UNIVERSIDADE ESTADUAL PAULISTA - UNESP

FACULDADE DE ODONTOLOGIA DE ARAÇATUBA - FOA

DEPARTAMENTO DE ODONTOLOGIA PREVENTIVA E RESTAURADORA

DISCIPLINA DE ENDODONTIA

LUCAS ORBOLATO CHALUB

Avaliação da dor pós-operatória e efetividade antimicrobiana no tratamento endodôntico com uso de irrigação ultrassônica versus irrigação convencional: Revisões sistemáticas e meta-análises de ensaios clínicos randomizados

Araçatuba - SP

2022

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Dissertação apresentada à Faculdade de Odontologia de Araçatuba, Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP, como partes dos requisitos para obtenção do título de Mestre, pelo Programa de Pós-Graduação em Ciência Odontológica, Área de Concentração em Endodontia.

Orientador: Prof. Ass. Dr. Gustavo Sivieri de Araújo

Araçatuba - SP

2022

Catalogação na Publicação (CIP)

Diretoria Técnica de Biblioteca e Documentação – FOA / UNESP

C441a

Chalub, Lucas Orbolato.
Avaliação da dor pós-operatória e efetividade antimicrobiana no tratamento endodôntico com uso de irrigação ultrassônica versus irrigação convencional : revisões sistemáticas e meta-análises de ensaios clínicos / Lucas Orbolato Chalub. - Araçatuba, 2022
90 f. : il. ; tab.

Dissertação (Mestrado) – Universidade Estadual Paulista, Faculdade de Odontologia de Araçatuba
Orientador: Prof. Gustavo Sivieri de Araújo

1. Ultrassom 2. Dor pós-operatória 3. Tratamento do canal radicular 4. Revisão sistemática 5. Metanálise 6. Desinfecção I. Título

Black D24
CDD 617.67

Claudio Hideo Matsumoto CRB-8/5550

Dedicatória

Dedico este trabalho aos meus pais, Carlos e Silvia, meus maiores incentivadores, por todos os sacríficos e esforços realizados, para garantir uma educação de qualidade para os seus filhos. Muitas vezes tirando de si próprio para fazer o melhor para nós. Serei eternamente grato pelo que fizeram e fazem para que meus objetivos pudessem ser alcançados. Se eu estou aqui hoje, foi graças aos esforços de vocês e jamais será esquecido. Vocês são os responsáveis por este momento. Essa conquista também pertence a vocês. Obrigado por tudo o que me ensinaram, pela base que me deram e por toda inspiração que me trazem. Amo vocês!

À minha namorada, esposa e companheira,

Tamires Cândida dos Santos, agradeço por todo seu amor e por todo cuidado e carinho que teve comigo em todos os momentos durante minha trajetória na pós-graduação. Você foi a pessoa que me levantava nos momentos de dificuldades e tristezas, toda essa trajetória se tornou mais leve e feliz ao seu lado. Essa conquista não existiria sem você, obrigado por todo o seu apoio, e por ser exatamente a pessoa que você é. Obrigado por estar sempre ao meu lado. Eu te amo!

AGRADECIMENTOS

Agradeço a **Deus** por guiar minhas escolhas e me dar forças para persistir diante todos os obstáculos, iluminando meu caminho em todos os momentos em que precisava, não permitindo que eu desistisse nesta caminhada. Obrigado meu Deus por colocar ao meu lado uma família amorosa, compreensiva que sempre esteve ao meu lado em todos os momentos. Obrigado Senhor por todas as graças concedidas e por cada momento que esteve comigo, protegendo-me e guiando-me nesse longo caminho de grandes realizações.

“Tenho-vos dito isso, para que em mim tenhais paz; no mundo tereis aflições, mas tende bom ânimo; eu venci o mundo.”

João 16:33

Quem é que vence o mundo, senão aquele que crê que Jesus é o Filho de Deus?

João 5:5

AGRADECIMENTOS

Aos meus Irmãos, **Bruno** e **Renan**, que mesmo com a distância e caminhos diferentes sempre estiveram presentes em minha vida, e sei que o nosso amor fraterno resiste ao tempo e a distância. “Ter um irmão é ter para sempre uma infância lembrada com segurança em outro coração”.

Aos meus Avós paternos**, Ruth Guimirães Chalub** *(in memorian)* **e Fares Chalub** *(in memorian),* Carrego um grande respeito por tudo que fizeram pela nossa família, os ensinamentos, e todo amor que tinham com todos, vocês fazem muita falta para nossa Família, são uma fonte de inspiração sem fim Obrigado.

A minha avó materna **Aparecida Cardoso Araújo** por ser uma mulher guerreira, e ter cuidado de seus três filhos sozinha numa época em que o simples fato de ser mulher já era uma dificuldade, por toda sua luta em conseguir dar educação para seus filhos, refletindo hoje em minhas escolhas e mostrando que o ensino é uma arma poderosa que pode mudar o mundo.

Obrigado por serem a base de nossa família!

Aos meus familiares, Tios, Primos e Amigos todos são e foram muito importante em minha vida, carrego muitas lembranças e carinho por todos vocês deixo registrada minha imensa gratidão.

Agradecimento especial...

Ao meu orientador **Prof. Ass. Dr. Gustavo Sivieri de Araújo**, por ser o meu orientador e mentor ao longo de toda a minha trajetória na Pós-Graduação, sempre serei grato pela oportunidade e confiança depositada em mim. Obrigado por todo ensinamento e dedicação que sem dúvidas contribuíram para o meu engrandecimento científico e profissional, por sempre estar presente mesmo durante esse período conturbado de pandemia, através de diversas reuniões via Skype, nunca deixou de demonstrar dedicação e nos mostrar o caminho a seguir. Meu muito obrigado.

Ao meu grupo de pesquisa, **Henrico**, **Henrique**, **Marcelo** e **Larissa** que tornaram essa jornada mais fácil, divertida e leve cada um teve sua participação e todos estarão sempre em minhas memórias por tudo que compartilhamos, as dificuldades, as alegrias e os ensinamentos.

Ao meu amigo, e mentor de revisões sistemáticas **Gabriel Pereira Nunes** meu muito obrigado, você sabe o quanto sou grato por sua ajuda, pelos seus ensinamentos, mesmo com pouco tempo sempre buscando ajudar e ensinar.

A todos os Pós-Graduandos, pela amizade, pelas conversas, por compartilharem conhecimentos e deixarem esse período mais descontraído e leve.

A todos os Professores da Pós-Graduação que fizeram parte desta jornada, agradeço pela oportunidade de poder ouvi-los e aprender com todos vocês, é realmente um privilégio poder aprender com os melhores

A Equipe de Docentes da Endodontia FOA/UNESP

Aos Docentes, os Professores Gustavo Sivieri de Araújo, Luciano Tavares Angelo Cintra, Eloi Dezan Junior, João Eduardo Gomes Filho e Rogério de Castilho Jacinto, por serem um grupo unido e em prol de um objetivo, colaborar com a ciência. Obrigado por serem grandes exemplos, a nós Pós-Graduandos, de como ser Professor, Educador e Cientistas. Vocês são grandes inspirações, obrigado por todo conhecimento dividido de alguma forma.

A todos os Funcionários e estimados amigos da Biblioteca da Faculdade de Odontologia de Araçatuba - UNESP, Cláudio Hideo Matsumoto, Ana Claudia Grieger Manzatti, Luzia Anderlini, Denise Haruyo Nakamura Maeda, Luís Cláudio Sedlacek, Ana Paula Rímoli de Oliveira e Maria Cláudia de

Castro Benez, pela atenção e eficiência com que sempre me atenderam.

Aos Funcionários da Seção de Pós-Graduação da Faculdade de Odontologia de Araçatuba- UNESP, Valéria de Queiroz M. Zagatto, Cristiane Regina Lui Matos, Lilian Sayuri Mada pelo excelente trabalho, atenção e grande disposição em sempre nos atender

Por fim, agradeço à **Universidade Estadual Paulista "Júlio de Mesquita Filho",** na pessoa do **Diretor da Faculdade de Odontologia de Araçatuba Prof. Tit. Glauco Issamu Miyahara e do Vice-Diretor Prof. Tit. Alberto Carlos Botazzo Delbem**, o qual agora posso me orgulhar de ter sido aluno FOA/UNESP.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Brasil - CAPES pela concessão da Bolsa durante os últimos doze meses de Mestrado, indispensável para a realização deste trabalho, que ela continue sempre auxiliando, fomentando e estimulando os futuros pesquisadores do nosso país.

Vamos valorizar a Ciência Brasileira!!

OBRIGADO!

Epígrafe

Ninguém vai bater mais forte do que a vida. Não importa como você bate e sim o quanto aguenta apanhar e continuar lutando; o quanto pode suportar e seguir em frente. É assim que se vence.

Sylvester Stallone

Resumo Geral

Chalub LO. Avaliação da dor pós-operatória e efetividade antimicrobiana no tratamento endodôntico com uso de irrigação ultrassônica versus irrigação convencional: Revisões sistemáticas e meta-análises de ensaios clínicos randomizados. 90 f. Dissertação (Mestrado). Universidade Estadual Paulista (Unesp), Faculdade de Odontologia, Araçatuba, 2022.

RESUMO GERAL

O objetivo deste estudo foi avaliar a efetividade antimicrobiana e a dor pós-operatória (PP) da irrigação ultrassônica (IU) em comparação com a irrigação convencional (CI), por meio de duas revisões sistemática e meta-análises de ensaios clínicos randomizados, para isto foram produzidos dois artigos, um para dor pós operatória e outro para avaliação antimicrobiana, desta forma a dissertação a seguir contará com dois capítulos. Essa revisão foi elaborada seguindo o guia PRISMA (*Preferred Reporting Items for Systematic Review and Meta-Analyses*). Após elaborada a pergunta clínica e a estratégia PICO de cada estudo, uma pesquisa bibliográfica foi realizada nas principais bases de dados científicas por meio de uma estratégia de busca elaborada com termos MeSH e termos livres adaptados para as bases de dados. As meta-análise foram conduzidas usando o software R com o pacote “META”, o efeito de medida de diferença média (MD) e odds ratio (OR) foi calculada e o modelo de efeito fixo foi aplicado com um intervalo de confiança (IC) de 95%. A escala da colaboração Cochrane foi usada para avaliar o risco de viés e a ferramenta GRADE para avaliar a qualidade das evidências.

Os resultados mostraram vantagem favorecendo o grupo irrigação ultrassônica em ambas as variáveis de interesse (dor pós-operatória e efetividade antimicrobiana), na dor pós-operatória, 6 ensaios clínicos randomizados (RCTs) foram incluídos para revisão sistemática e quatro para meta-análise. IU resultou em menor PP em 3 dos 5 períodos, 6 horas (MD -1,40 [CI -2,38 a -0,42] p = 0,0052), 24 horas (MD -0,73 [CI -1,07 a -0,39] p = 0,0001), e 48 horas (MD -0,36 [CI -0,59 a -0,13] p = 0,022). No entanto, a PP não apresentou diferenças significativas entre os grupos em 72 horas e 7 dias (p> 0,05). Um baixo risco de viés foi observado para a maioria dos domínios, exceto a alocação que foi considerada pouco clara. A certeza da evidência foi classificada em moderada (24 horas, 48 horas e 7 dias) e baixa (6 e 72 horas). Já na efetividade antimicrobiana, 12 RCTs foram incluídos para a revisão sistemática e oito para as meta-análises onde 4 foram utilizadas para (MD) e 4 para (OR). Em ambas análises a IU resultou em melhor efeito antimicrobiano em comparação com a CI MD -1,42 [-1,60; -1,23] p <0,0001, I2 = 80%

e OR 3.86 [1.98; 7.53] p< 0.0001, I2 = 28.7%. Um baixo risco de viés foi observado para a maioria dos domínios, exceto a alocação que foi considerada pouco clara. A certeza das evidências foi considerada moderada na meta-análise utilizando OR, devido aos achados de imprecisão, e baixa na meta-análise utilizando MD devido a presença de inconsistência e imprecisão. Desta forma é possível concluir que dentro das limitações das presentes revisões sistemáticas a IU apresentou resultados favoráveis tanto para dor pós-operatória quanto para o aumento da efetividade antimicrobiana. Contudo ensaios clínicos randomizados mais robustos são necessários para corroborar com esses achados.

Palavras-chave: Ultrassom. Dor pós-operatória. Tratamento do canal radicular. Revisão sistemática. Metanálise. Desinfecção.

Abstract

Chalub LO. Evaluation of postoperative pain and antimicrobial effectiveness in endodontic treatment using ultrasonic irrigation versus conventional irrigation: Systematic reviews and meta-analyses of randomized clinical trials. 90 f. Thesis (Master's degree). São Paulo State University (Unesp), School of Dentistry, Araçatuba, 2022.

ABSTRACT

The aim of this study was to evaluate the antimicrobial effectiveness and postoperative pain (PP) of ultrasonic irrigation (UI) compared to conventional irrigation (CI), through two systematic reviews and meta-analyses of randomized clinical trials for this, two articles were produced, one for postoperative pain and another for antimicrobial evaluation, so the dissertation below will have two chapters. This review was prepared following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses). After preparing the clinical question and the PICO strategy for each study, a literature search was carried out in the main eletronic databases through a search strategy elaborated with MeSH terms and free terms adapted to the databases. Meta-analyses were conducted using the R software with the "META" package, the mean difference (MD) and odds ratios (OR) was the measure effect necessary and the fixed-effect model was applied with a 95% confidence interval (CI). The Cochrane Collaboration Scale was used to assess the risk of bias and the GRADE tool to assess the quality of evidence. The results showed an advantage favoring the ultrasonic irrigation group in both variables of interest (postoperative pain and antimicrobial effectiveness), in postoperative pain, 6 RCTs were included for systematic review and four for meta-analysis. UI resulted in lower PP in 3 of the 5 periods, 6 hours (MD -1.40 [CI -2.38 to -0.42] p = 0.0052), 24 hours (MD -0.73 [CI -1 .07 to -0.39] p = 0.0001), and 48 hours (MD -0.36 [CI -0.59 to -0.13] p = 0.022). However, PP did not show significant differences between groups at 72 hours and 7 days (p>0.05). A low risk of bias was observed for most domains, except the allocation was considered unclear. The certainty of the evidence was classified as moderate (24 hours, 48 hours and 7 days) and low (6 and 72 hours). In the study of antimicrobial effectiveness, 12 RCTs were included for the systematic review and 8 for the meta-analyses where 4 were used for (MD) and 4 for (OR). In both analyses, UI resulted in better antimicrobial effect compared to CI MD -1.42 [-1.60; -1.23] p<0.0001, I2 = 80% and OR 3.86 [1.98; 7.53] p< 0.0001, I2 = 28.7%. A low risk of bias was observed for most domains, except the allocation was considered unclear. The certainty of evidence was considered moderate in the meta-analysis using OR, due to the imprecision findings, and low in the meta-analysis using MD due to the presence of inconsistency and imprecision. Thus, it is possible to conclude that, within the limitations of the present systematic reviews, UI presented favorable results both for postoperative pain and for the increase in antimicrobial effectiveness. However, more robust randomized controlled trials are needed to corroborate these findings.

Keywords: Ultrasonic. Postoperative pain. Root Canal Therapy. Systematic review. Meta-analysis. Disinfection.

SUMÁRIO

Introdução Geral

1. INTRODUÇÃO GERAL

O objetivo principal do tratamento endodôntico é devolver a função do elemento dental, para tal precisamos realizar a modelagem e a limpeza do sistema de canais radiculares (SCR) (Tomson & Simon 2016, Rath et al., 2020). A modelagem ou *"Shaping*" é a instrumentação mecânica do SCR permitindo a remoção da dentina infectada, polpa dentária e conteúdo séptico possibilitando ainda a criação de espaço para que as soluções irrigadoras possam agir (Zehnder 2006, Tomson & Simon 2016). Contudo, nenhum instrumento atual é capaz de "tocar" e limpar todas as paredes do SCR, possibilitando que áreas permaneçam intocadas pelos instrumentos endodônticos (Siqueira Junior et al., 2018). Desta forma, a limpeza ou *"cleaning"* é necessária, utilizando-se de soluções químicas. Essa etapa é crucial no tratamento do canal radicular pois é ela que vai ser capaz de alcançar as áreas onde o instrumento não conseguiu atuar e em combinação com a instrumentação promove uma adequada desinfecção de todo o SCR. Para isso os irrigantes devem ser capazes de se difundir nos túbulos dentinários promovendo seu efeito antimicrobiano (Tomson & Simon 2016, Dioguardi et al., 2018, Siqueira Junior et al., 2018)

O hipoclorito de sódio (NaOCl) é o irrigante mais utilizado na Endodontia, devido sua capacidade antimicrobiana, capacidade de desorganizar biofilmes bacterianos, e na dissolução de matéria orgânica. (Zehnder 2006, Mohammadi 2008). Os micro-organismos podem penetrar em profundidade nos istmos, ramificações, canais laterais e acessórios e túbulos dentinários o que dificulta as ações dos agentes irrigantes (Haapasalo & Orstavik 1987, Hahn & Hanford 2021). Foi mostrado que o NaOCl a 3% possui melhor efeito antimicrobiano em profundidade na dentina quando comparado ao NaOCl 0,5% e utilizando irrigação somente com agulha e seringa dificilmente o NaOCl penetraria essas regiões de forma efetiva (Wong & Cheung 2014). Contudo esta solução é extremamente tóxica para os tecidos periapicais, principalmente em concentrações mais elevadas, podendo causar inflamação e dor pós-operatória (Mostafa et al., 2020).

A técnica de irrigação convencional possui limitações, dentre elas a dificuldade em levar o irrigante de forma eficiente ao terço apical do SCR, isso acontece, devido a profundidade de penetração da agulha e da morfologia de cada canal radicular (Altundasar et al., 2011, İriboz et al., 2015). O irrigante avança apenas 1mm além da ponta da agulha, e caso agulha seja posicionada muito próxima do periapice e a solução injetada com muita pressão, há o risco de forçar o irrigante para a região periapical, podendo causar danos aos tecidos e dor (Boutsioukis et al., 2010, Altundasar et al., 2011, Mostafa et al., 2020). O tipo de agulha utilizado no método convencional pode influenciar na quantidade de extrusão, na capacidade antimicrobiana e ne remoção de detritos. (Boutsioukis et al., 2009, Boutsioukis et al., 2010). Os tipos de agulha podem ser divididos em dois grupos: aberto ou fechado, o aberto são as agulhas cuja solução irrigadora vai ser expelida no seu ápice que é aberto, já a fechada possui o ápice fechado e a saída da solução é na lateral da agulha, diminuindo a chance de extravasamento (Boutsioukis et al., 2009).

Desta forma os métodos de irrigação convencional por agulha são eficazes principalmente nos terços cervical e médio do SCR, entretanto deixam a desejar no terço apical (Tanomaru-Filho et al., 2015). Dessa forma, é importante o clínico conhecer outras técnicas de irrigação a fim de obter melhores resultados, como por exemplo a técnica ultrassônica. Esta técnica tem a capacidade de potencializar a penetrabilidade das soluções irrigadoras promovendo um melhor espalhamento das soluções químicas por toda complexidade anatômica do canal radicular (Van Der Sluis et al., 2007, Macedo et al., 2014). A técnica ultrassônica utiliza um inserto acoplado a um dispositivo de ultrassom, e quando introduzido no canal radicular por meio de ondas ultrassônicas que induzem fenômenos hidrodinâmicos de cavitação, *microstreaming* acústico e efeitos térmicos sob a solução irrigadora, possibilita alcançar áreas onde a seringa e agulha não chegam de maneira efetiva (Van Der Sluis et al., 2007, Robinson et al., 2018), mais especificamente para regiões como istmos, canais laterais e região apical, propiciando assim, maior eficiência na atividade antimicrobiana promovida pelos agentes químicos (Van Der Sluis et al., 2007, Schmidt et al. 2015, Robinson et al,. 2018).

Desta forma, embora estudos *in vitro* pressupõe que o ultrassom como mecanismo de ativação de solução irrigadora melhora sua agitação e espalhamento por meio dos fenômenos hidrodinâmicos, supostamente reduzindo a ocorrência de dor pós-operatória endodôntica, e a sua efetividade antimicrobiana, nos estudos clínicos randomizados estas vantagens ainda não estão claras. Assim somado com a escassez de revisões sistemáticas e um consenso na literatura sobre a temática em questão, o objetivo destas revisões sistemáticas serão: 1: avaliar se o uso da irrigação ultrassônica resulta em menor dor pós operatória em comparação a irrigação convencional em pacientes submetidos ao tratamento endodôntico, e 2: se a irrigação ultrassônica promove melhor efetividade antimicrobiana em comparação com a irrigação convencional com seringa e agulha.

Chapter 1

2. CHAPTER 1 - POSTOPERATIVE PAIN IN ROOT CANAL TREATMENT WITH ULTRASONIC VERSUS CONVENTIONAL IRRIGATION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

2.1 ABSTRACT

Objective: The objective of this systematic review and meta-analysis (SRM) was to answer the question whether the use of ultrasonic irrigation (UI) results in less postoperative pain (PP) compared to conventional irrigation (CI).

Methods: A literature search was performed within the main scientific databases carried out until May 2021. The eligibility criteria were randomized clinical trials (RCTs). Meta-analysis was conducted using R software with the "META" package, the mean difference (MD) measure of effect was calculated and the fixed effect model was applied with a 95% confidence interval (CI). The Cochrane collaboration scale was used to assess risk of bias and the GRADE tool to assess the quality of evidence.

Results: Six RCTs were included for systematic review and four for meta-analysis. UI resulted in less PP in 3 of 5 periods, at 6 hours (MD -1.40 [CI -2.38 to -0.42] p= 0.0052), 24 hours (MD -0.73 [CI -1.07 to -0.39] p= 0.0001), and 48 hours (MD -0.36 [CI -0.59 to -0.13] p=0.022). However, PP showed no significant differences between the groups at 72 hours and 7 days ($p > 0.05$). A low risk of bias was observed for most domains, except allocation that was considered unclear. The certainty of evidence was classified as moderate (24 hours, 48 hours, and 7 days) and low (6 and 72 hours).

Conclusion: Within the limitations of this SRM, UI presented less occurrence of PP than CI. Further randomized clinical trials are needed to corroborate these findings.

Clinical Relevance: UI should be used by clinicians as it reduces postoperative pain in patients undergoing endodontic treatment.

Keywords: Conventional irrigation; Endodontic treatment; Meta-analysis; Postoperative pain; Systematic review; Ultrasonic irrigation.

† Standardization according to Clinical Oral Investigations https://www.springer.com/journal/784/submission-guidelines?IFA

2.2 INTRODUCTION

The main objective of endodontic treatments is the complete disinfection of the root canal system (RCS) [1–3]. The success of this treatment includes the use of several therapeutic processes, such as biomechanical preparation (BP) of the root canal, and the use of irrigating solutions and intracanal medication [3–5].

Due to the anatomical complexity of the RCS, some intraradicular regions are not completely reached by endodontic instruments during the instrumentation process, making the use of chemical solutions a crucial factor for efficient disinfection of root canals [6, 7]. This disinfection is not related only to the antimicrobial activity promoted by irrigating solutions, but also to the ability to lubricate the RCS, facilitating its path through the canal space. Furthermore, the solutions remove debris remaining from RCS preparation and the dissolution of necrotic organic compounds and the smear layer [8, 9].

Despite the considerable effect, the clinical question of the irrigation stage is how far it can act. It is noteworthy that, although well established, conventional irrigation (CI) with syringe and endodontic suction cannula fail in some principles of contemporary endodontics, as they act mostly in the main canal, so that accessory and lateral canals are not benefited by this method, in addition to failing to remove debris [8–10]. Therefore, as the conventional technique is unlikely to adequately eliminate pathogenic microorganisms present there, other irrigation techniques have been proposed to overcome this limitation, among them, ultrasonic irrigation (UI) [8, 9, 11].

Alternative techniques for activating irrigating solutions have been recommended to enhance their penetrability and thus promote better spread of chemical solutions throughout the anatomical complexity of the root canals [12]. The ultrasonic technique uses an insert coupled to an ultrasonic device. When introduced into the root canal by means of ultrasonic waves that induce hydrodynamic phenomena, it generates agitation and/activation of the irrigating solution present there, more specifically to regions such as isthmuses, lateral canals, and the apical region, thus providing greater efficiency in the antimicrobial activity [10, 12, 13]. However, root canal irrigation can also be associated with the extrusion of chemical solutions (eg, sodium hypochlorite/NaOCl) beyond the apex, which is considered undesirable and can cause postoperative pain (PP), swelling, and tissue damage [6, 14]. Postoperative pain in endodontics is an adverse effect for both patients and professionals [15]. This is attributed to psychological, mechanical, chemical, and microbiological factors, being commonly caused by acute inflammation in the periradicular tissue arising from the migration of microorganisms through the apical foramen and extravasation of debris and irrigants [2, 16, 17]. Recent studies have shown that the type of irrigation technique used, as well as the type of irrigating solution, can influence the occurrence of postoperative pain [16, 18]. Pain affects the patient's quality of life, as it may increase the level of general stress in the body, which can negatively affect the body's immune function, increasing the chance of treatment failure [19, 20].

Thus, assuming that the use of the ultrasonic method as an irrigation solution activation mechanism improves its agitation and spread through vibration, supposedly reducing the occurrence of endodontic postoperative pain, and added to the lack of systematic reviews and consensus in the literature on the subject in question, the aim of this systematic review was to answer the clinical question whether the use of ultrasonic irrigation results in less postoperative pain compared to conventional irrigation in patients undergoing endodontic treatment.

2.3 METHODS

Protocol and registry

This review was conducted according to the guidance in the Cochrane Handbook for Systematic Reviews of Interventions [21] and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement www.prisma-statement.org) [22]. The review protocol was registered in the PROSPERO database (http://www. crd.york.ac.uk/PROSPERO) under number CRD42021244013.

Focused question

This systematic review was conducted to answer the following question: “Does ultrasonic irrigation result in less postoperative pain compared to conventional irrigation in patients who have undergone endodontic treatment?”

Search strategy

An extensive literature search was performed in the following databases: PubMed (MEDLINE), Scopus, Web of Science, Embase, Cochrane Library, Clinical Trials. The grey literature was also searched using the System for Information on Grey Literature in Europe (SIGLE) through OpenGrey. The search was carried out until May 13, 2021, with search alerts as a self-updating tool. A specialized librarian guided the entire electronic search strategy, using MeSH terms and free terms appropriately adapted for the databases (see Appendix A). The present systematic review and the search strategy were developed only with articles published in English language and with no publication time restrictions. A manual search was also performed for articles published in the following journals: *Journal of Endodontics, International Endodontic Journal, Australian Endodontic Journal, Iranian Endodontic Journal, European Endodontic Journal, Clinical Oral Investigations, Journal of Dentistry*. Manual screening of the reference lists of all included studies was performed, so that no relevant articles would be missed.

Eligibility criteria

For the systematic review, the studies were required to meet the following inclusion criteria: (a) randomized clinical trials (RCTs) that assessed postoperative pain in conventional root canal treatment using conventional irrigation (needle-manual) versus ultrasonic irrigation; (b) studies with a follow-up of the initial period post-treatment and a maximum of 1 month; (c) patients without complications or systemic diseases; (d) studies with patients without severe pain and/or acute apical abscess; and (e) studies with at least 12 patients per group. Studies not meeting the inclusion criteria were excluded. The PICOS strategy described below was used:
(P)—Population: patients with indication of conventional endodontic treatment;

(I)—Intervention: ultrasonic irrigation;

(C)—Comparison: syringe irrigation (conventional irrigation)

(O)—Outcome: postoperative pain;

(S)—Study design: randomized controlled trials;

No comparisons or study designs were used in the search strategy to maximize the results.

Study selection

In the first stage, all references recorded through all databases were imported into reference management online (EndNote Web; Thomson Reuters Inc., Philadelphia, PA, USA). After the elimination of duplicate studies, two reviewers (L.O.C. and G.P.N.) independently assessed all titles and abstracts. In cases of titles and abstracts with insufficient information, full texts were obtained. Any disagreements were resolved by discussion, and a third author (G.S.A.) was consulted. Agreement between the two reviewers regarding title and abstract selection was evaluated by the Cohen's kappa coefficient (κ). Subsequently, full texts of the remaining articles were analyzed, and those meeting the inclusion criteria were included.

Data extraction process

Details associated with the study were acquired through customized extraction forms, in which the following parameters were recorded: study details (authors, year of publication, and location), intervention groups (n), sex and age, systemic condition/disease, tooth root and tooth type, clinical condition/diagnosis of pre-operative status, pain evaluation scale, time of pain evaluation, outcome variable, pre-operative pain evaluation, number of patients requiring analgesics, results, and conclusions. If necessary, the authors were contacted through email to request additional information.

Risk of bias in the included studies

Quality was assessed according to Cochrane Collaboration [23] for randomized clinical trials. To assess the risk of bias, we considered random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Studies presented a low risk of bias if the key domains (random sequence generation, allocation concealment, blinding of participants and personnel, and other source of bias) were judged adequate. Contrarily, when a study was judged as unclear in the key domains, we tried to contact the authors to obtain more information to allow a definitive judgement of either “yes” or “no”. If the final judgement remained unclear for one or more key domains, the studies were considered to present an unclear risk of bias [23].

Blinding of participants and personnel and blinding of outcome were considered low risk since it was applicable only for the patient. Ultrasonic irrigation was performed through an insert attached to an ultrasound device, and using local anesthesia during the treatment. Therefore, blinding the endodontists was not possible, due to the use of either manual syringes or ultrasonic irrigation. The patients recorded their pain experience on a visual analogue scale.

Summary measurements

The quantitative analyses were performed using R software with “Meta” package, version 3.6.3 to evaluate the postoperative pain in ultrasonic irrigation versus conventional irrigation in the root canal treatment. Five meta-analyses were performed according to the reported period of evaluation (6, 24, 48, 72 hours, and 7 days). The mean difference (MD) was the effect measure required and the fixed effect model was applied with 95% confidence interval (CI). Heterogeneity was tested using the I^2 index, and an I^2 index ≥ 50% was considered substantial or high. To access the publication bias, the funnel plot (n=2) and trim-and-fill method (n ≥ 3) were used. In addition, the trim-and-fill method was also used to evaluate bias in the meta-analysis.

Certainty of the evidence by Grading of recommendations, assessment, development and evaluation

The quality of the evidence (certainty in the estimates of effect) was evaluated through the application of the Grading of Recommendations, Assessments, Development, and Evaluations approach (GRADE) criteria using the software GRADEpro GDT. Randomized clinical studies were initially considered as the highest level of evidence, following which a decrease in the level of evidence to moderate, low, or very low was attributed to the presence of serious or very serious issues associated with a risk of bias, inconsistency, indirectness, imprecision, and publication bias [24]. Additionally, the quality of the evidence could be upgraded if the magnitude of effect is either large or very large, or if all plausible confounding factors reduced the effect or indicated the presence of a spurious effect. Therefore, the quality of the evidence can vary from very low to high. The evaluations were carried out by two researchers independently (G.P.N. and L.O.C.) and then compared.

2.4 RESULTS

Literature search

The database search retrieved 814 studies: 376 from PubMed/MEDLINE, 205 from Cochrane Library, 168 from Scopus, 49 from Web of Science, 15 from Embase, and 1 from manual searching (Fig. 1). After removal of duplicates, 604 studies remained for verification of titles and abstracts. This step resulted in 15 studies for full reading, of which nine studies were excluded because they did not meet the eligibility criteria. Thus, six randomized clinical trials were included in the review [18, 25–29]. The kappa score for articles included in all databases showed an acceptable level of inter-examiner agreement (k = 0.92).

Description and characteristics of the included studies

The characteristics of the 6 included studies are listed in Table 1. A total of 554 patients with a mean age of ≅ 41.6 years were evaluated. The number of patients in each group (control and intervention) was 277. Two studies were conducted in Turkey, [18, 28], 2 in India, [27, 29], and 2 in China [25, 26]. Five studies assessed pain using the Visual Analog Scale (VAS) to evaluate pain intensity (subjective assessment) [18, 25, 27–29], and three studies analyzed the pain outcome using a parameter established for the incidence of pain [25–27]. Regarding the follow-up, the evaluations ranged from 6 hours after the procedure to up to 7 days after endodontic treatment.

All six studies evaluated only healthy patients [18, 25–29]. Regarding type of tooth, two studies analyzed inferior molars [18, 27], one study analyzed inferior premolars [28], two studies analyzed uniradicular teeth [26, 29], and one study analyzed both root morphologies [25]. The teeth diagnoses were apical periodontitis [25–27], symptomatic irreversible pulpitis [18, 28], teeth with irreversible pulpitis, and teeth with pulp necrosis [29]. All studies reported the concentration of the irrigant solutions used in the trials. NaOCl concentrations of 2.5% [25, 26, 29], 3% [18, 28], and 5.25% were tested [27].

In general, the highest levels of pain were found in the first 24 hours after endodontic treatment, with decreases in PP over time. Three studies evaluated pain incidence [25–27], among which two studies [25, 27] suggested a higher rate of postoperative pain incidence in the endodontic treatment performed using the conventional irrigation/control group. In relation to PP level, three studies showed that ultrasonic agitation resulted in less PP than syringe irrigation with a needle [25, 27, 29] and two studies concluded that PP level was similar between evaluated groups [18, 28]. Analgesic consumption was a condition evaluated in 4 of the 6 studies [18, 27–29], among which two studies [27, 28] suggested higher use of drugs in the control group, one study in the ultrasonic group [18], and the other study had no medication intake [29].

Risk of bias in the included studies

According to the Cochrane scale, the RCTs demonstrated a “low risk of bias” for generating a random sequence (selection bias), except for one study [25] which presented an “unclear risk of bias”. The main factors contributing to the “unclear risk of bias” were the lack of clarity/quality in the randomization processes (allocation concealment) [18, 25, 26] and the lack of information on the participant and evaluator blinding (performance bias) [26]. In reporting bias, one study [26] was classified as not reporting all pre-specified primary outcomes and follow-up periods. All studies were classified as “low risk of bias” for blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and other bias (Fig. 2).

Meta-analysis and quantitative assessment of bias

Four studies were included in this analysis [18, 27–29]. The remaining studies, in addition to data on the incidence pain, did not contain sufficient data for quantitative analysis, even after contact attempts, and therefore were not included in the analysis.

Quantitative pooling from 2 (from 6 hours follow-up) [18, 29] and 4 (24 and 48 hours follow-up) [18, 27–29] studies showed that the use of ultrasonic agitation reduces PP compared with conventional irrigation in both periods – 6 hours: MD -1.40 [-2.38, -0.42] $p = 0.0052$, $I^2 = 0\%$ (Fig. 3A); the funnel plot did not find publication bias (Fig. 3B); 24 hours: MD -0.73 [-1.07, -0.39] $p < 0.0001$, $I^2 = 64\%$ (Fig. 3C); and publication and meta-analysis bias were not observed with the trim-and-fill method (Fig. 3D); 48 hours: MD -0.36 [-0.59, -0.13] $p = 0.022$, $I^2 = 76\%$ (Fig. 3E). Publication and meta-analysis bias were observed with the trim-and-fill method (Fig. 3F).

No statistically significant results were found for PP between the groups in 72 hours and 7 days. Two studies [18, 27] evaluated 72 hours: MD -0.39 [-2.89, -2.10] $p = 0.75$, $I^2 = 0\%$ (Fig. 4A); the funnel plot did not find publication bias (Fig. 4B); the analysis of studies [18, 28] that evaluated PP in 7 days follow-up showed no significant difference between ultrasonic and conventional irrigation: MD 0.00 [-0.09, 0.09] $p =1.0000$, $I^2 = 0\%$ (Fig. 4C); and publication and meta-analysis bias were not observed with the funnel plot (Fig. 4D).

Level of Evidence

The GRADE approach was used in all meta-analyses and the certainty of the evidence was moderate (24 hours, 48 hours, and 7 days periods) and low (6 and 72 hours periods), due to findings of inconsistency, and inconsistency and imprecision, respectively. Explanations for each group are included in Table 2.

2.5 DISCUSSION

The present study sought to answer the focused clinical question: "Does ultrasonic irrigation result in less postoperative pain compared to conventional irrigation in patients undergoing endodontic treatment?". Only randomized controlled trials were selected. The meta-analyses performed showed that endodontic irrigation used with the ultrasonic device had favorable results in reducing pain in the postoperative periods (6, 24, and 48 hours) when compared to the conventional technique using a syringe and needle. The probable explanations for the reduction in PP with the use of UI may be related to its physical action (movement towards the cervical) [12, 30, 31], lower extrusion of the irrigating solution [27, 32], greater debris removal [31, 32], and better tissue dissolution capacity due to its performance in complex anatomical regions unattainable by conventional irrigation [12], thus enhancing its antimicrobial effect [33, 34].

Extrusion of debris and irrigating agent occurs when the solution pressure in the apical foramen exceeds the periapical area counter pressure [35], which can induce postoperative pain and periradicular tissue damage [36]. It is possible the technique using the ultrasonic device can modulate the amount of extrusion of debris and irrigating solution, since in addition to the physico-chemical effect reported above, the tip activation in continuous ultrasonic irrigation is placed at no more than 75% of the working length [27]. Unlike conventional irrigation, the irrigating solution advances on average only 1mm beyond the tip of the needle, so that to obtain an adequate irrigating action, the needle should be positioned as close as possible to the real length of the tooth, thus there is a greater chance of extravasation of solutions via the foramen [28, 36].

Furthermore, agitation of the irrigating solution by the ultrasonic device promotes better dissolution of the smear layer, pulp remains, and dentin debris, in addition to improving its disinfection capacity [33]. UI also generates high shear stress in the apical third, resulting in reduced bacterial biofilm adhesion compared to syringe irrigation [37], which has reduced activity in the apical region [12, 38].

Regarding the occurrence of postoperative pain, it is noteworthy that PP levels are frequently reported in the initial periods after the endodontic treatment, up to 48 hours, which is considered a critical period for a painful sensation [15, 39]. Subsequent periods decrease PP, as observed in the studies analyzed in this systematic review [18, 27, 28]. Thus, these findings justify the results of the meta-analysis for the periods after 48 hours of follow-up, which showed that the PP indices were similar between the groups at 72 hours and 7 days of evaluation.

It is important to mention that preoperative pain has been established as the main determinant (prognostic factor) of postoperative pain or relapse [15, 40]. Two of the studies included [18, 28], did not report any statistical difference regarding the level of PP between the CI and UI groups. However, these studies evaluated teeth with irreversible and symptomatic pulpitis prior to the procedure. Thus, patients with higher preoperative pain scores are more likely to experience of PP [41]. This effect may be caused by the presence of inflamed pulp tissue that exacerbates pain after the procedure, which may result in a similar outcome between interventions [2], and is thus considered an important confounding factor among studies. In addition to this, studies that isolated this variable by evaluating only asymptomatic teeth [25–27] observed a lower incidence and level of PP for endodontic treatment performed with ultrasonic irrigation. Regarding the irrigating agent used, all eligible studies analyzed NaOCl. It is important to report that there is a significant increase in the dissolution capacity of organic material by NaOCl when it is agitated by the ultrasonic device [42]. In addition, the rise in temperature caused by this device is also mentioned [43–45] which may be a viable explanation for its improved performance. Furthermore, when NaOCl is used at a higher concentration, its effectiveness appears to increase [46, 47]. In the present systematic review, this point was verified in the study by Middha et al., (2016) [27] who used a concentration of 5.25% NaOCl, and noted less postoperative pain for the UI group. It is speculated that in endodontic interventions using NaOCl at higher concentrations, the UI technique would reduce the undesirable effects related to the extravasation of this irrigating solution when compared to CI [38, 48].

All studies included in this review evaluated only healthy patients, thus there were no systemic factors related to the general health of patients that could impact the outcome of postoperative pain. Furthermore, the studies did not include patients who used any type of pre-operative drug, such as analgesics, anti-inflammatories, or antibiotics. However, postoperative analgesic medication consumption was higher for patients in the CI control group (n = 17) than in the UI group (n = 13).

Several studies report the relationship of different variables that can influence pain related to postoperative endodontics [39, 40, 49]. However, information about postoperative pain after using an ultrasonic versus conventional system is limited. In our study, the use of an ultrasonic irrigation system resulted in a lower level of postoperative pain compared to irrigation with a conventional syringe. This difference demonstrates the importance of how postoperative pain is measured and assessed. It is very important to assess pain, however there are difficulties in its measurement, since it is multifactorial, subjective in nature, and modulated by sensory, cognitive, emotional, and motivational responses, past experiences, traumas, stress, and anxiety [39, 40, 49]. Furthermore, factors related to the characteristics or conditions of the teeth should be taken into account, such as factors that affect their reliability and validity [49]. The methods of reporting the patient's pain must be clear enough to be understood by the patients and easily interpreted by the evaluators. The scale (VAS) is a validated instrument and within the available assessments this scale proved to be reliable [49].

Therefore, the VAS was used as the outcome variable to perform the meta-analyses in this review. Regarding the quality of the studies reviewed, in general, the studies presented a low risk of bias, which may indicate their high methodological quality. However, three studies showed an obscure (unclear) risk of bias in allocation concealment (selection bias) [18, 25, 26].

Regarding the certainty of evidence, the GRADE approach showed moderate and low evidence for the analyses by evaluation period (24 hours, 48 hours, and 7 days) and (6 hours and 3 days), respectively. As this systematic review was designed only with RCT studies, they start with a grading of high quality of evidence, however some domains such as risk of bias, heterogeneity, inconsistency, and imprecision are evaluated to establish the quality of evidence. Thus, in the aforementioned periods there were failures for imprecision and/or inconsistency, reducing the level of starting evidence.

This systematic review highlights methodological differences and variability in studies conducted in the literature to verify the effect of the ultrasonic irrigation system and postoperative pain resulting from root canal treatment. Thus, the results of this review must be analyzed with caution. The findings also reinforce the need to conduct new standardized clinical trials regarding the following variables: preoperative particularities, factors inherent to the patient (age and sex), the condition of the dental element (morphology, pulp status, periapical diagnosis, and presence of previous symptoms), and factors related to the trans-operative period (such as the irrigating agent used, concentration, volume, type of technique used). These facts can be considered a limitation and should be taken into account when analyzing the results. In addition, it is notable to report the reasons that made it impossible to perform meta-analyses with all eligible studies: the discrepancy between the periods of analysis of the PP in the included studies, as well as the absence of available data, as even after successive contacts with the authors to clarify these variables, we received no responses.

Thus, controlling and minimizing these conditions are crucial factors to reduce data heterogeneity, the risk of bias, and, consequently, a higher level of evidence of the findings. In addition, endodontic treatment involves a series of complex processes and each step has the potential to trigger pain. More robust randomized clinical trials are needed with direct comparisons between the two therapies, in order to present standardization and isolation of the aforementioned variables.

2.6 CONCLUSION

Within the limitations of this study, the evidence suggests that ultrasonic irrigation of root canals has a lower incidence of postoperative pain than conventional needle irrigation. Due to the low number of studies and heterogeneity of data, further randomized clinical trials are recommended to provide better understanding and support of the findings obtained in this review.

ACKNOWLEDGEMENTS

The authors thank the librarian Ana Claúdia Martins Grieger Manzatti for the instructions regarding the search strategy of this review and the researchers.

AUTHOR CONTRIBUTIONS:

All authors contributed to the study conception and design. Data collection and analysis were performed by Lucas Orbolato Chalub, Gabriel Pereira Nunes, Túlio Morandin Ferrisse, Henrico Badaoui Strazzi Sahyon and Paulo Henrique dos Santos. The first draft of the manuscript was written by Lucas Orbolato Chalub and Gabriel Pereira Nunes. The final draft was written and revised by Lucas Orbolato Chalub, Gabriel Pereira Nunes, Túlio Morandin Ferrisse, Gustavo Sivieri Araujo (systematic review methods), João Eduardo Gomes-Filho, Luciano Tavares Angelo Cintra and Gustavo Sivieri Araujo (endodontics), and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

COMPLIANCE WITH ETHICAL STANDARDS:

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

FUNDING

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the Authors.

INFORMED CONSENT

For this type of study, formal consent is not required.

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48. Tasdemir T, Er K, Celik D, Yildirim T (2008) Effect of Passive Ultrasonic Irrigation on Apical Extrusion of Irrigating Solution. Eur J Dent 2:198

49. Alí A, Olivieri, J. G., Duran-Sindreu, F., Abella, F., Roig, M., & García-Font, M (2016) Influence of preoperative pain intensity on postoperative pain after root canal treatment:

A prospective clinical study. J Dent 45:39–42. https://doi.org/10.1016/J.JDENT.2015.12.002

Table Legends

Table 1. General data on the selected studies.

Table 2. Evidence profile: Postoperative pain in endodontic treatment in conventional irrigation vs. ultrasonic irrigation.

Figure Legends

Figure 1: PRISMA Flow chart - Flow diagram showing the entire search process.

Figure 2: Summary of the risk of bias assessment—Cochrane scale.

Figure 3: Meta-analysis for the periods of 6h, 24h and 48h. A: Meta-analysis of 6h. B: Analysis of publication bias of 6h (Funnel plot); C: Meta-analysis of 24h; D: Analysis of publication bias and meta-analysis of 24h (trim-and-fill); E: Meta-analysis of 48h; F: Analysis of publication bias and meta-analysis of 48h (trim-and-fill)

Figure 4: Meta-analysis for the periods of 72h and 7 days. A: Meta-analysis of 72h; B: Analysis of publication bias of 72h (Funnel plot); C: Meta-analysis of 7 days; D: Analysis of publication bias;

Table 1. General data on the selected studies.

Author/ year (Country)	G1- Control group G2 – Intervention group (N patients)	Sex (M/F) and Age (y)	Systemic Condition /Disease	Tooth root and Tooth type	Clinical condition/ Diagnosis Pre-op status	Final irrigating agent and concentration/ amount final irrigation	Pain Assessments	Pain evaluation periods	Medication Use (n patients)	Outcome: Postoperative pain [Mean ± SD] or percentage	Conclusion
Gündoğar et al., 2020 (Turkey)	G1: 30 G2: 30	G1: 14/16 Age: 41 G2: 15/15 Age: 39	Healthy	Uni mandibular premolar teeth	Symptomatic / Irreversible pulpitis	3% NaOCL	Visual analogue scale (VAS)	8, 24, 48 h and 7 days	G1: 4 G2: 3	G1: Preop. pain: 6.63 ± 0.49 8h: 3.60 ± 1.90 24h: 1.80 ± 1.03 48h: 0.23 ± 0.63 7days: 0.03 ± 0.18 G2: Preop. Pain: 6.87 ± 0.3 8h: 3.77 ± 1.22 24h: 1.40 ± 0.86 48h: 0.20 ± 0.61 7days: 0.03 ± 0.18	Postoperative pain level was similar between the groups
Palanisamy et al., 2020 (India)	G1: 40 G2: 40	Age: 18 to 55	Healthy	Single rooted teeth	Symptomatic / irreversible pulpitis and pulpal necrosis	2.5% NaOCL	Visual analogue scale (VAS)	6, 12, 24 and 48 h	G1: 0 G2: 0	G1: Preop pain: 5.58 ± 2.448 6h: 3.85 ± 2.486 12h: 2.53 ± 1.961 24h: 1.38 ± 1.409 48h: 0.78 ± 1.050 G2 Preop pain:5.20 ± 2.643 6h: 2.40 ± 1.997 12h: 0.93 ± 1.366 24h: 0.35 ± 0.7 48h: 0.08 ± 0.267	Ultrasonic resulted in significant reduction in post-operative pain when compared to needle irrigation.
Topçuoglu et al., 2018 (Turkey)	G1: 42 G2: 42	G1:20/22 Age 40 G2:19/23 Age: 38	Healthy	Multi Mandibular molar teeth	Diagnosis: symptomatic irreversible pulpitis	3% NaOCL	Visual Analogue scale (VAS)	6,24,48,72 h and 7days	G1: 2 G2: 3	G1: Preop. pain: 61.7 ± 16.6 6 h: 32.4 ± 19.3 24 h: 25.2 ± 16.7 48 h: 11.2 ± 12.1 72h: 4.3 ± 7.0 7days: 2.6 ± 5.8	Postoperative pain level was similar between the groups

										G2: Preop. pain: 60.1 ± 18.5 6 h: 35.0 ± 21.3 24 h: 26.2 ± 20.3 48 h: 10.1 ± 12.1 72h: 5.0 ± 9.9 7days: 2.6 ± 5.8	
Middha, et al., 2016 (India)	G1: 35 G2: 35	G1: 17/18 Age 27.4 G2: 19/16 Age 27	Healthy	Mandibular molars	Non-vital pulps/ apical periodontitis	5.25% NaOCL	Visual analogue scale (VAS) AND Incidence of pain 24h	1,2,3,4,5,6 and 7 days	G1:11 G2:7	G1: Preoperative 43.97 ± 23.2 1d 13.40 ± 15.5 2d 8.34 ± 11.2 3d 4.11 ± 8.5 4d 2.60 ± 6.4 5d 1.65 ± 4.7 6d 1.45 ± 4.9 7d 1.02 ± 4.3 G2: Preoperative 41.42 ± 25.4 1d 5.82 ± 9.4 2d 3.42 ± 6.6 3d 2.77 ± 5.8 4d 1.82 ± 5.2 5d 0.42 ± 2.5 6d 0.00 ± 0.0 7d 0.00 ± 0.0 Pain Incidence: 24h G1: 18/35 (51.4%) G2: 11/35 (31.4%)	A significant difference in postoperative pain scores was observed on the first day between the groups. However, the difference was small and may not reach the threshold for clinical significance
Chen et al., 2016 (China)	G1: 30 G2: 30	G1: 18/12 Age 37.97 G2: 16/14 Age: 42.07	Healthy	Uni Anterior teeth/premolars G1: 17/13 G2: 16/14	Diagnosis: periapical periodontitis	2.5% NaOCL	Incidence of Pain	----	N.R.	Pain Incidence G1= 1/30 (3.3%) G2= 4/30 (13.3%)	The incidence of pain in both groups was similar

Tang et al., 2015 (China)	G1:100 G2.1: 100 G2.2: 100	G1 52/48 G2.1 51/49 G2.2 50/50 61.3 mean age	Healthy	G1 Ant:35 Premol:30 Molar:53 G2.1 / G2.2 Ant: 39 / 40 Premol: 22 / 27 Molar: 59 / 56	Chronic periapical periodontitis	G1 and G2.1: 2.5% NaOCL G2.2: Silver Ion antibacterial solution	Visual analogue scale (VAS) And Clinical Evaluation	24h	N.R.	**Mild pain** G1: 26 G2.1: 15 G2.2: 14 **Moderate pain** G1: 17 G2.1: 4 G2.2: 4 **Severe pain** G1: 4 G2.1: 2 G2.2: 1 **Pain incidence**: 24h G1: 47/100 (39.83%) G2.1: 21/100 (17.5%) G2.2: 19/100 (15.58%)	Ultrasonic Agitation resulted in less Postoperative Pain than syringe irrigation with needle

Table 2. Evidence profile: Postoperative pain in endodontic treatment in conventional irrigation vs. ultrasonic irrigation.

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Conventional]	[Ultrasonic]	Absolute (95% CI)	
Pain (6h)										
2	randomised trials	not serious	serious	not serious	serious	none	82	82	**MD 1.40 SD higher (2.38 lower to 0.42 lower)**	⊕⊕◯◯ LOW
Pain (24h)										
4	randomised trials	not serious	serious	not serious	not serious	none	147	147	**MD 0.73 SD higher (1.07 lower to 0.39 lower)**	⊕⊕⊕◯ MODERATE
Pain (48h)										
4	randomised trials	not serious	serious	not serious	not serious	none	147	147	**MD 0.36 SD lower (0.59 lower to 0.13 lower)**)	⊕⊕⊕◯ MODERATE
Pain (72h)										
2	randomised trials	not serious	serious	not serious	serious	none	77	77	**MD 0.39 SD higher (2.89 lower to 2.10 lower)**	⊕⊕◯◯ LOW
Pain (7 days)										
2	randomised trials	not serious	serious	not serious	not serious	none	72	72	**MD 0.00 SD lower (0.09 lower to 0.09 lower)**	⊕⊕⊕◯ MODERATE

CI: Confidence interval; SD: Standard Deviation; **MD:** mean difference

Figure 1. PRISMA Flow chart - Flow diagram showing the entire search process.

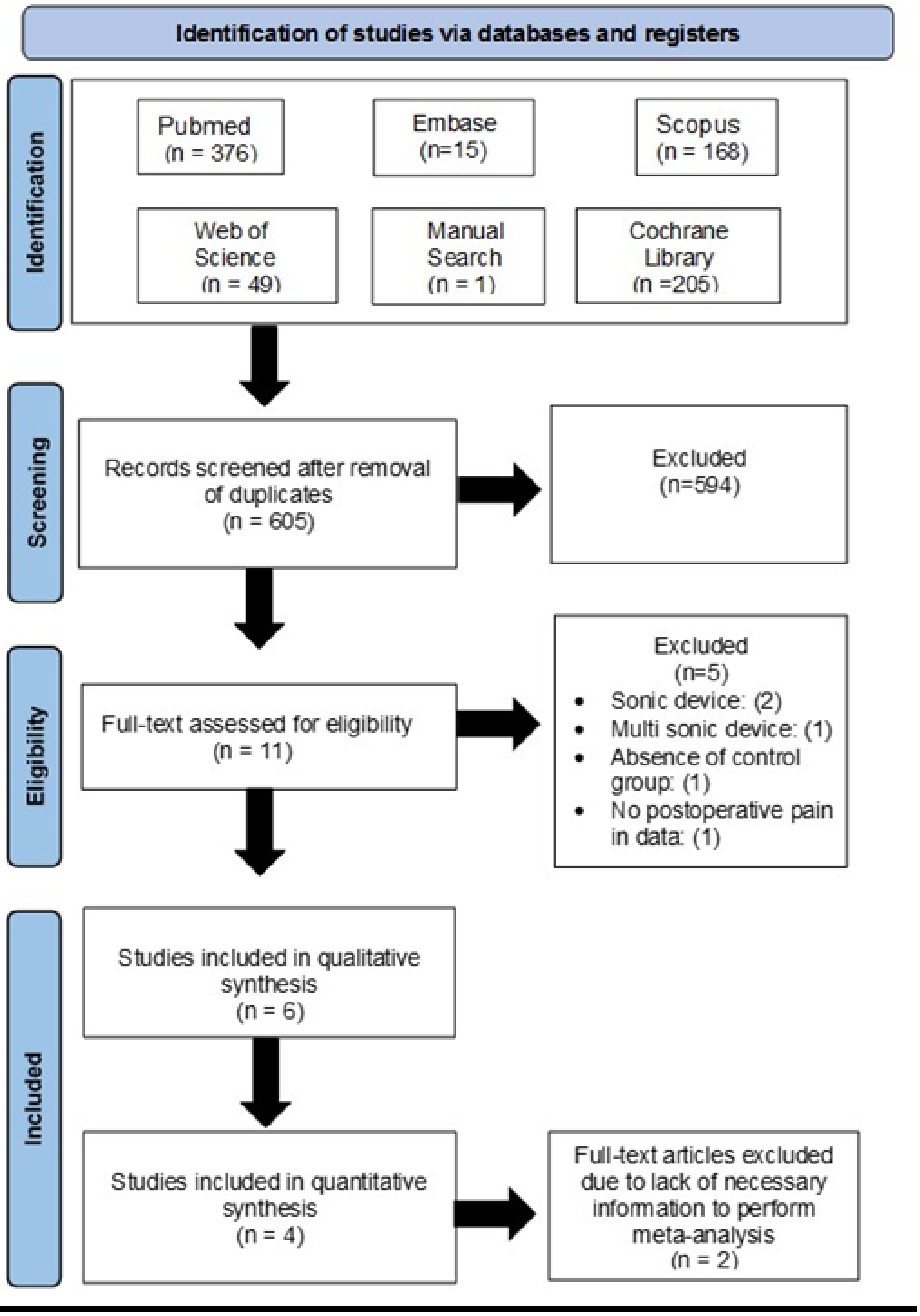


Figure 2. Summary of the risk of bias assessment—Cochrane scale.

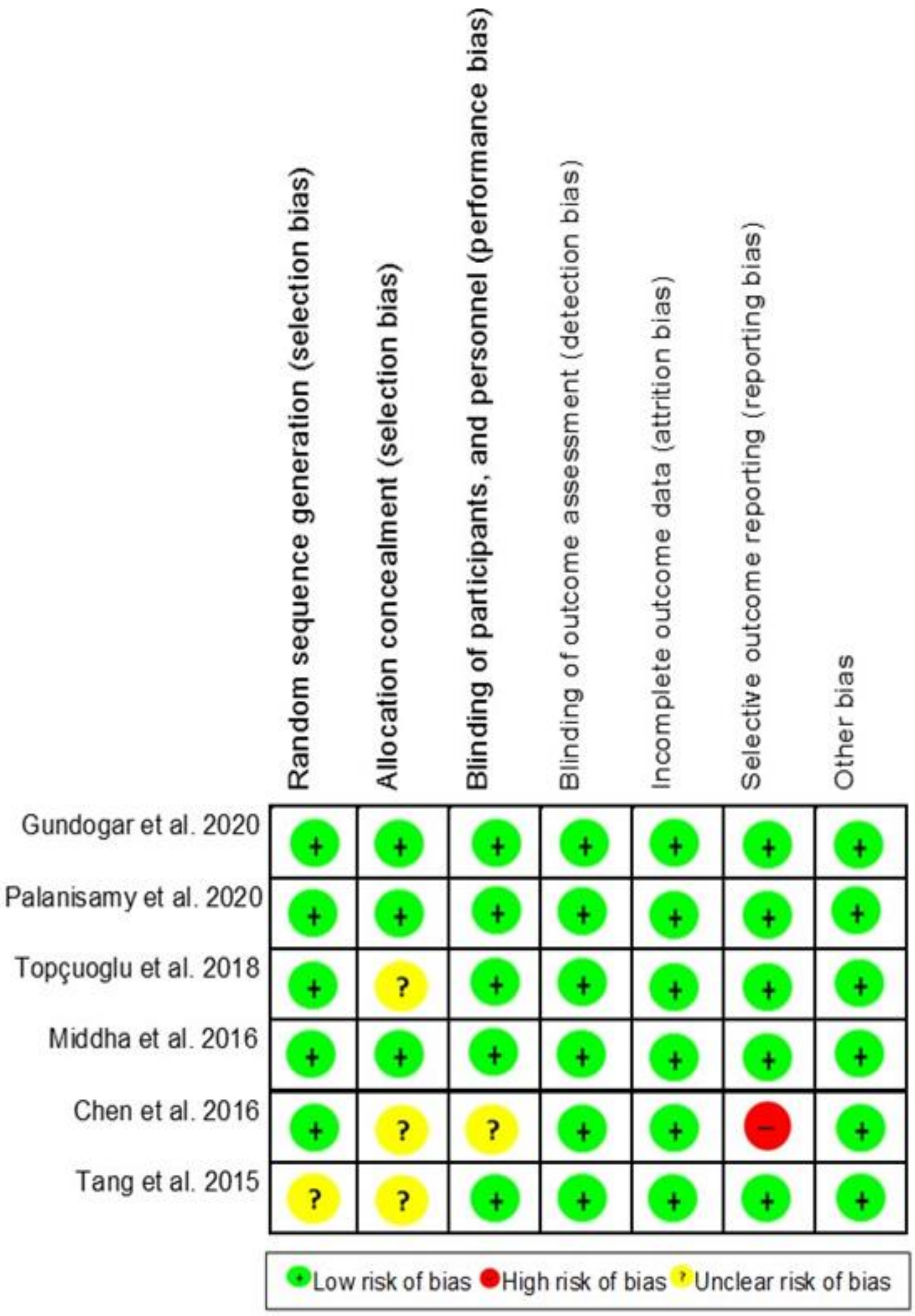
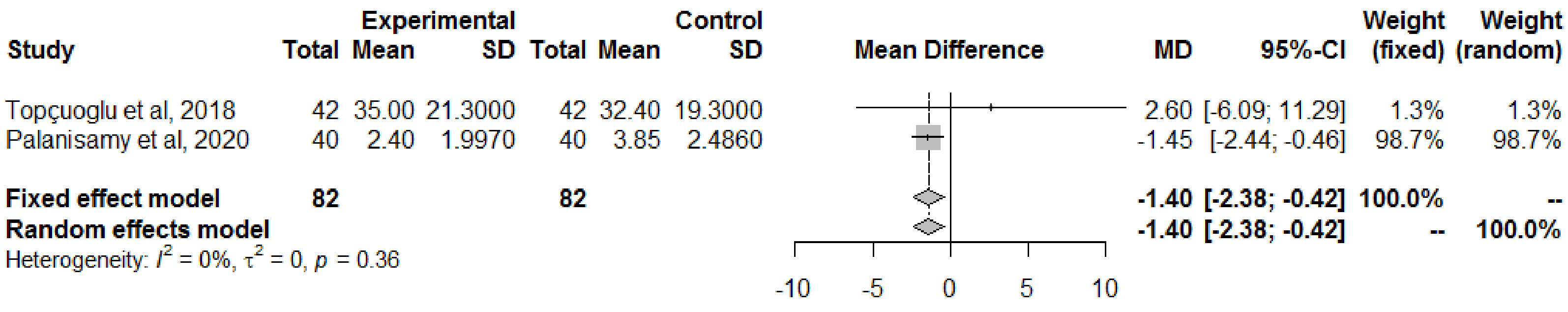
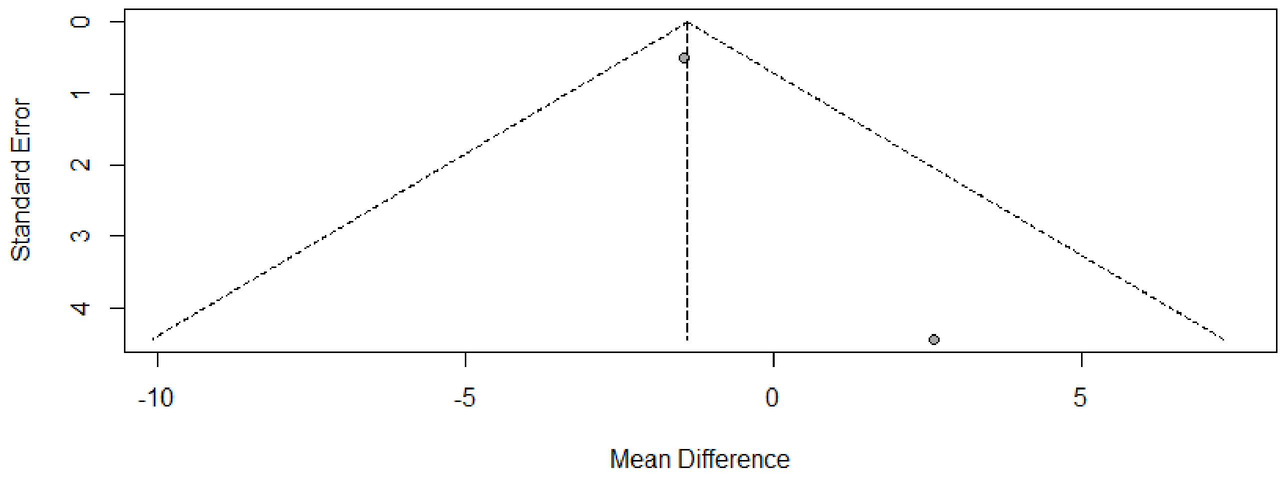


Figure 3. Meta-analysis for the periods of 6h, 24h and 48h. A: Meta-analysis of 6h. B: Analysis of publication bias of 6h (Funnel plot); C: Meta-analysis of 24h; D: Analysis of publication bias and meta-analysis of 24h

A



B

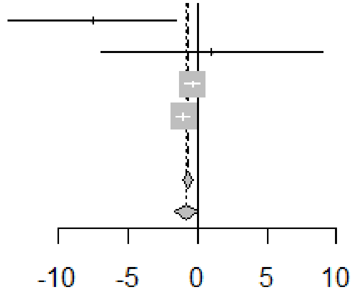


C

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight (fixed)	Weight (random)
Middha, et al. 2016	35	5.82	9.4000	35	13.40	15.5000	-7.58	[-13.59; -1.57]	0.3%	1.9%
Topçuoglu et al, 2018	42	26.20	20.3000	42	25.20	16.7000	1.00	[-6.95; 8.95]	0.2%	1.1%
Gündoğar et al, 2020	30	1.40	0.8600	30	1.80	1.0300	-0.40	[-0.88; 0.08]	50.5%	48.6%
Palanisamy et al, 2020	40	0.35	0.7000	40	1.38	1.4090	-1.03	[-1.52; -0.54]	49.0%	48.4%
Fixed effect model	**147**			**147**			**-0.73**	**[-1.07; -0.39]**	**100.0%**	--
Random effects model							**-0.83**	**[-1.68; 0.02]**	--	**100.0%**

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.3271$, $p = 0.04$

Mean Difference

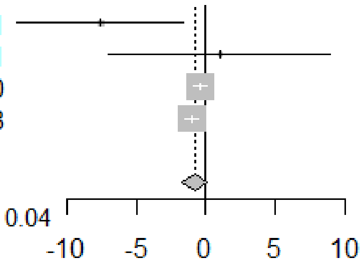


D

Study	TE	seTE	MD	95%-CI	Weight
Middha, et al. 2016	-7.58	3.0641	-7.58	[-13.59; -1.57]	1.9%
Topçuoglu et al, 2018	1.00	4.0561	1.00	[-6.95; 8.95]	1.1%
Gündoğar et al, 2020	-0.40	0.2450	-0.40	[-0.88; 0.08]	48.6%
Palanisamy et al, 2020	-1.03	0.2488	-1.03	[-1.52; -0.54]	48.4%
Random effects model			**-0.83**	**[-1.68; 0.02]**	**100.0%**

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.3271$, $p = 0.04$

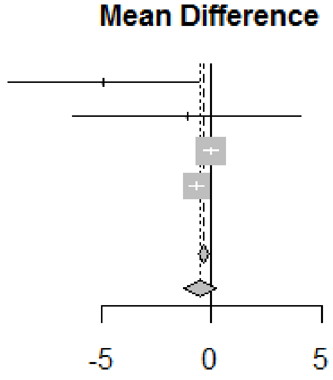
Mean Difference



E

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight (fixed)	Weight (random)
Middha, et al. 2016	35	3.42	6.6000	35	8.34	11.2000	-4.92	[-9.23; -0.61]	0.3%	2.7%
Topçuoglu et al, 2018	42	10.10	12.1000	42	11.20	12.1000	-1.10	[-6.28; 4.08]	0.2%	1.9%
Gündoğar et al, 2020	30	0.20	0.6100	30	0.23	0.6300	-0.03	[-0.34; 0.28]	53.1%	48.0%
Palanisamy et al, 2020	40	0.08	0.2670	40	0.78	1.0500	-0.70	[-1.04; -0.36]	46.4%	47.4%
Fixed effect model	**147**			**147**			**-0.36**	**[-0.59; -0.13]**	**100.0%**	**--**
Random effects model							**-0.50**	**[-1.22; 0.23]**	**--**	**100.0%**

Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.2594$, $p < 0.01$



F

Study	TE	seTE	MD	95%-CI	Weight
Middha, et al. 2016	-4.92	2.1974	-4.92	[-9.23; -0.61]	3.0%
Topçuoglu et al, 2018	-1.10	2.6404	-1.10	[-6.28; 4.08]	2.1%
Gündoğar et al, 2020	-0.03	0.1601	-0.03	[-0.34; 0.28]	45.1%
Palanisamy et al, 2020	-0.70	0.1713	-0.70	[-1.04; -0.36]	44.6%
Filled: Topçuoglu et al, 2018	0.42	2.6404	0.42	[-4.76; 5.59]	2.1%
Filled: Middha, et al. 2016	4.24	2.1974	4.24	[-0.07; 8.54]	3.0%
Random effects model			**-0.36**	**[-1.14; 0.41]**	**100.0%**

Heterogeneity: $I^2 = 71\%$, $\tau^2 = 0.3209$, $p < 0.01$

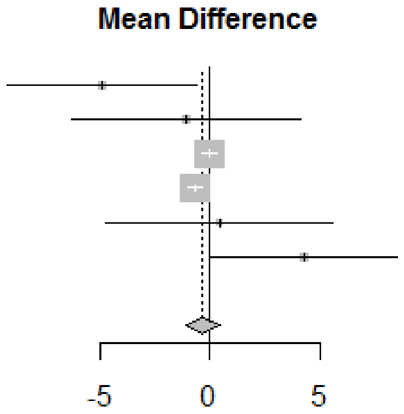
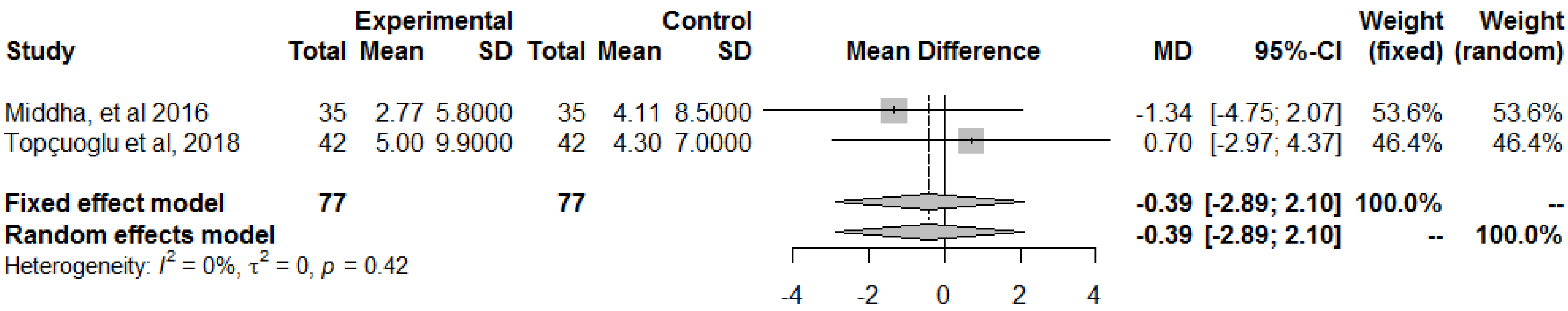
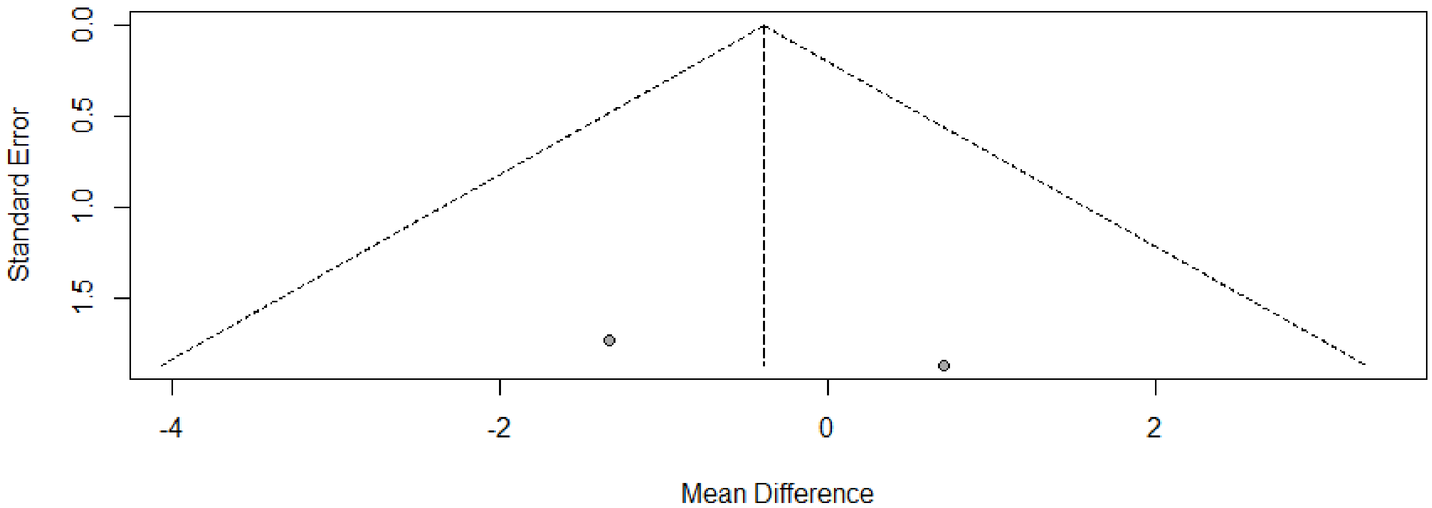


Figure 4. Meta-analysis for the periods of 72h and 7 days. A: Meta-analysis of 72h; B: Analysis of publication bias of 72h (Funnel plot); C: Meta-analysis of 7 days; D: Analysis of publication bias

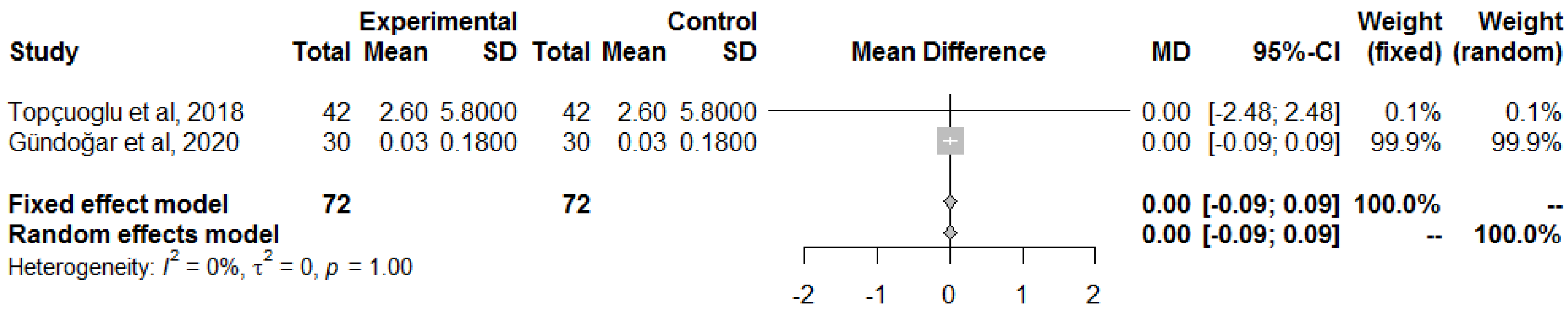
A



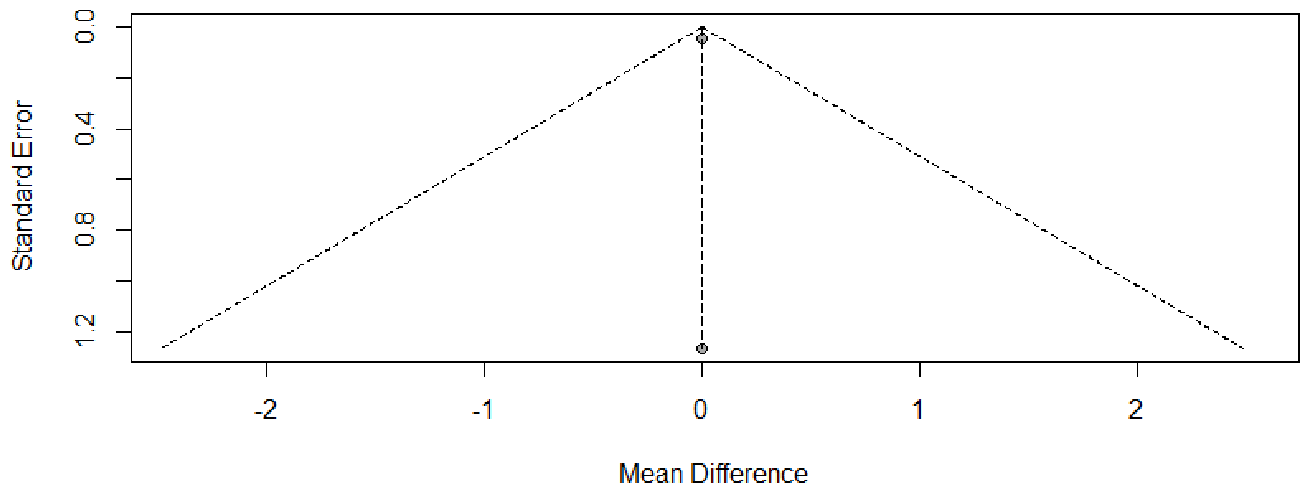
B



C


Experimental
Control
Study
Total
Mean
SD
Total
Mean
SD
Mean Difference
MD
95%-CI
Weight (fixed)
Weight (random)
Topçuoglu et al, 2018 42 2.60 5.8000 42 2.60 5.8000 0.00 [-2.48; 2.48] 0.1% 0.1%
Gündoğar et al, 2020 30 0.03 0.1800 30 0.03 0.1800 0.00 [-0.09; 0.09] 99.9% 99.9%
Fixed effect model 72 72 0.00 [-0.09; 0.09] 100.0% --
Random effects model 0.00 [-0.09; 0.09] -- 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00
-2
-1
0
1
2

D


Standard Error
0.0
0.4
0.8
1.2
-2
-1
0
1
2
Mean Difference

Chapter 2

3. CHAPTER 2 - ANTIMICROBIAL EFFECTIVENESS OF ULTRASONIC IRRIGATION IN ROOT CANAL TREATMENT: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS AND META-ANALYSIS

3.1 ABSTRACT

Introduction: New devices and techniques are studied to promote satisfactory spreading and disinfection of irrigating solutions in the root canal systems. The aim of this systematic review and meta-analysis (SRM) was to investigate the existing evidences on the disinfection capacity of irrigating solutions in root canals with ultrasonic activation compared to conventional irrigation. **Methods:** Literature search was performed within the main scientific databases carried out until October 2021 for the identification of randomized controlled trials (RCTs). Two meta-analysis was conducted using R software with the "META" package, the mean difference (MD) and odds ratio (OR) was the effect measure required and the fixed effect model was applied with a 95% confidence interval. The Cochrane collaboration scale was used to assess risk of bias and the GRADE tool to assess the quality of evidence. **Results:** A total of 1782 records were screened, and 12 studies meeting the criteria were included for this review. A low risk of bias was observed for most domains, except allocation concealment that was considered unclear. The certainty of evidence was classified as moderate in OR meta-analyses and low in MD meta-analyses. Ultrasonic irrigation resulted in better antimicrobial effect in both meta-analyses, MD 1.42 [1.60; 1.23] $p < 0.0001$, $I^2 = 80\%$; and OR 3.86 [1.98; 7.53] $p < 0.0001$, $I^2 = 28.7\%$. **Conclusion:** Within the limitations of this SRM, ultrasonic irrigation presents better antimicrobial efficacy compared to conventional irrigation. New robust randomized clinical trials are needed to corroborate these findings.

Keywords: Disinfection; Meta-analysis; Root canal irrigants; Root canal therapy; Systematic review; Ultrasonics.

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† Standardization according to Journal of Endodontics https://www.jendodon.com/content/authorinfo

3.2 INTRODUCTION

The main objective of endodontic treatment is the complete disinfection of root canal systems (RCS) and re-establish the function of the dental elements (1–3). For that, cleaning and shaping of the RCSs are essentials steps during root canal treatment (3,4). The knowledge of the anatomy of root canals is essential, as there are several variations regarding the numbers, shapes, curvatures, isthmuses, apical ramifications, oval canals, C-shaped or flattened canals (5–7).

However, the endodontics instruments can act principally in the major canal, making irrigation a fundamental part of root canal disinfection mainly from areas of anatomical complexity. Thus, a fundamental question to be considered in the irrigation process is whether the irrigating agent effectively reaches the anatomical complexities (6,8–10).

Furthermore, studies show even with the use of conventional irrigation, the RCS is still not totally free from microorganisms, especially in cases of persistent infections, which can lead to failures in endodontic treatments (4,9,11). This is mainly due to the complexity of the endodontic microbiota, where the environment favors anaerobic or facultative aerobic bacteria and, similarly to what occurs on the coronal surface, a biofilm is formed that serves as protection against antibacterial actions (4,11). In addition, microorganisms are able to enter into areas of anatomical complexity, reaching more than 500 µm in depth in the dentinal tubules (12).

In order to overcome part of this limitation, alternative techniques such as ultrasonic irrigating (UI) have been explored, which promotes the agitation of irrigating solutions, enhancing their ability to penetrate deep on complex regions, such as the apical, isthmus and lateral canals, and consequently increasing their antimicrobial efficacy (8,10,13).

Thus, presupposing that the use of the ultrasonic method as an irrigating solution activation mechanism improves its agitation and spread through vibration, we ask what would be the real influence of ultrasonic agitation on antimicrobial properties in endodontic treatment. Added to the lack of systematic reviews with randomized controlled trials on the subject in question, the aim of this systematic reviews and meta-analysis (SRM) was to answer the clinical question whether the use of ultrasonic irrigation results in better antimicrobial activity in root canal disinfection compared to conventional irrigation (CI).

3.3 METHODS

3.3.1 *Study design*

This review was performed meeting the guidelines of PRISMA (*Preferred Reporting Items for Systematic Review and Meta-Analyses* - www.prisma-statement.org) (14) and conducted according to the guidance in the Cochrane Handbook for Systematic Reviews of Interventions (15), according to different published studies (14,16). The review protocol was registered in the public registry of systematic review PROSPERO database (http://www. crd.york.ac.uk/PROSPERO) under number (CRD42021286306).

3.3.2 *Review question and PICOS*

The goal of this SRM was to answer the following question: "Does ultrasonic irrigation result in better antimicrobial efficacy in root canal disinfection compared to conventional irrigation?" The PICOS strategy described below was used:

(P) — Population: Patients who have received conventional endodontic treatment;
(I) — Intervention: Ultrasonic irrigation;
(C) —Comparison: Syringe irrigation (conventional)
(O) —Outcome: Antimicrobial effectiveness
(S)— Study design: Randomized clinical trials

3.3.3 *Search strategy*

The literature search was carried out in electronic databases: PubMed (MEDLINE), Scopus, Web of Science, Embase, Cochrane Library, Clinical Trials. The grey literature was also searched using the System for Information on Grey Literature in Europe (SIGLE) through OpenGrey. The search was carried out until October 20, 2021

A librarian guided the electronic search strategy, using MeSH terms and free terms appropriately adapted for the databases (see Appendix A). The present systematic review and the search strategy were developed with no language restriction and with no publication time restrictions. There were no language and publication time restrictions. A manual search was also performed for articles published in the following journals: *Journal of Endodontics, International Endodontic Journal, Australian Endodontic Journal, Iranian Endodontic Journal, European Endodontic Journal, Clinical Oral Investigations, and Journal of Dentistry*. Manual screening of the reference lists of all included studies was performed, so that no relevant articles would be missed.

3.3.4 *Eligibility criteria*

(A) randomized controlled trials (RCTs) that evaluated antimicrobial efficacy in conventional root canal treatment using conventional irrigation (manual needle) versus ultrasonic irrigation; (B) studies with initial and post-irrigation antimicrobial collection; (C) patients without changes/complications or systemic diseases. Studies not meeting the inclusion criteria were excluded.

3.3.5 *Study selection*

All studies recorded were imported into reference management online (EndNote Web; Thomson Reuters Inc., Filadélfia, PA, EUA). The elimination of duplicated studies was performed by two reviewers (L.O.C. and G.P.N.) independently assessing all titles and abstracts. In cases of titles and abstracts with insufficient information, the full texts were accessed. Any disagreements were resolved by discussion, and a third author (G.S.A.) was consulted if necessary. Agreement between the two reviewers regarding title and abstract selection was evaluated by the Cohen's kappa coefficient (κ). After selection by titles and abstracts, full texts of the articles were analyzed, and those meeting the inclusion criteria were included.

3.3.6 *Data extraction process*

Data associated with the study were acquired through customized extraction forms, in which the following parameters were recorded: study details (authors, year of publication, and location), number of patients, sex and age, systemic condition/disease, tooth root and type, clinical condition/diagnosis of pre-operative status, final irrigating agent and concentration evaluation methods, outcome, and conclusions. The authors were contacted through email to request additional information if necessary.

3.3.7 *Risk of bias*

An independent quality assessment was performed by two reviewers (L.O.C and G.P.N.) with the intervention of a third one (G.S.A.) when disagreement occurred. The Cochrane Collaboration's tool was used to assess the risk of bias of the randomized clinical trials (17). The assessment criteria contained the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Any disagreements of any studies were resolved between the reviewers through discussion, and if needed, by the involvement of a third author.

Studies were at low risk of bias if the key domains (random sequence generation, allocation concealment, blinding of participants and personnel, and other source of bias) were judged adequate. Contrarily, when a study was judged as unclear in their key domains, we tried to contact authors to obtain more information to allow a definitive judgement of either “yes” or “no”. If the final judgement remained unclear for one or more key domains, the studies were considered to be at unclear risk of bias (17).

Blinding of participants and personnel, and blinding of outcome was considered low risk since it was applicable only for the patient. Ultrasonic irrigation was performed by insert attached to an ultrasonic device. Therefore, blinding the endodontists was not possible, attributed to the use of either manual syringes or ultrasonic irrigation.

3.3.8 *Summary measurements*

The quantitative analyses were performed using R software with “Meta” package, version 3.6.3. Meta-analyses were performed, to evaluate bacterial reduction, the mean difference (MD) and odds ratio (OR) were the effect measure required. In both analyses, the fixed-effect model was applied with a 95% confidence interval (CI). Heterogeneity was tested using the I^2 index, and it was considering substantial or high to I^2 index $\geq 50\%$. To access the publication bias, the trim-and-fill method was applied. In addition, the trim-and-fill method was also used to evaluate bias on meta-analysis.

3.3.9 *Certainty of the evidence by Grading of recommendations, assessment, development and evaluation*

The evidence level was measured using the Grading of Recommendations, Assessment, Development and Evaluation Pro software (GRADEpro Guideline Development Tool, available online at gradepro.org). It grades the quality of evidence in four levels: very low, low, moderate and high. ‘High quality’ suggests that the true effect lies close to the estimate of the effect. ‘Very low quality’ suggests that there is very little confidence in the effect estimate, and the estimate reported can be substantially different from what was measured. This tool considers five aspects for rating the quality of evidence: risk of bias, inconsistency, indirectness, imprecision and other considerations (18). The evaluations were carried out by two researchers independently (G.P.N. and L.O.C.) and then compared.

3.4 RESULTS

Literature search

The database search retrieved 1782 studies: 1223 from PubMed/MEDLINE, 213 from Web of Science, 144 from Embase, 113 from Cochrane Library, 84 from Scopus, and 5 from manual searching (Fig. 1). After removal of duplicates, 1393 studies remained for verification of titles and abstracts. This step resulted in 17 studies for full reading, of which five studies were excluded because they did not meet the eligibility criteria. Thus, 12 randomized clinical trials were included in the review (10,19–29). The cohen´s kappa score for articles included in all databases showed an acceptable level of inter-examiner agreement (k = 0.876).

Description and characteristics of the included studies

The characteristics of the 12 included studies are listed in Table 1. Three studies were conducted in Brazil (10,24,25), four in United States of America (21,22,30,31), two in India (27,29), one in China (23), Turkey (28) and Egypt (26). All studies used bacteriologic culture to assess antimicrobial effect except for two studies, who used the Real Time Quantitative Polymerase Chain Reaction (qPCR) for antimicrobial analysis (24,28). In addition to bacteriologic culture Orozco et al., 2019 (25) used a second evaluation method, the checkerboard DNA-DNA hybridization to assess the number of bacterial species. Two studies used Limulus Amebocyte Lysate assay to assess endotoxin levels (10,24). Regarding dental diagnosis, all studies were diagnosed with apical periodontitis except by two studies (26,29), who analyzed only teeth with pulp necrosis. Lastly it is noteworthy that in one study retreatment was performed (28).

Regarding irrigation solution, sodium hypochlorite was the agent used in all included studies, except for one study (23). The sodium hypochlorite irrigating solution concentration ranged from 1% to 6% in the studies evaluated. Regarding the number of roots, seven studies assessed single root canals (23–26,28,29,31), two studies evaluated both types of roots (10,27), and three studies investigated multirooted teeth (21,22,30).

Risk of bias in the included studies

According to the Cochrane scale, in general, studies showed a ‘’low risk of bias’’. Regarding the generating a random sequence (selection bias) the RCTs demonstrated a “low risk, except two studies (27,31), which presented an “unclear risk of bias” due to the lack of sufficient information for the judgment. Moreover, in the concealment allocation domain (selection bias) six studies also demonstrated “unclear risk of bias” (21–23,26,28,30). In the four domains: blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias) all studies were classified as "low risk of bias". For “Other bias” domain, two studies were classified as high risk to the absence of sample calculation and the low number of patients analyzed (10,26) (Fig. 2).

Meta-analysis, quantitative assessment of bias and level of evidence

The remaining studies did not contain sufficient data for quantitative analysis, even after contact attempts, and therefore were not included in the analysis (10,24-26). Two meta-analyses were performed, one using mean difference (MD) as the necessary effect measure, and the other using odds ratio (OR). In meta-analysis using MD, four studies were included (21,23,27,30), quantitative pooling showed that the use of ultrasonic agitation promotes an increase in antimicrobial reduction compared to conventional irrigation: MD 1.42 [1.60; 1.23] $p < 0.0001$, $I^2 = 80\%$ (Fig. 3A). Publication and meta-analysis bias were observed with the trim-and-fill method in one study (21) (Fig. 3B). After trim-and-fill method remained with statistical difference between groups: random effect: MD 1.51 [2.73; 0.29] $p = 0.0155$. In the meta-analysis using OR, four other studies were included (20,22,28,29), the quantitative analysis also showed favorable results for ultrasonic irrigation: OR 3.86 [1.98; 7.53] $p < 0.0001$, $I^2 = 28.7\%$ (Fig. 4A). Publication and meta-analysis bias were observed with the trim-and-fill method in two study (22,28) (Fig. 4B). After trim-and-fill method remained with statistical difference between groups: random effect: OR 5.71 [2.37; 13.75] $p < 0.0001$.

The certainty of the evidence was classified as moderate in the OR meta-analysis, due to the presence of imprecision, and low in MD meta-analyses (Table 2), due to inconsistency and imprecision have been categorized as serious, due to the clinical heterogeneity and sample size of the studies included.

3.5 DISCUSSION

The most challenging and important aspect during root canal treatment of pulp necrosis is efficiently removing microorganisms, their products, and necrotic tissue from the RCSs (9,22). This difficulty is attributed to several factors, but the main one is due to the complexity of the RCSs, which generates non-instrumented areas even after biomechanical preparation, making bacterial disinfection a complex step during the root canal treatment (7,9).

Thus, the present SRM sought to answer the clinical question: "Does ultrasonic irrigation result in better antimicrobial efficacy in root canal disinfection compared to conventional irrigation?". Only randomized clinical trials were retrieved. Two meta-analysis was carried out with 8 studies (21–23,27–31), using the fixed-effect model with 95% confidence interval, showing favorable results to ultrasonic irrigation compared to conventional irrigation. In addition, in the qualitative analysis of the included studies, eight of the twelve studies showed an advantage favoring ultrasonic irrigation (10,23,24,26,27,29–31).

The greater microbial reduction can be explained because ultrasonic irrigation is related to four main factors: the hydrodynamic phenomena, acoustic microstreaming and cavitation, and other two factors, the removal of the apical vapor lock and the increase in the temperature of the irrigating solution (NaOCl) (11,32–36). The acoustic microstreaming effect moves the fluid (irrigation solution) quickly around the ultrasonic tip, promoting constant agitation of the solution, generating a tension that leads to shear stress on the walls around it, increasing its ability to remove debris, bacteria and its biofilm mainly in areas of anatomical complexity (32,37,38).

Another effect is the micro cavitation, which is also generated due to the high agitation of the fluids around the ultrasonic tip, which generate bubbles (small voids) of gas and when these bubbles collapse, it generates the phenomenon of cavitation, producing energy waves that spread through the irrigation solution and leads to an increase in its temperature (30,34,39). Furthermore, this phenomenon has the ability to damage the membranes and cell walls of microorganisms, and allows the deagglomeration of bacterial biofilms adhered to the walls of root canals, making the bacteria more susceptible to irrigating solutions (30,34,39).

Vapor lock is a blockage generated by gas or air bubbles in the apical region from instrumentation/irrigation and also by chemical reactions, hindering the action of irrigating agents in this region (40,41). Ultrasonic activation of the irrigating solution has the ability to prevent and eliminate this blockage through the phenomena of micro cavitation and acoustic microstreaming, allowing greater efficiency of the irrigating agents in the apical region. Finally, it is speculated that the temperature increase generated by the use of ultrasonic agitation, approximately 15ºC, would be able to increase the antimicrobial efficiency of chemical agents such as sodium hypochlorite, as this becomes more chemically reactive (35,42,43).

In general, in the methodologies used for microbiological quantification, paper tips are used to collect the material present inside the root canal. However, this collection is restricted to the main canal, as well as it does not differ on the origin of the microorganisms in relation to the root thirds, making it impossible to obtain information about all microbiome that colonize areas of anatomical complexity. Thus, the material collected may not fully represent the entire microbial population present there. Therefore, it is possible to assess the antimicrobial effectiveness, however there is no way to elucidate a close-to-real approach in relation to biofilm removal, since it is strongly adhered to the dentin walls, which is valuable information, as the remaining bacteria remain organized in biofilms are the main cause of therapy failure and directly influence the longevity and outcome of endodontic treatment.

Regarding root morphology, it is important to mention that 8 of the 9 studies that analyzed single-rooted teeth observed greater antimicrobial action with the use of UI (10,23,24,26–29,31). As for multirooted teeth, 3 of the 5 eligible studies that addressed this variable showed a potentiated effect of the use of ultrasonic compared to CI (10,27,30). This data is important considering that UI was effective even for multirooted teeth, as there is concern about endodontic therapy in this group of teeth, as it presents greater anatomical complexity, as well as lower disinfection activity by conventional irrigation, as corroborated in literature (24,44). Thus, this finding is directly related to the explanations mentioned above and attributed to the greater effectiveness of the irrigating agent when activated by ultrasonic device (45). Furthermore, it is noteworthy that of the two studies that showed a similar effect between therapies for multirooted teeth (21,22), one used 1% sodium hypochlorite for teeth with apical periodontitis (22), this concentration being below that recommended for such a pulp condition (46,47).

Regarding irrigating agents, sodium hypochlorite was mostly used in the included studies (10,21,22,24–31). NaOCl concentrations in the studies ranged from 1% to 6%. It is known that the antimicrobial effect of NaOCl is dose-dependent (48–50). This evidence available in the literature was also corroborated with the findings of the present systematic review for ultrasonic irrigation. However, of the studies that used high concentration NaOCl (5.25% and 6%) only one study reported no difference between the control and intervention groups (21). However, the irrigation protocol adopted in this study was different from the others, since the entire biomechanical preparation process of the root canals was carried out under irrigation with saline solution, and NaOCl was used only in the final irrigation, so that may have negatively influenced the reduction of microbial load.

Furthermore, the success of endodontic therapy is also conditioned by the elimination of endotoxins, such as Lipopolysaccharide and Lipoteichoic acid (51–53). These endotoxins are the main cause of the pathogenesis of apical periodontitis and periapical bone resorption, in addition to acting as a limiting factor in the success of endodontic therapy (51–53). Of the included studies, two evaluated the expression of endotoxins (10,24), and concluded that CI and UI showed a high reduction in endotoxin levels, however with a similar effect between therapies. It is noteworthy that the studies predominantly analyzed single-rooted teeth, which may have favored the conventional technique, since they are teeth with little anatomical complexity, and are more susceptible to disinfection using the needle method. Thus, new, more robust and standardized tests must be conducted to address the therapy of teeth with complex morphologies.

In this systematic review only one study evaluated secondary endodontic treatment (28). In this type of condition, there is the presence of a more complex microbiota than in primary treatments, in addition to more adhered biofilms (54). One of the microorganisms with a high prevalence in retreatment cases is *Enterococcus faecalis*, which was analyzed in that study (28). A 19% greater reduction was identified in the activated ultrasonic group compared to the non-activated one, showing ultrasound superiority even with super resistant bacteria (28). This result is important, especially considering complementary therapies and the mechanism of action of the ultrasonic device, since this microorganism has some means of defense that make it more resistant than other bacteria, such as the ability to survive with a low metabolic rate for a long period (12) and its deep infiltration into dentinal tubules (12,55,56).

Although the studies presented, in general, low risk of bias, the quality of the evidence - GRADE presented a low certainty of the evidence in MD meta-analyses and moderate certainty of the evidence in OR meta-analyses, thus, and in addition to other aspects mentioned above, the results of this systematic review and meta-analysis should be carefully analyzed. In this manner, it is strongly recommended to conduct new and more robust standardized randomized clinical trials, minimizing methodological variations observed in the studies included in this systematic review, such as the differentiation of irrigating agents activation protocols, volume and concentration of irrigating solution used, time of irrigating agent action in contact with the roots, insertion depth of the ultrasonic insert, and the final conicity of the preparation. Furthermore, the use of investigation protocols should be considered, addressing the randomization and allocation phases, as well as an accurate report on the use of each intervention. Therefore, it is essential to adhere to the CONSORT guidelines for reporting randomized clinical trials, and its use in future trials.

3.6 CONCLUSION

With the results presented, ultrasonic irrigation has better antimicrobial efficacy compared to conventional irrigation. However, the results of this systematic review and meta-analysis should be interpreted with caution, due to heterogeneity of data, and the methodologies employed. Further robust randomized clinical trials are needed to corroborate these findings.

ACKNOWLEDGMENT

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

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

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Table Legends

Table 1. General data on the selected studies.

Table 2. Evidence profile: Microbiologic effect in endodontic treatment in conventional irrigation vs. ultrasonic irrigation.

Figure Legends

Figure 1. PRISMA Flow chart - Flow diagram showing the entire search process.

Figure 2. Summary of the risk of bias assessment—Cochrane scale.

Figure 3. Meta-analysis using mean difference (MD) as effect measure. A: Forest plot. B: Analysis of publication bias and meta-analysis (trim-and-fill).

Figure 4. Meta-analysis using odds ratio (OR) as effect measure. A: Forest plot; B: Analysis of publication bias and meta-analysis (trim-and-fill).

Table 1. General data on the selected studies.

Author/ year (Country)	N patients	Sex (M/F) and age (y)	Systemic condition / Disease	Tooth root and type	Clinical condition/ Diagnosis Pre-op status	Final irrigating agent and concentration	Evaluation methods	Outcome: [Mean ± SD] / Percentage G1- Control group; G2 – Intervention group	Conclusion
Carver et al., 2007 (USA)	G1: 16 G2: 15	G1: 34.8 mean G2: 40.3 mean	Healthy	Mandibular molars	Pulp necrosis and periapical periodontitis	6% NaOCl	CFU	**log CFU counts** **G1:** Initial: 12.1 ± 2.6 Post CI: 3.4 ± 3.7 **G2:** Initial: 13.0 ± 1.6 Post UI: 1.2 ± 2.6	Ultrasonic irrigation reduced CFU counts and was 7 times more likely to yield a negative culture than no hand and rotary instrumentation alone.
Bellingham 2011 (USA)	MTAD 10 NaOCl 10	14 years or older mature apex	Healthy	Single root	Pulp necrosis and periapical periodontitis	5.25% NaOCl and MTAD	CFU	**Positive Culture:** MTAD: Initial: 10/10 (100%) Post CI: 5/10 (50%) Post UI: 2/10 (20%) NaOCl Initial: 10/10 (100%) Post CI: 4/10 (40%) Post UI: 2/10 (20%) **% Reduction bacterial** G1: 55% (11/20) G2: 80% (16/20)	The incidence of bacterial growth was significantly less after ultrasonic irrigation, and a trend was observed towards reduction in colony count. These results add to previous research indicating this new irrigant agitation and delivery device imparts a significant antimicrobial advantage.
Johnson 2011 (USA)	G1: 10 G2: 10	G1: 52.70 G1: 47.60	Healthy	Molars	Necrotic pulp with chronic apical periodontitis	0.9% sterile saline solution 10mL 6% sodium hypochlorite (final rinse)	CFU	**log CFU counts** **G1** Initial: 4.46 ± 0.94 Post CI: 3.19 ± 0.51 **G2:** Initial: 5.63 ± 1.49 Post UI: 3.80 ± 1.64	There was no statistical difference between the groups.

Beus et al., 2012 (USA)	G1: 25 G2: 25	NR	NR	Posterior tooth	Apical periodontitis	1% NaOCl	Bacteriologic culture	**Positive culture** G1: 5/25 (20%) G2: 4/25 (16%) **% Reduction bacterial** G1: 80% (20/25) G2: 84% (21/25)	There was no statistical difference between the groups.
Chunhui & Qun 2017 (China)	G1: 20 G2: 20	G1:20/22 Age 40 G2:19/23 Age: 38	Healthy	Uni	Chronic apical periodontitis	NR	CFU	**log CFU counts** G1: Initial: 6.301 ± 0.152 Post CI : 1.824 ± 0.417 G2: Initial: 6.165 ± 0.083 Post UI: 0.345 ± 0.093 **% reduction Bacterial:** G1: 71.02 ± 6.70 G2: 94.41 ± 1.47	Bacterial reduction is more effective on ultrasonic group.
Nakamura et al., 2018 (Brazil)	G1: 25 G2: 25	G1: 20/5 G2:17/8 Age 18 to 65 mean age 39	Healthy	Single rooted teeth / root with a single canal from multi-rooted teeth.	Necrotic pulps / apical periodontitis	2.5% NaOCl	qPCR / endotoxin levels (LAL assay).	**Q pcr: Median values of bacteria** (Median) **G1**: Initial: 8.55×10^5 (1.91×10^2 - 4.66×10^7) Post CI: 1.08×10^4 (0 - 3.38×10^5) **G2:** Initial: 1.49×10^6 (2.66×10^3 - 3.29×10^7) Post UI: 4.29×10^3 (0 - 2.22×10^4) **endotoxin levels (median)** **G1:** Initial: 64.95 (10 -195) Post CI: 5.75 (0 - 14.8) **G2:** Initial: 57.45 (10 – 309) Post UI: 6.53 (0 - 19.4)	Ultrasonic activation was more effective than the non-activated irrigation protocol in reducing bacteria. It was, however, as effective as the non-activated irrigation protocol in reducing intracanal endotoxin levels.

Orozco et al., 2019 (Brazil)	G1: 10 G2: 10	10/10 Age 18 to 60	Healthy	Single rooted teeth	Pulp necrosis / apical periodontitis	2.5% NaOCl	CFU and Species number (DNA hybridization)	**log CFU counts** G1: Initial: $2.31x10^5 \pm 4.70x10^5$ Post CI :$5.72x10^3 \pm 1.10x10^4$ G2: Initial: $2.58x10^5 \pm 4.70x10^5$ Post UI: 6 ± 19 **Species Number:** G1: Initial: 10.2 ± 5.9 Post CI: 8.6 ± 6.9 G2: Initial: 9 ± 3.8 Post UI: 10.7 ± 6.7	Both treatments significantly decreased the number of bacterial species, no difference between ultrasonic irrigation and conventional irrigation groups was detected.
Aldean et al., 2020 (Egypt)	G1: 8 G2: 8	NR	NR	Single rooted, single-canal	Pulp necrosis	5 ml of 2.5% NaOCl	CFU	**log CFU counts**: Aerobic G1: Initial: 4.700×104 ± 1.794 Post CI: 3.650×103 ± 1.156 G2: Initial: 4.900×104 ± 1.745 Post UI: 0.725×103 ± 0.396 Anaerobic G1: Initial: 3.825×104 ± 1.122 Post UI: 3.813×103 ± 1.156 G2: Initial: 3.339×104 ± 1.094 Post UI: 1.075×103 ± 0.443 % Reduction Bacterial Aerobic G1: 91.8 ± 1.74 G2: 98.6 ± 0.40 Anaerobic	Irrigation–activation increases the efficacy of irrigation concerning the microbial reduction and PUI is the most recommended method of activation.

								G1: 89.6 ± 2.88 G2: 96.4 ± 1.88	
Aveiro et al., 2020 (Brazil)	G1: 8 G2: 8	Mean age: 44.2 G1: Female: 2 Male: 6 G2: Female: 5 Male: 3	Healthy	G1: Single-rooted: 4 Multi-rooted: 4 G2: Single-rooted: 6 Multi-rooted: 2	Pulp necrosis and periapical periodontitis	6% NaOCl	CFU Lipopolysaccharide Lipoteichoic Acid	**Log CFU: Median values of bacteria** G1**:** Initial**:** 5.6 x 10^5 Post CI: 0 G2: Initial: 6.21 x 10^5 Post UI: 0 **Lipopolysaccharide:** G1: (Median) Initial: 16.75 Post CI: 0.04 G2: Initial :19.10 Post UI: 0.01 **Lipoteichoic Acid:** G1: (Median) Initial: 411.50 Post CI: 179.00 G2: Initial :387.00 Post UI: 152.50	Ultrasonic activation was the most effective technique in reducing the concentration and microbial diversity within root canals.

Ballal et al., 2020 (India)	G1: 20 G2: 20	Mean age 41	Healthy	Any tooth	Asymptomatic apical periodontitis	2.5% NaOCl	CFU	**log CFU counts** G1: Initial: 12.40 ± 9.28 Post CI: 1.09 ± 3.56 G2: Initial: 16.60 ± 44.82 Post UI: 0.0055 ± 0.32	Needle irrigation was associated with significantly more colony forming units when compared to ultrasonic irrigation.
Bilgin et al., 2020 (Turkey)	12	18 years or older	Healthy	Single root and a single canal	Retreatment with periapical periodontitis	2.5% NaOCl	qPCR CFU	**Log CFU counts** G1: Initial: $8.94\times10^4 \pm 1.48\times10^5$ Post CI: $1.71\times10^4 \pm 1.88\times10^4$ G2: Initial: $8.94\times10^4 \pm 1.48\times10^5$ Post UI: $1.55\times10^4 \pm 2.29\times10^4$ **% reduction Bacterial:** G1: 65% G2: 84%	All disinfection methods were effective in reducing E. faecalis from infected root canals with no statistical differences.
Palanisamy 2020 (India)	G1: 40 G2: 40	Age: 18 to 55	Healthy	Single rooted teeth	Symptomatic / irreversible pulputis and pulpal necrosis	2.5% NaOCl	Bacteriologic culture	**Positive Culture** G1: Initial: Positive: 22/40 55% positive Post CI: Positive: 13/40 32,5% positive G2: Initial: Positive: 27/40 67.5% positive Post UI: Positive: 4/40 10% positive	There was a significant difference in negative cultures between two groups. Passive ultrasonic irrigation resulted in a 57 % reduction of positive cultures when compared with the first bacterial sample while side-vented needle irrigation resulted in a 22.5 % reduction of positive cultures.

								% Reduction bacterial G1: 41% G2: 85.2%	

Abbreviations: NR = not reported; NaOCl = sodium hypochlorite; MTAD = irrigation agent (doxycycline, citric acid, and a detergent tween 80); CFU = colony forming unit

Table 2. Evidence profile: Microbiologic effect in endodontic treatment in conventional irrigation vs. ultrasonic irrigation

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Ultrasonic]	[Conventional]	Absolute (95% CI)	
4	RCT	not serious	serious	not serious	serious	none	65	66	**MD 1.42 SD higher (1.60 lower to 1.23 lower)**	⨁⨁◯◯ LOW

CI: Confidence Interval; SD: Standard Deviation **MD:** Mean Difference.

4	RCT	not serious	not serious	not serious	serious	none	97	97	**OR 3.86 SD higher (7.53 lower to 1.98 lower)**	⨁⨁⨁◯ MODERATE

CI: Confidence Interval; SD: Standard Deviation**;** OR: Odds Ratio

Figure 1. PRISMA Flow chart

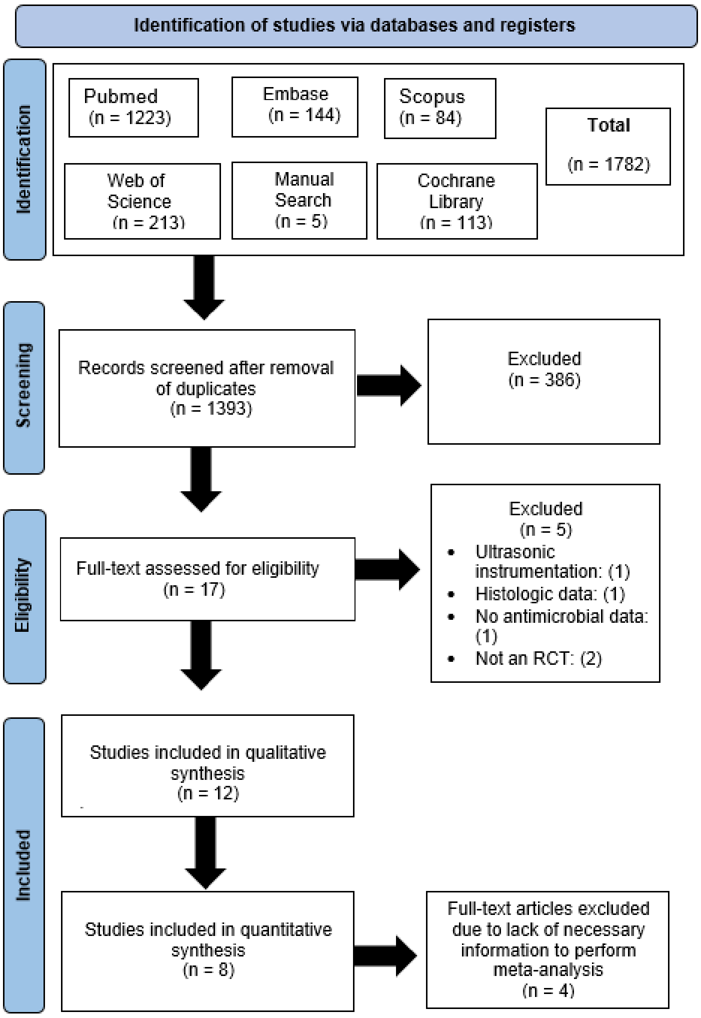


Figure 2. Summary of the risk of bias assessment—Cochrane scale

Figure 3. Meta-analysis using mean difference (MD) as effect measure. A: Forest plot. B: Analysis of publication bias and meta-analysis (trim-and-fill).

A

B

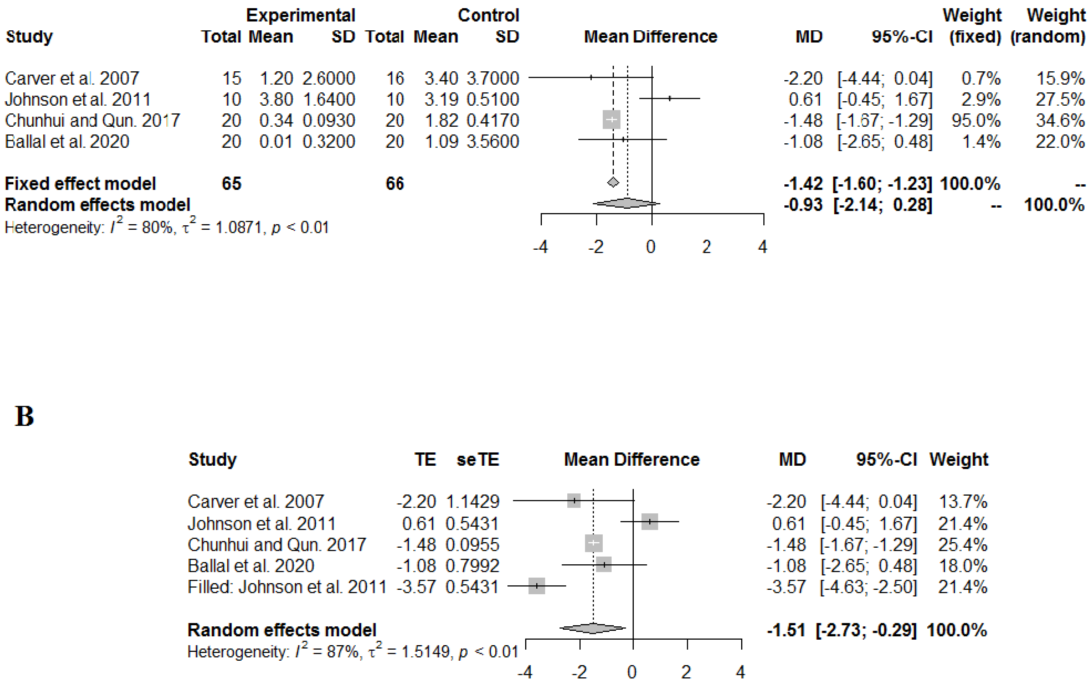
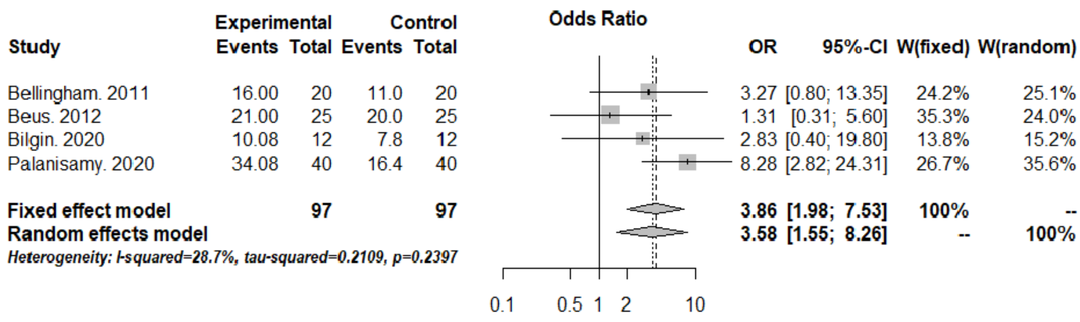
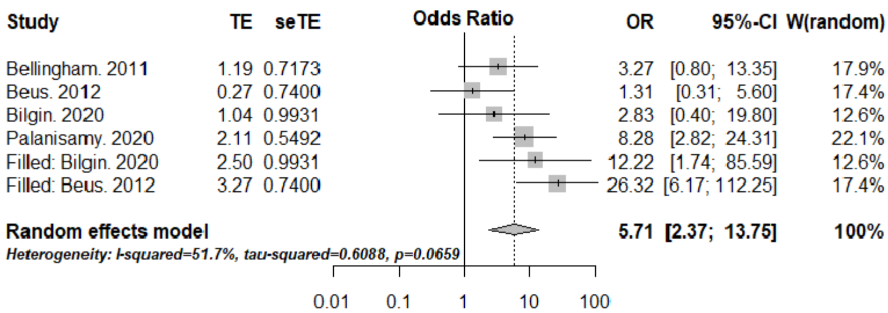


Figure 4. Meta-analysis using odds ratio (OR) as effect measure. A: Forest plot; B: Analysis of publication bias and meta-analysis (trim-and-fill).

A



B



Conclusão Geral

4. CONCLUSÃO GERAL

Dentro das limitações das Revisões Sistemáticas apresentadas, as evidências sugerem que a irrigação ultrassônica dos canais radiculares leva a uma menor incidência de dor pós-operatório, assim como, um aumento na efetividade antimicrobiana em comparação com a irrigação convencional. No entanto, devido a heterogeneidade dos dados, ensaios clínicos randomizados mais robustos são recomendados para fornecer melhor compreensão e suporte dos achados obtidos.

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ANEXOS

ANEXOS

ESTRATÉGIA DE BUSCA CAPITULO 1

Search Strategy
#1 (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontic therapy) OR (endodontic treatment) OR (root canal treatment) OR (RCT) OR (endodontic procedure) OR (Root Canal Irrigants) OR (Canal Irrigant, Root) OR (Canal Irrigants, Root) OR (Irrigant, Root Canal) OR (Irrigants, Root Canal) OR (Root Canal Irrigant) OR (Root Canal Medicament) OR (Root Canal Medicaments) OR (Canal Medicament, Root) OR (Canal Medicaments, Root) OR (Medicament, Root Canal) OR (Medicaments, Root Canal) OR (Root Canal Preparation) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Therapeutic Irrigation) OR (Irrigation, Therapeutic) OR (Irrigations, Therapeutic) OR (Therapeutic Irrigations) OR (Lavage) OR (Lavages) OR (Douching) OR (Douchings) #2 (Ultrasonic Therapy) OR (Therapy, Ultrasonic) OR (Therapies, Ultrasonic) OR (Ultrasonic Therapies) OR (activation device) OR (active irrigation) OR (activated irrigation) OR (active irrigation device) OR (Ultrasonic) OR (passive ultrasonic irrigation) OR (PUI) #3 (Pain, Postoperative) OR (Post-surgical Pain) OR (Pain, Post-surgical) OR (Post surgical Pain) OR (Pain, Post-operative) OR (Pain, Post operative) OR (Postsurgical Pain) OR (Pain, Postsurgical) OR (Post-operative Pain) OR (Post operative Pain) OR (Post-operative Pains) OR (Postoperative Pain) OR (Postoperative Pain, Chronic) OR (Pain, Chronic Postoperative) OR (Chronic Postoperative Pain) OR (Chronic Post-surgical Pain) OR (Chronic Post surgical Pain) OR (Pain, Chronic Post-surgical) OR (Post-surgical Pain, Chronic) OR (Chronic Postsurgical Pain) OR (Chronic Postsurgical Pains) OR (Pain, Chronic Postsurgical) OR (Postsurgical Pain, Chronic) OR (Persistent Postsurgical Pain) OR (Pain, Persistent Postsurgical) OR (Postsurgical Pain, Persistent) OR (Post-operative Pain, Chronic) OR (Pain, Chronic Post-operative) OR (Post operative Pain, Chronic) OR (Chronic Post-operative Pain) OR (Chronic Post operative Pain) OR (Postoperative Pain, Acute) OR (Pain, Acute Postoperative) OR (Acute Postoperative Pain) OR (Acute Post-operative Pain) OR (Acute Post operative Pain) OR (Post-operative Pain, Acute) OR (Pain, Acute Post-operative) OR (post-operative discomfort) OR (pain) #1 AND #2 AND #3

ESTRATÉGIA DE BUSCA CAPITULO 2

Search Strategy
#1 (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontic therapy) OR (endodontic treatment) OR (root canal treatment) OR (RCT) OR (endodontic procedure) OR (Root Canal Irrigants) OR (Canal Irrigant, Root) OR (Canal Irrigants, Root) OR (Irrigant, Root Canal) OR (Irrigants, Root Canal) OR (Root Canal Irrigant) OR (Root Canal Medicament) OR (Root Canal Medicaments) OR (Canal Medicament, Root) OR (Canal Medicaments, Root) OR (Medicament, Root Canal) OR (Medicaments, Root Canal) OR (Root Canal Preparation) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Therapeutic Irrigation) OR (Irrigation, Therapeutic) OR (Irrigations, Therapeutic) OR (Therapeutic Irrigations) OR (Lavage) OR (Lavages) OR (Douching) OR (Douchings) #2 (Ultrasonic Therapy) OR (Therapy, Ultrasonic) OR (Therapies, Ultrasonic) OR (Ultrasonic Therapies) OR (activation device) OR (active irrigation) OR (activated irrigation) OR (active irrigation device) OR (Ultrasonic) OR (passive ultrasonic irrigation) OR (PUI) OR (continuous ultrasonic irrigation) OR (CUI) #3 (Manual irrigation) OR (Needle irrigation) OR (Conventional irrigation) OR (Syringe irrigation) OR (Cannulae) OR (Side vented needles) OR (End vented needles) OR (Endodontic irrigation) #4 (Bacteria) OR (Eubacteria) (antimicrobial) OR (disinfection) OR (bacterial reduction) OR (microbial reduction) OR (microbial outcome) OR (culture) OR (microbial diagnosis) OR (molecular microbial) OR (antimicrobe) OR (Infections) OR (Infection Control Dental) OR (Microbiology) #1 AND #2 AND #3