional image, and periapical radiolucency may be underestimated due to the overlap of three-dimensional anatomical structures. Thus, the use of CBCT is essential due to the fact that it allows a three-dimensional analysis of the image, in addition to the possibility of manipulating these images with filters and other tools that facilitate the diagnosis and follow-up assessments (42,43).

Moreover, the present meta-analysis has found homogeneity in the included trials. The statistical test of heterogeneity obtained a result of 0%, which means that the estimates of the pooled studies are considered similar and consistent, which is favorable for the reliability of the meta-analysis findings (44). This aspect of our study is in contrast with a previous systematic review on the same outcome (22), which has included two RCTs that did not carry out follow-up assessments of the root canal treatment (8,45), and also this study has not performed a meta-analysis of the findings.

It is clear that more high-impact RCTs on the topic with a larger sample size, longer follow-up periods, and following RCTs quality reporting guidelines are needed to fully understand the impact of PUI on the periapical healing outcome. However, the literature supports the use of PUI and shows several benefits that could potentially lead to a more favorable outcome in root canal treatment, such as reduced overall microbial load (46,47), increased hard tissue debris removal (48), increased efficacy on the removal of the vapor-lock phenomenon (49), increased efficacy on the removal of interappointment calcium hydroxide dressings (50) and reduced post-operative pain (51,52).

5 Conclusion

The evidence generated from this meta-analysis was considered inconclusive, and the certainty of this evidence was considered moderate. Moreover, high-quality RCTs with a larger sample size are necessary to disclose if this intervention could increase the therapy outcome. However, the findings from this meta-

analysis showed that the use of PUI had a greater impact on the periapical healing rate of nonsurgical primary root canal treatment when compared with CSI.

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Figure legends

Figure 1. Flowchart showing the search strategy based on the PRISMA 2020 Statement.

Figure 2. Findings from the risk of bias analysis

Figure 3. Group meta-analysis comparing PUI vs. CSI

Figure 4. Trial sequence analysis assessing bone healing after using PUI or CSI.

3 CONCLUSÃO

A evidência gerada pela meta-análise foi considerada inconclusiva, e a certeza de evidência foi considerada moderada. Além disso, são necessários ensaios clínicos randomizados de alta qualidade com um tamanho de amostra maior para revelar se esta intervenção poderia aumentar o resultado da terapia. Entretanto os resultados mostraram que o uso da IUP teve um impacto maior na taxa de cicatrização periapical do tratamento endodôntico não cirúrgico quando comparado com a ICS.

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ANEXOS

Anexo 1 - Verificação de originalidade e prevenção de plágio

Impacto irrigação passiva

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