Ricardo Pedro da Silva

O ozônio é eficaz na redução da dor, edema e trismo após cirurgia de terceiro molar? uma meta-análise.

Is ozone effective in reducing pain, edema and trismus after third molar surgery? A meta-analysis.

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia para obtenção de Título de Mestre em Clínica Odontológica.

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Orientador: Prof. Dr. Luiz Renato Paranhos

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Reuniu-se no Anfiteatro/Sala 23 bloco 4L Anexo A, Campus Umuarama, da Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Odontologia, assim composta: Professores Doutores: Cláudia Jordão Silva (UFU); Flaviana Soares Rocha (UnB); Luiz Renato Paranhos (UFU) orientador(a) do(a) candidato(a). Profa. Dra. Flaviana Soares Rocha , participou da defesa de tese por meio de vídeo-conferência desde a cidade de Brasília; e os demais membros da Banca participaram *in loco*.

Iniciando os trabalhos o(a) presidente da mesa, Dr(a). Luiz Renato Paranhos, apresentou a Comissão Examinadora e o candidato(a), agradeceu a presença do público, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

A seguir o senhor(a) presidente concedeu a palavra, pela ordem sucessivamente, aos(às) examinadores(as), que passaram a arguir o(a) candidato(a). Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu o resultado final, considerando o(a) candidato(a):

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Nada mais havendo a tratar foram encerrados os trabalhos. Foi lavrada a presente ata que após lida e achada conforme foi assinada pela Banca Examinadora.

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SUMÁRIO

RESUMO

A extração de terceiros molares inferiores está frequentemente associada a complicações pós-operatórias como dor, edema e trismo resultantes do processo inflamatório. Assim, este estudo teve como objetivo avaliar a eficácia da terapia com ozônio na redução da dor, inchaço e trismo após a extração de terceiros molares inferiores. Um protocolo de Revisão Sistemática foi submetido na base de dado PROSPERO. Foram utilizadas seis bases de dados eletrônicas (PubMed, Scopus, LILACS, SciELO, Embase e Web of Science). O OpenGrey e o OATD foram as bases utilizadas para capturar parcialmente a "literatura cinza" para minimizar o viés de seleção e publicação. Apenas ensaios clínicos randomizados foram incluídos. A ferramenta JBI foi usada para avaliar o risco de viés. Foi realizada uma meta-análise com um modelo de efeitos aleatórios e a heterogeneidade dos estudos foi avaliada com a estatística I^2. A ferramenta GRADE foi usada para avaliar a qualidade da evidência e a força das recomendações nos estudos incluídos. A pesquisa produziu 3.386 resultados, dos quais apenas três artigos foram elegíveis. No geral, os indivíduos que receberam ozônio relataram escores mais baixos de dor em comparação ao grupo controle (SMD = -2,12; IC95%: -2,62; -1,61; p <0,001). Os indivíduos que receberam ozonioterapia poderiam abrir a boca 0,69 mm a mais do que os indivíduos do grupo controle. A avaliação do edema foi dividida em dois tipos de medidas: a distância do trágus ao canto da boca (T-C) e a distância do trágus ao pogônio (T-P). Para T-C, o grupo intervenção apresentou edema de 2,34 cm maior que o grupo controle. Para T-P, não houve diferença entre os grupos. Os presentes estudos apresentam resultados divergentes, embora o uso de ozônio seja promissor para reduzir a dor pós-operatória; em relação à edema e ao trismo, a terapia com ozônio não foi considerada eficaz.

Palavras-chaves: Edema, Ozônio, Trismo.

ABSTRACT

Extraction of lower third molars is often associated with postoperative complications such as pain, edema and trismus resulting from the inflammatory process.Thus, this study aimed to evaluate the effectiveness of ozone therapy in reducing pain, swelling and trismus after extraction of lower third molars. A Systematic Review protocol was submitted to the PROSPERO database. Six electronic databases (PubMed, Scopus, LILACS, SciELO, Embase, and Web of Science) were used. OpenGrey and OATD were the bases used to partially capture “gray literature” to minimize selection and publication bias. Only randomized clinical trials were included. The JBI tool was used to assess the risk of bias. A meta-analysis with a random effects model was performed, and the heterogeneity of the studies was evaluated with I^2 statistics. The GRADE tool was used to assess the quality of evidence and strength of the recommendations across the included studies. The search yielded 3,386 results, of which only 3 articles were eligible. Overall, individuals who received ozone reported lower pain scores compared to the control group (SMD = -2.12; 95% CI: -2.62; -1.61; $p < 0.001$). Individuals receiving ozone therapy could open their mouths 0.69 mm more than individuals in the control group. The evaluation of edema was divided into two types of measures: the distance from the tragus to the corner of the mouth (T-C) and the distance from the tragus to the pogonion (T-P). For T-C, the intervention group presented edema of 2.34 cm greater than the control group. For T-P, there was no difference between the groups. The present studies present divergent results, although the use of ozone is promising to reduce postoperative pain; in relation to edema and trismus, ozone therapy was not considered effective.

Keywords: Edema**,** Ozone, Trismus.

INTRODUÇÃO E REFERENCIAL TEÓRICO

A exodontia dos terceiros molares inferiores impactados é um dos procedimentos cirúrgicos mais frequente no consultório odontológico (Mojsa *et al.,* 2017). Em 2007, Friedman relatou que apenas no EUA são removidos cerca de 10 milhões de terceiros molares anualmente. As indicações para sua remoção são: Pericoronarites, cáries, falta de função, reabsorção dental, doença periodontal, cistos e tumores associados ao terceiro molar, apinhamentos dentais, remoção prévia a confecção de próteses, indicações ortodônticas, infecções (Steed *et al.,* 2014) e pacientes que irão ser submetidos a cirurgia ortognática (Pereira *et al.,* 2017). Aproximadamente 82% dos pacientes adultos que possuem terceiros molares erupcionados apresentam alguma doença dental associado a estes, cerca de 74 % apresentam doenças em terceiros molares semi-inclusos e 33% quando os terceiros molares se encontram inclusos (Ventä *et al.,* 2017).

Entretanto as complicações pós operatórias como dor, edema e trismo (Seymour *et al.,* 1996), podem alterar a qualidade de vida do paciente com efeito negativo maior no primeiro dia, diminuindo ao longo do acompanhamento. (Duarte *et al.,* 2018). A diminuição da capacidade de mastigar, disfagia, trismo, deficiência na percepção do paladar e diminuição do sono são condições que acontecem geralmente no primeiro dia de pós-operatório (Adebayor *et al.,* 2017), sendo assim as condições bucais na qualidade de vida é um resultado importante e necessário na tomada de decisão sobre o tratamento (Deliverska *et al.,* 2016). Informar aos pacientes essas condições previamente ao procedimento cirúrgico é uma importante conduta.

Segundo a IASP (Associação Internacional para o Estudo de Dor), a dor é definida como uma desagradável sensação sensorial e emocional associada a dano tecidual real ou potencial (Macintyre *et al.,* 2014). Quando aguda, no pós operatório de cirurgia de terceiros molares, é esperado que seu pico de intensidade ocorra em até 12 horas após o procedimento (Markovi| *et al.,* 2006). Reduzir a dor de forma eficiente significa aumentar a satisfação do paciente e diminuir os custos após a cirurgia, além de diminuir as chances de catastrofização da dor no pós-operatório tardio (Reenam *et al.,* 2011).

O edema é resultado de um acúmulo de líquido no espaço intersticial ocorrendo quando a filtração capilar excede os limites da drenagem linfática, apresentando sinais e sintomas clínicos perceptíveis (Kathryn *et al.,* 2013). Na cirurgia de terceiros molares o edema, assim como a dor e o trismo é influenciado pelo resultado do processo inflamatório tecidual, com sinais cardinais de inflamação (Kumar *et al.,* 2010). O Trismo após a extração de um terceiro molar é uma complicação que surge devido à desenvolvimento de edema ao redor do músculo masseter e pode ser influenciado pela dor (Pedersen *et al.,* 1985).

Existem consideráveis variações individuais na ocorrência e gravidade dos sintomas apresentados devido a inflamação após o trauma cirúrgico. A intensidade dos sintomas pode variar de acordo com a extensão do trauma, o que está diretamente relacionado ao grau de dificuldade cirúrgica (Rodrigues *et al.,* 2019). Na tentativa de minimizar os efeitos dos sinais inflamatórios, o uso de medicações é encorajado (Brucoli e*t al.,* 2019). A administração de antibióticos, analgésicos e anti-inflamatórios esteroidais ou não esteroidais com a intenção de melhorar a qualidade de vida do paciente no pós operatório, podem trazer efeitos colaterais, assim como existem contra indicações acerca do uso de tais medicações (Levent *et al.,* 2017; Iguchi *et al.,* 2020)

A busca por uma terapia que apresente menores efeitos colaterais, possua menos contra indicações e promova o reparo é constante em relação a cirurgia de terceiros molares. A crioterapia, laser de baixa potência, o uso de tapings e a terapia com ozônio são opções atuais de terapias complementares usadas no pós operatório de cirurgia de terceiros molares (Nascimento *et al*., 2019; Gozluklu *et al.,* 2020; Glória *et al.,* 2020; Asutay *et al.,* 2020). O ozônio medicinal melhora a circulação, a oxigenação tecidual, o metabolismo em geral, regula positivamente as enzimas antioxidantes e melhora a liberação de fatores de crescimento (Jacobs, 1982). Seu uso na cirurgia de terceiros molares inferiores traz benefícios associados aos mecanismos citados, sendo que a sua propriedade analgésica reduz a dor de forma considerável se comparado com a terapêutica tradicional sem a sua adição (Sivalighan *et al.,* 2017).

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Is ozone effective in reducing pain, edema and trismus after third molar surgery? A meta-analysis

Abstract

Objectives: This study aimed evaluate the efficacy of ozone therapy in reducing pain, swelling and trismus after lower third molar extraction.

Methods: The protocol was registered in PROSPERO. Six electronic databases (PubMed, Scopus, LILACS, SciELO, Embase, and Web of Science) were used. Open Gray and OATD were used to partially capture “gray literature” to minimize selection and publication bias. Only randomized clinical trials were included. The JBI tool was used to assess the risk of bias. A meta-analysis with a random effects model was performed, and the heterogeneity of the studies was evaluated with I^2 statistics. The GRADE tool was used to assess the quality of evidence and strength of the recommendations across the included studies.

Results: The search yielded 3,386 results, of which only 3 articles were eligible. Overall, individuals who received ozone reported lower pain scores compared to the control group (SMD = -2.12; 95% CI: -2.62; -1.61; $p < 0.001$). Individuals receiving ozone therapy could open their mouths 0.69 mm more than individuals in the control group. The evaluation of edema was divided into two types of measures: the distance from the tragus to the corner of the mouth (T-C) and the distance from the tragus to the pogonion (T-P). For T-C, the intervention group presented edema of 2.34 cm greater than the control group. For T-P, there was no difference between the groups.

Conclusions: The present studies present divergent results, although the use of ozone is promising for reducing postoperative pain; in terms of edema and trismus, ozone therapy was not considered effective.

Keywords: Ozone, Pain, Swelling, Trismus, Edema

1 INTRODUCTION

Lower third molar extraction is often associated with postoperative complications resulting from the inflammatory process (*Lago-Méndez et al*., 2007). Symptoms such as pain, edema and trismus are related to the complexity of the surgical procedure (*Pell and Gregory*, 1933) and individual characteristics of the patients (*Yuasa and Sugiura*, 2004). In general, painful symptoms after third molar removal are acute and may vary from moderate to severe (*Barden et al*., 2004). Pain reaches maximum intensity 5–6 h after the surgical procedure, continues for approximately 2 days, and gradually diminishes until the seventh day. Swelling reaches peak intensity in 12–48 h, resolving between the fifth and seventh days postoperatively. As the pain and swelling subside, trismus decreases (*LaPelusa and Dave*,2019). Postoperative complications negatively impact patient quality of life during the recovery period (*Chuang* et al., 2008). To address this, corticosteroids and nonsteroidal anti-inflammatory drugs are conventionally used as therapeutic strategies for symptom control. However, the majority of these drugs may manifest side effects such as gastrointestinal irritation, allergic reactions (*Bamgbose et al*., 2005), inhibition of platelet aggregation and increased bleeding time, especially in individuals with blood dyscrasias *(Arachchillage and Makris*, 2016).

Alternative therapies for the control of postoperative complications after impacted lower third molar extraction, such as cryotherapy (*Libonati et al*., 2019), low level laser therapy (*Bittencourt et al*., 2017) and ozone therapy (*Osunde et al*., 2014; *Ahmedi et al*., 2016), are recognized. Ozone therapy has been used for many years in medicine for the treatment of infections and orthopedic, pulmonary, hematological and neurodegenerative diseases (*Azarpazhooh et al*., 2009). Ozone can be administered parenterally or topically (*Bocci*, 2006) and is available as a gel, liquid or gas (*Sivalingam et al*., 2017). The therapeutic efficacy of ozone

therapy may be partly due to the controlled oxidative stress produced by the reactions of ozone with several biological components. In optimal doses, ozone can react with blood components and positively affect oxygen metabolism and cell energy, activating antioxidant defense systems (*Bocci,* 2004). Additionally, ozone influences the cellular and humoral immune system by stimulating the proliferation of immunocompetent cells and the synthesis of immunoglobulins. It also activates macrophages and increases the sensitivity of microorganisms to phagocytosis (*Shilpa et al*., 2013). In dentistry, ozone therapy has been used to treat caries (*Lim and Ngeow,* 2017), endodontic (*Ajeti et al.,* 2018) and periodontal diseases (*Walker et al.,* 1995), and temporomandibular joint dysfunction (*Dray,* 1995; *Domb,* 2014). In addition, this therapy has been used during maxillofacial surgery to promote hemostasis, enhance local oxygen supply (*Bianco et al.,* 2019) and minimize postoperative discomfort (*Jing,* 2018). Despite the versatility of ozone therapy, the clinical results reported in the literature are controversial regarding the reduction of postoperative complications after third molar extraction. Thus, this systematic review aims to answer the following question: Is local ozone useful in the control of pain, swelling and trismus after impacted lower third molar surgery?

2 METHODS AND MATERIALS

2.1 Protocol and registration

This systematic review was performed according to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes Protocols) recommendation list (*Moher et al.,* 2009) and Cochrane guidelines (*Higgins et al.,* 2018). The research protocol was registered in the Prospective International Register of Systematic Reviews (PROSPERO) (CDR [*Blinding*]).

2.2 Study design and eligibility criteria

The systematic review was designed to answer the guiding question based on the PICO strategy: Population (individuals submitted to impacted lower third molar extraction); Intervention (ozone therapy); Control (individuals not undergoing ozone therapy); and Outcome (pain, edema and trismus).

Only randomized controlled trials evaluating the influence of postoperative ozone therapy on pain, edema and trismus after impacted lower third molar surgery were included. The available quantitative data evaluating impacted third molars of similar difficulty, according to the classification proposed by Pell and Gregory (*Pell and Gregory*, 1933), were obtained. The search was unrestricted for year, language and publication status.

The following were excluded: 1) unrelated studies; 2) review studies, case reports, brief communications, observational studies, editorials or letters to the editor, monographs, conference summaries, and book / book chapters; 3) studies that included teeth other than the third molars; and 4) studies that included patients under 18 years of age.

2.3 Sources of information and search

The primary sources were the Embase, Latin American and Caribbean Health Sciences Literature (LILACS), PubMed (including MEDLINE), SciELO, Scopus and Web of Science databases. Open Gray and OATD were used to partially capture “gray literature”. In addition, a manual search was performed on the references of the articles eligible after the electronic search. All steps were performed to minimize selection and publication bias.

MeSH (medical subject headings), DeCS (health sciences descriptors) and Emtree (Embase subject headings) resources were used to select search descriptors according to the specificity of each database (Table 1). The bibliographic search was performed in February 2019. The records obtained were exported to EndNote Web™ software (Thomson Reuters™, Toronto, Canada), where duplicates were automatically removed. The remaining records were exported to Microsoft Word ™ 2010 (Microsoft ™ Ltd, Washington, USA), and the remaining duplicates were removed manually.

2.4 Study selection

First, as a calibration exercise, three reviewers discussed the eligibility criteria and applied them to a sample consisting of 20% of the records to determine interexaminer agreement. After obtaining an adequate level of agreement (Kappa ≥ 0.81), the selection of studies was performed in two stages, and the study titles and abstracts were methodically reviewed independently by

two eligibility reviewers (RPS and VLA), who were not blinded to the names of the authors and journals. Studies that did not answer the research question were deleted at this time. Studies whose titles corresponded to the study objectives but did not have available abstracts were fully analyzed.

In the second stage, the full texts of the eligible preliminary studies were obtained and evaluated to verify whether they met the eligibility criteria. When the two reviewers did not agree both in the first and second stage, a third reviewer (LRP) was consulted to make a final decision. The rejected studies were recorded separately, with the reasons for their exclusion made clear.

Table 1- Strategies for database search.

Database	Search Strategy (February, 2019)
PubMed **http://www.ncbi.nlm.nih.gov/pubmed**	(("Somatosensory Disorders" OR "Neurosensory Disorders" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Mouth Opening") AND ("Ozone" OR "Ozonotherapy" OR "O3" OR "Ozone Therapy"))
Scopus **http://www.scopus.com/**	(("Somatosensory Disorders" OR "Neurosensory Disorders" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Mouth Opening") AND ("Ozone" OR "Ozonotherapy" OR "O3" OR "Ozone Therapy"))
LILACS **http://lilacs.bvsalud.org/**	tw:(pain AND ozone) AND (instance:"regional") AND (db:("LILACS")) Trismus AND Ozone tw:(swelling AND ozone) AND (instance:"regional") AND (db:("LILACS")) edema AND ozone AND (instance:"regional") AND (db:("LILACS")) tw:(dolor AND ozono) AND (instance:"regional") AND (db:("LILACS")) [Spain] Trismo AND Ozono [Spain] tw:(edema AND ozono) AND (instance:"regional") AND (db:("LILACS")) [Spain]
SciELO **http://www.scielo.org/**	Pain AND Ozone Trismus AND Ozone Swelling AND Ozone Edema AND Ozone Dolor AND Ozono [Spain] Trismo AND Ozono [Spain] Edema AND Ozono [Spain]
Embase **http://www.embase.com**	('somatosensory disorders'/exp OR 'somatosensory disorders' OR 'neurosensory disorders' OR 'pain'/exp OR 'pain' OR 'edema'/exp OR 'edema' OR 'swelling'/exp OR 'swelling' OR 'trismus'/exp OR 'trismus' OR 'mouth opening'/exp OR 'mouth opening') AND ('ozone'/exp OR 'ozone' OR 'ozonotherapy' OR 'o3' OR 'ozone therapy'/exp OR 'ozone therapy')
Web Of Science **http://apps.webofknowledge.com/**	((("Somatosensory Disorders" OR "Neurosensory Disorders" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Mouth Opening") AND ("Ozone" OR "Ozonotherapy" OR "O3" OR "Ozone Therapy")))
OpenGrey **http://www.opengrey.eu/**	Pain AND Ozone Trismus AND Ozone Swelling AND Ozone Edema AND Ozone
Open Access Theses and Dissertations (OATD) **https://oatd.org/**	Pain AND Ozone Trismus AND Ozone Swelling AND Ozone Edema AND Ozone

2.5 Process of data collection and extraction

After they were selected, the articles were analyzed, and their data were extracted independently by two reviewers (RPS and VLA). The following information was collected: authors of the article, country and year of publication, sample number, mean age, dental position classification, anesthetic solution used, surgery time, postoperative drug protocol, ozone administration method, postoperative pain evaluation method, mouth opening evaluation method and edema assessment method.

To ensure consistency between the reviewers, a training exercise was conducted with both reviewers (RPS and VLA) in which information was extracted by both reviewers from the same eligible study. Any disagreement between the reviewers was resolved through discussion, and when these two reviewers could not reach an agreement, a third reviewer (LRP) was consulted to make a final decision. In case of doubt regarding the methodology or the results of the articles, the respective authors were contacted by e-mail.

2.6 Risk of individual bias of the studies

The risk of bias and the individual quality of the selected studies were assessed using the JBI Critical Appraisal Checklist for Randomized Controlled Trials tool (*Tufanaru et al,.* 2017). Two authors (RSP and WAV) independently assessed each study according to the PRISMA-P recommendations (*Moher et al.,* 2009). Any disagreements between the reviewers were resolved by discussing the evaluated items, and when these two reviewers could not reach an agreement, a third reviewer (LRP) was consulted to make a final decision.

Each study was categorized according to the percentage of positive answers obtained with the assessment tool. The risk of bias was considered high when the study obtained up to 49% of the answers were "yes"; moderate when the study obtained 50% to 69% “yes” answers and low when the study had more than 70% "yes" answers.

2.7 Summary results

The meta-analysis was performed using Stata software version 15.1 (StataCorp., College Station, TX, USA). Even though ozone was used in different

ways, with varying methods of application, all methods were pooled by the number of days after surgery for each of the three outcomes analyzed (pain, trismus, and swelling). Information about the preoperative period was described for trismus and swelling. Pooled standardized mean differences (SMD) were estimated by the method of Cohen using random-effect models. Swelling was assessed using two types of measurements; hence, the meta-analysis for this outcome were stratified according to the type of measure taken.

2.8 Quality of evidence collection

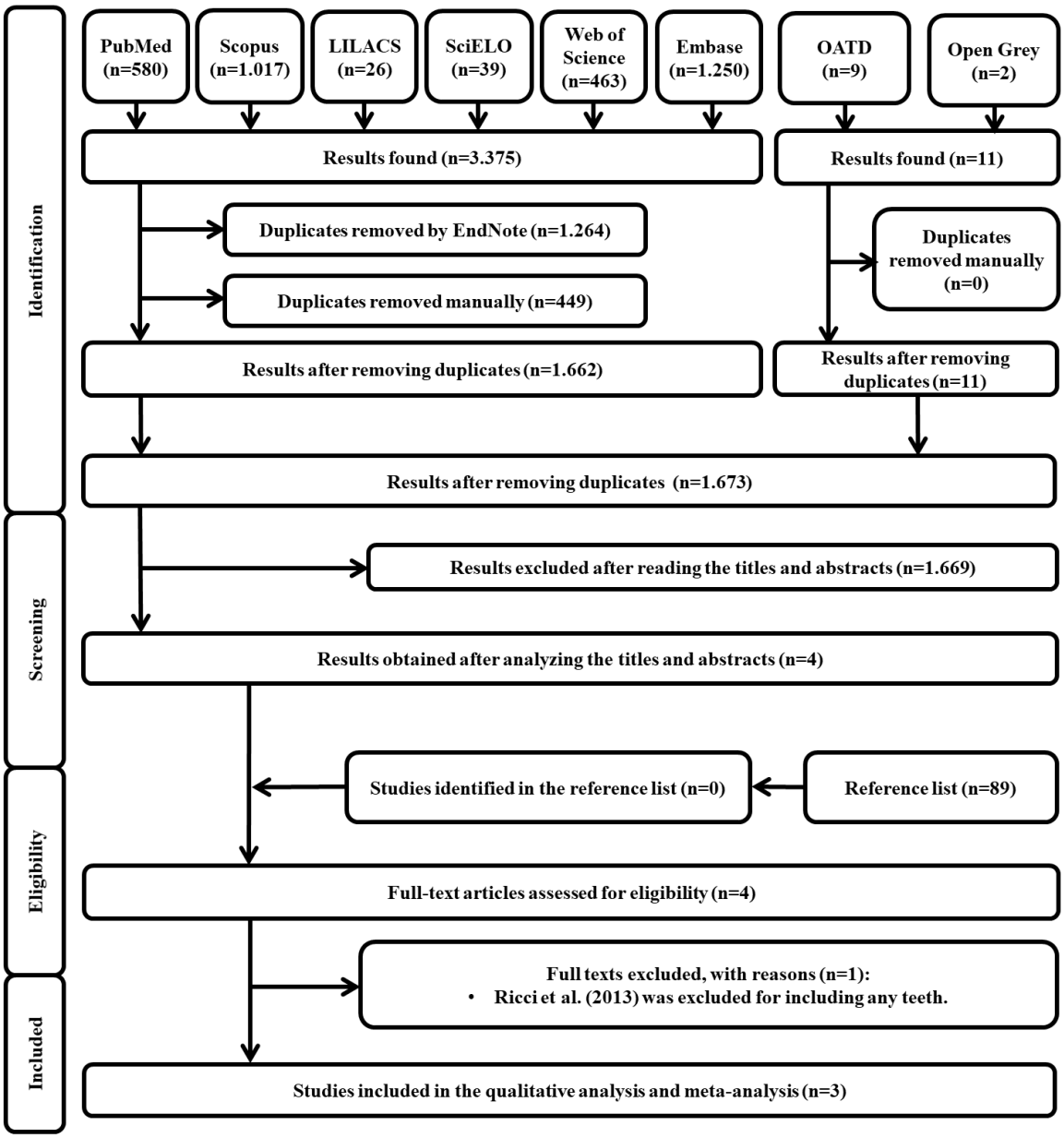
The quality of evidence and the strength of recommendation were assessed using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) tool (*Balshem et al.,* 2011). GRADE Pro GDT software (http://gdt.guidelinedevelopment.org) was used to summarize the results. This assessment was based on study design, methodological limitations, inconsistencies, indirect evidence, inaccuracies and other considerations. The quality of evidence was characterized as high, moderate, low or very low (*Balshem et al.,* 2011).

3 RESULTS

3.1 Study selection

During the first phase of the study selection, 3,386 records were found in eight electronic databases, including the gray literature. Following the removal of duplicate records, 1,673 proceeded to the review of titles and abstracts. After this analysis, only four records were eligible for full-text analysis. References from the four potentially eligible articles were carefully evaluated, and no additional records were selected; thus, there were a total of four studies for full-text reading. After reading the full text, one text was eliminated because it included the extraction of teeth other than the third molars. Thus, three studies were selected for qualitative and quantitative analysis. Figure 1 describes the search process and identification, inclusion and exclusion of the articles.

Figure 1. Flowchart of strategies used for the identification, screening and inclusion of studies in the systematic-adapted review of the PRISMA.



3.2 Characteristics of eligible studies

The studies were published between 2013 and 2017 and were conducted in India (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b) and Turkey (*Sivalingam et al.,* 2017). All three studies (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b; *Sivalingam et al.,* 2017) respected the established ethical parameters and collected consent forms from all volunteers who

participated in the study. Only one study (*Sivalingam et al.,* 2017) mentioned using CONSORT guidelines, and none reported registration in clinical trial databases.

The total sample included 133 patients who underwent impacted lower third molar extraction surgery. In all studies, the patients were prescribed anti-inflammatory medication postoperatively. Only one study (*Sivalingam et al.,* 2017) did not prescribe antibiotics postoperatively. The mean operation time ranged from 20 to 25 minutes. One study had a negative control group [30], and one study had a positive control group (*Sivalingam et al.,* 2017) (Table 2).

In two studies, ozone was applied in the masseter region on the 1st, 3rd, and 7th postoperative days by injecting ozone gas produced by a generator (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b). In the third study, ozone therapy was performed with the application of an ozone gel in the region of the socket where the surgery was performed, twice daily for 3 days after the surgical procedure (*Sivalingam et al.,* 2017). In all studies, postoperative pain was assessed using a visual analog scale (VAS). Trismus was assessed in all studies by measuring the maximal interincisal opening. Edema was measured as the distances from the tragus to the corner of the mouth (T-C) and from the tragus to the pogonion (T-P) in two studies generator (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b), and in one study (*Sivalingam et al.,* 2017), it was measured by the mean of the distances from the tragus to the corner of the mouth (T-C), from the tragus to the pogonion (T-P) and from the lateral corner of the eye to the lowest point of the mandible angle.

Table 2 - Summary of the main features of the eligible studies.

Author, country and year of publication	Sample (n)	Average age (Years)	Dental arrangement classification	Anesthetic solution used	Surgery time (minutes)	Postoperative medication protocol	Method of administration of ozone therapy	Postoperative pain assessment method	Mouth opening evaluation method	Edema assessment Method
Kazancioglu et al., 2013 Turquia	GC: 20 GE: 20	22.6 ± 2.3	Class III B (Pell and Gregory)	2.5% articaine hydrochloride + 1: 100.000 epinephrine	GC: 25 ± 11 GE: 22 ± 9	1 g amoxicillin and 550 mg oral naproxen sodium when needed.	The ozone generator was applied extraorally at the insertion point of the masseter muscle immediately after surgery and on the first, third and seventh postoperative day, with intensity of 80% for 10 seconds.	Visual analog scale (VAS)	Maximal interincisal opening	Measurements of the distances from the tragus to the corner of the mouth (T-C) and from the tragus to the pogonion (T-P)
Kazancioglu et al., 2014 Turquia	Control Side and Study Side (Split mouth method): 60 32 ♂ 28 ♀	22.6 ± 2.3	Class III B (Pell and Gregory)	2.5% articaine hydrochloride + 1: 100.000 epinephrine	GC: 25 ± 11 GE: 22 ± 9	1 g amoxicillin and 550 mg oral naproxen sodium when needed.	The ozone generator was applied extraorally at the insertion point of the masseter muscle immediately after surgery and on the first, third and seventh postoperative day, with intensity of 80% for 10 seconds.	Visual analog scale (VAS)	Maximal interincisal opening	Measurements of the distances from the tragus to the corner of the mouth (T-C) and from the tragus to the pogonion (T-P)
Sivalingam et al., 2017 India	Control Side and Study Side (Split mouth method): 33 16 ♂ 17 ♀	25.6 ± 4.4	+	2% lidocaine hydrochloride + 1: 80.000 adrenaline	GC: 20 ± 12 min GE: 22 ± 14 min	Ibuprofen 400 mg paracetamol (333 mg) three times daily for two days. 500 mg of amoxicillin and 400 mg of Flagyl every 8 hours for 5 days.[1]	Ozone gel was administered topically to the extraction site well twice daily for three days.	Visual analog scale (VAS)	Maximal interincisal opening	Mean measurements of the distance from the tragus to the corner of the mouth (T-C), from the tragus to the pogonion (T-P) and from the lateral corner of the eye to the lowest point of the mandible angle.

[1] Only the control group received antibiotic therapy
GC: Control side
GE: Study side

3.3 Risk of individual bias of the studies

Two studies generator (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b) showed a low risk of bias, and one study (*Kazancioglu et al.,* 2014a)

showed a moderate risk of bias. Detailed information on the risk of bias of the included studies can be found in Table 3. Item 1 was marked “Unclear” in two studies (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b), as the randomization method was not explicit. Only one study *Kazancioglu et al*., 2014b) made it clear that patients were blinded to the group in which they were allocated, so two studies (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b) were marked as “No” for item 4. Item 5 was marked “No” in one study (*Sivalingam et al.,* 2017) because the author who performed the surgery also applied the ozone gel topically (Table 3).

Table 3 - Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for Randomized Controlled Trials [50].

Authors	Q. 1	Q. 2	Q. 3	Q. 4	Q. 5	Q. 6	Q. 7	Q. 8	Q. 9	Q.1 0	Q.1 1	Q.1 2	Q.1 3	% yes / risk
Kazancioglu et al., 2013	U	U	√	--	U	√	√	√	√	√	√	√	--	62% yes/ moderate risk of bias
Kazancioglu et al., 2014	U	√	√	√	√	√	√	√	√	√	√	√	√	92% yes/ low risk of bias
Sivalingam *et al*., 2017	√	√	√	--	--	√	√	√	√	√	√	√	√	85% yes/ low risk of bias

Q1. Was true randomization used for assignment of participants to treatment groups? Q2. Was allocation to treatment groups concealed? Q3. Were treatment groups similar at the baseline? Q4. Were participants blind to treatment assignment? Q5. Were those delivering treatment blind to treatment assignment? Q6. Were outcomes assessors blind to treatment assignment? Q7. Were treatment groups treated identically other than the intervention of interest? Q8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Q9. Were participants analyzed in the groups to which they were randomized? Q10. Were outcomes measured in the same way for treatment groups? Q11. Were outcomes measured in a reliable way? Q12. Was appropriate statistical analysis used? Q13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?; √ - Yes; -- - No; U – Unclear.

3.4 Results of eligible studies

All studies evaluated pain, trismus and edema after the surgical procedure. Regarding postoperative pain, in all studies (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b; *Sivalingam et al.,* 2017), the highest values were found on the first day after surgery, and the lowest values were found seven days after surgery for both the control and ozone groups. On the first day, pain scores

ranged from 7.48 to 8.42 in the control group and from 4.22 to 5.45 in the experimental group. On the seventh day, the scores ranged from 0.94 to 2.33 in the control group and from 0.06 to 0.89 in the experimental group (Table 4).

Table 4 - Summary of pain assessment scores from the first to the seventh postoperative day.

Author	Group	Score			
		1st Day	3st Day	5st Day	7st Day
Kazancioglu et al., 2013	Control	8.42 ± 1.40	5.81 ± 1.32	*	2.33 ± 1.26
	Experimental	4.62 ± 3.12	2.49 ± 1.15	*	0.81 ± 0.32
Kazancioglu et al., 2014	Control	7.52 ± 2.43	5.76 ± 1.24	4.42 ± 1.51	2.30 ± 1.26
	Experimental	4.22 ± 3.32	2.39 ± 1.55	1.62 ± 0.24	0.89 ± 0.65
Sivalingam et al., 2017	Control	7.48	5.15	*	0.94
	Experimental	5.45	2.97	*	0.06

* Data not measured by the authors.

For trismus, in all studies, the lowest values of mouth opening were observed on the first day, and the highest values were observed on the seventh day (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b; *Sivalingam et al.,* 2017), regardless of the group. On the first day, the values ranged from 21.61 mm to 32.4 mm in the control group and from 25.1 mm to 31.9 mm in the experimental group. On the seventh day, the values ranged from 37.3 mm to 41.48 mm in the control group and from 36.8 mm to 46.64 mm in the experimental group (Table 5).

Table 5 - Summary of scores for preoperative mouth opening on the seventh postoperative day.

Author	Evaluation Method	Group	Score (mm)				
			Preoperative	1st Day	3st day	5st day	7st day
Kazancioglu et al., 2013	Maximal interincisal opening	Control	41.1 ± 2.2	22.1 ± 4.6	27.4 ± 7.3	*	37.3 ± 5.2
		Experimental	41.3 ± 3.2	25.1 ± 4.2	29.3 ± 3.5	*	38.6 ± 7.2
Kazancioglu et al., 2014	Maximal interincisal opening	Control	42.1 ± 2.6	32.4 ± 5.4	35.4 ± 8.3	38.9 ± 3.5	40.9 ± 2.3
		Experimental	43.3 ± 4.2	31.9 ± 4.4	36.3 ± 2.5	39.6 ± 4.6	41.1 ± 4.6
Sivalingam et al., 2017	Maximal interincisal opening	Control	47.03	21.61	29.33	*	41.48
		Experimental	47.21	29.27	35.61	*	45.64

* Data not measured by the authors.

Regarding edema, only two studies that had the same outcome measurement method were considered for this meta-analysis (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b). While these studies provided individual measures of the distance between the tragus to the commissure (T-C) and pogonium (T-P), respectively, (*Sivalingam et al.,* 2017) used, in addition to these measurements, the distance between the lateral corner of the eye and the lowest point of the mandibular angle. On the first day, the T-C values ranged from 12.11 cm to 14.11 cm in the control group and from 12.95 cm to 14.41 cm in the experimental group. Additionally, the T-P values ranged from 16.02 cm to 18.22 cm in the control group and from 16.30 cm to 18.33 m in the experimental group. On the seventh day, the T-C values ranged from 11.44 cm to 12.44 cm in the control group and from 11.81 cm to 12.81 cm in the experimental group. Additionally, the T-P values ranged from 16.41 cm to 15.32 cm in the control group, and in the experimental group, both presented a final value of 15.35 cm (Table 6).

Table 6 - Summary of scores for the evaluation of preoperative edema on the seventh postoperative day.

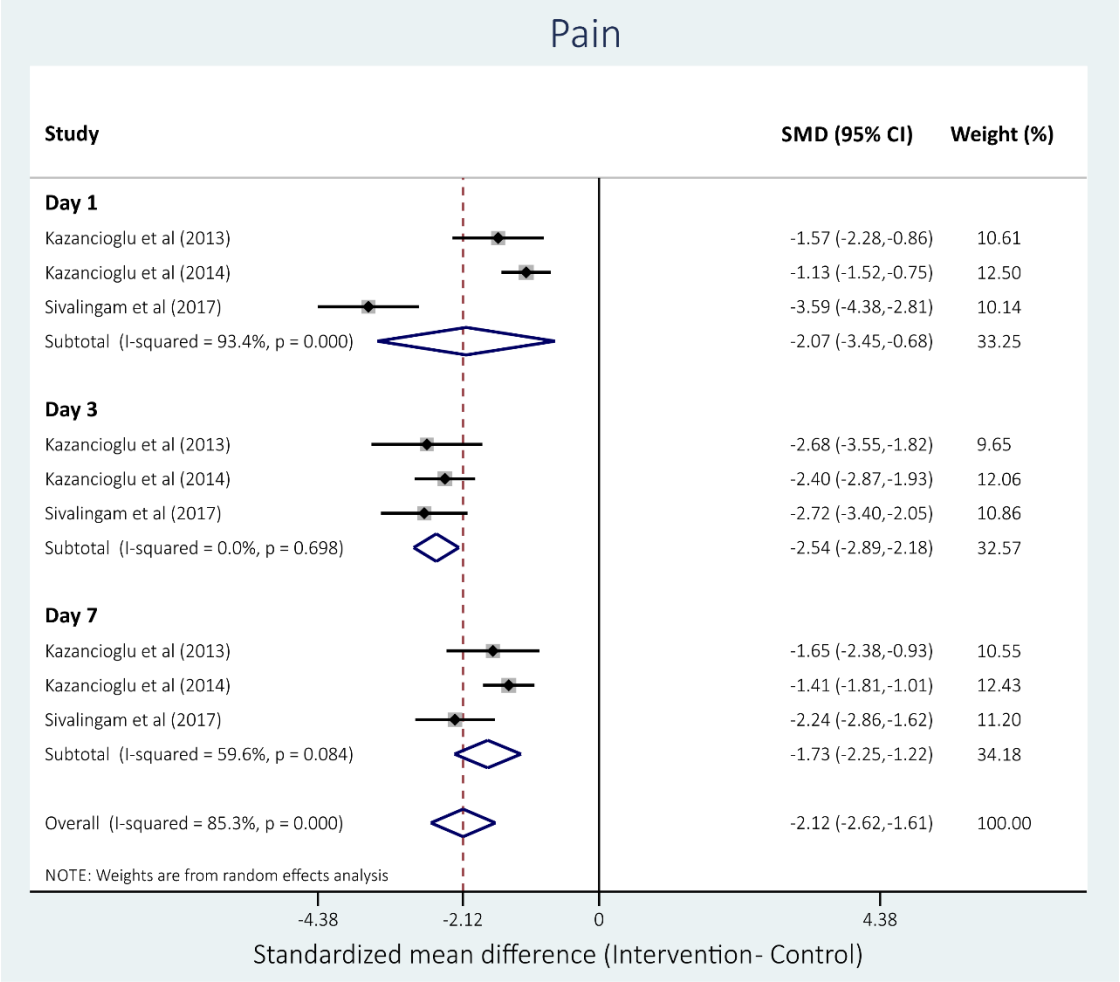
Author	Sample	Method	Score (cm)				
			Preoperative	1st Day	3st Day	5st Day	7st Day
Kazancioglu et al., 2014	Control N=20	T-C	12.22 ± 0.21	14.11 ± 0.25	13.01 ± 0.42	*	12.44 ± 0.32
		T-P	16.33 ± 0.31	18.22 ± 0.35	17.01 ± 0.80	*	16.41 ± 0.35
	Experimental N=20	T-C	11.35 ± 0.41	14.41 ± 0.11	14.76 ± 0.14	*	12.81 ± 0.67
		T-P	15.24 ± 0.10	18.33 ± 0.34	18.21 ± 0.50	*	15.35 ± 0.34
Kazancioglu et al., 2014	Control N=60	T-C	11.34 ± 0.34	12.11 ± 0.23	12.01 ± 0.65	11.94 ± 0.22	11.44 ± 0.87
		T-P	15.23 ± 0.29	16.02 ± 0.84	16.01 ± 0.82	15.75 ± 0.11	15.32 ± 0.20
	Experimental N=60	T-C	11.35 ± 0.41	12.95 ± 0.11	12.76 ± 0.14	12.01 ± 0.85	11.81 ± 0.67
		T-P	15.24 ± 0.10	16.30 ± 0.33	16.21 ± 0.50	15.95 ± 0.12	15.35 ± 0.34
Sivalingam et al., 2017	Control N=33	**	*	141.48	127.39	*	112.58
	Experimental N=33	**	*	123.09	113.88	*	104.55

* Data not measured by the authors. ** Method used: Postoperative (AC + AD + BE) - Preoperative (AC + AD + BE): T-C: Tragus to mouth commissure; T-P: Tragus to the pogonion; AC: Most posterior point of the tragus to the commissure of the mouth; AD: Most posterior point of the tragus to the soft tissue of the pogonion; BE: Lateral corner of the eye to the lowest point of the mandible angle.

3.5 Synthesis of results and supplemental analysis

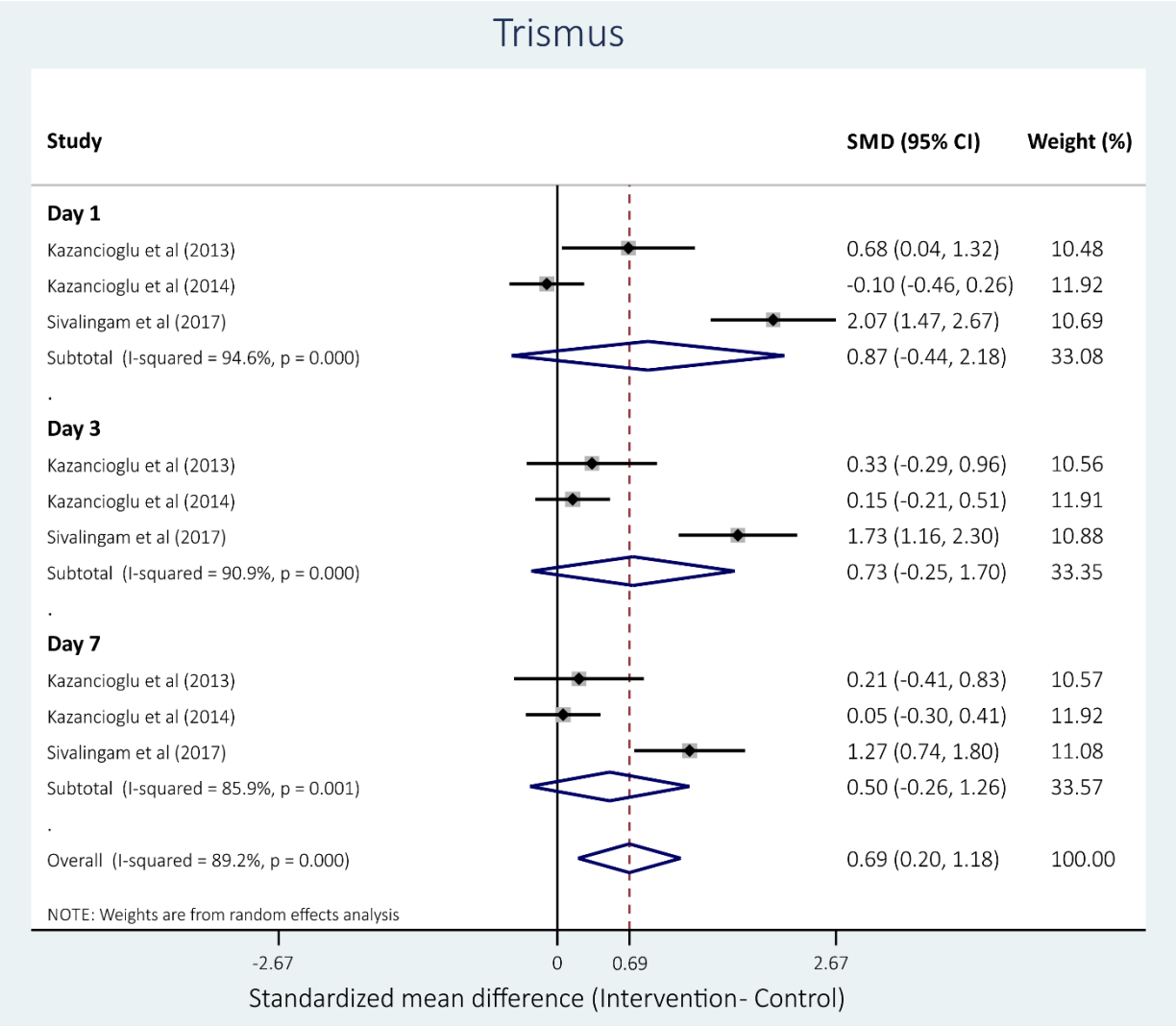
Three studies provided data on postoperative pain, assessing scores of pain on the first, third and seventh days after surgery (see Figure 2). High heterogeneity was observed among the pain scores on the first day after surgery (I^2 = 93.4%). Overall, individuals from the intervention group reported lower pain scores compared to the control group (SMD = -2.12; 95% CI: -2.62; -1.61; $p < 0.001$). The greatest difference occurred three days after surgery, when the pain score for the intervention group was 2.54 lower than that of the control group (95% CI: -2.89; -2.18).

Figure 2. Forest plot comparing postoperative pain levels between the study and control groups in the eligible studies.



Trismus was assessed by millimeters of mouth opening. There was no significant difference between the intervention and control groups at any time points (Figure 3). However, the overall estimate showed that individuals receiving ozone therapy could open their mouths 0.69 mm more than the control group.

Figure 3. Forest plot comparing mouth opening during the postoperative period between the study and control groups in the eligible studies.



Data on swelling were available for only two studies and were divided into two types of measures: i) the distance (in cm) from the tragus to the corner of the mouth (T-C) (Figure 4) and ii) the distance (in cm) from the tragus to the pogonion (T-P) (Figure 5). Analyzing the T-C measurement, it was possible to see that the swelling of individuals who received the ozone therapy was 2.34 cm greater (95% CI: 1.05; 3.63) than that of the control group. Regarding the T-P measurement, there was no difference in swelling between the intervention and control groups.

Figure 4. Forest plot comparing postoperative edema, as measured by the distance in centimeters from the tragus to the corner of the mouth, in the two studies with available data.

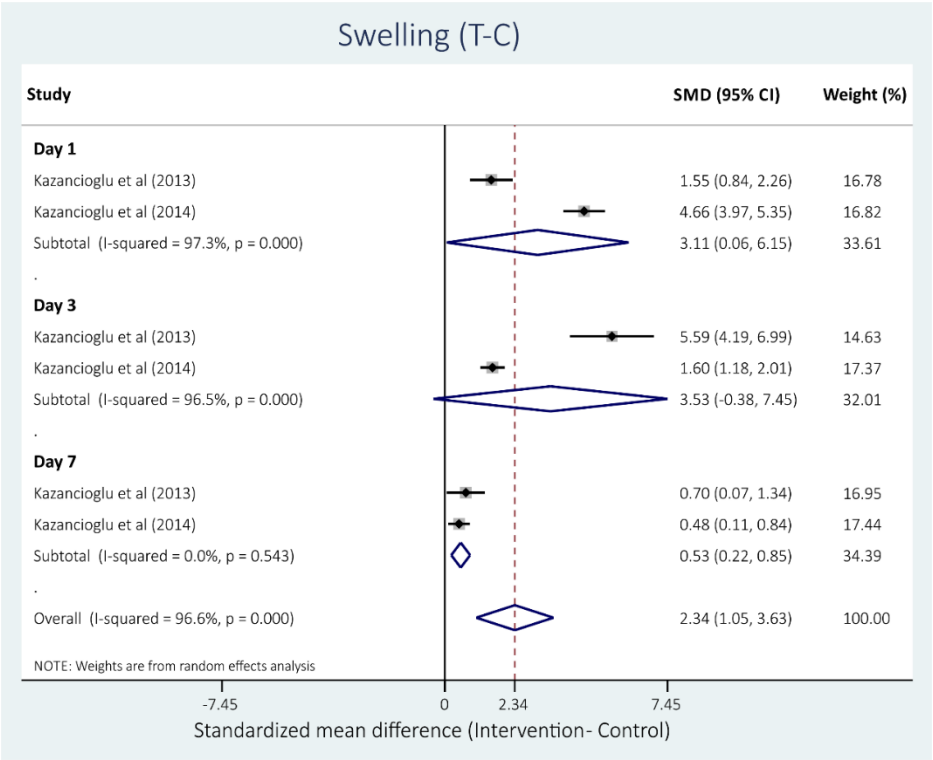
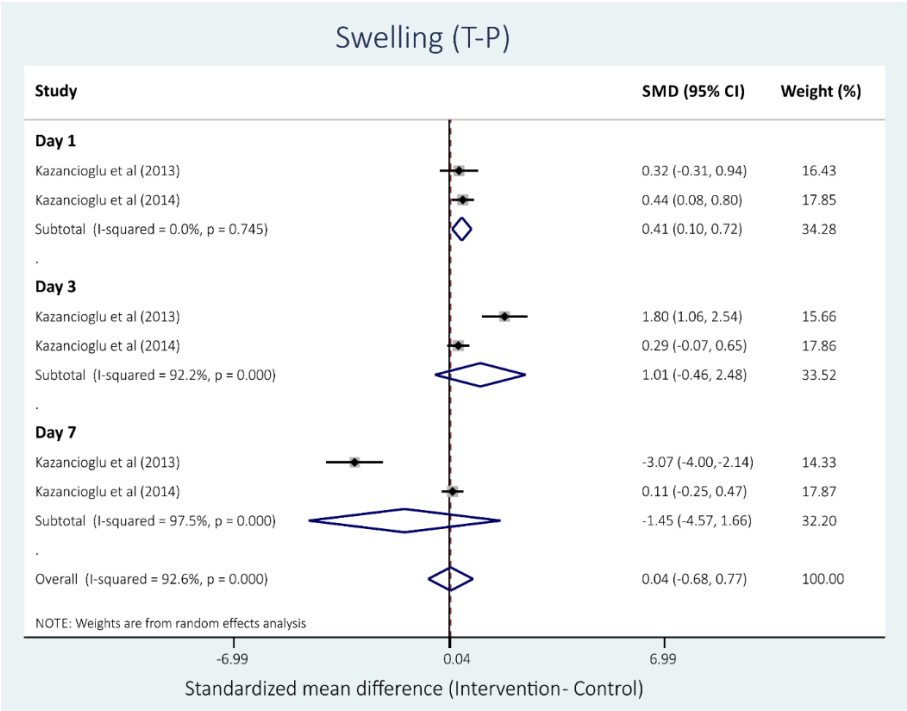


Figure 5. Forest plot comparing postoperative edema, as measured by the distance in centimeters from tragus to pogonion, in the two studies with available data.



3.6 Certainty of evidence

Three outcomes were assessed with the GRADE tool (*Balshem et al.,* 2011). All outcomes were classified as having low levels of evidence, which means the true effect may be substantially different from the estimated effect. Table 7 shows more details for each outcome.

Table 7. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Summary of Findings Table for the Outcomes of the Systematic Review.

Certainty assessment							Summary of results	Impact	Certainty	Importance
Nº of studies	*Study design*	*Risk of bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Other considerations*	**Effect random-effect models (95% CI)**			
Postoperative pain (follow up: range 1 days to 7 days)										
3	randomi zed trials	Serious [1]	Serious [2]	not serious	not serious	none	Day 1: -2.07 (-3.45 - -0.68) Day 3: -2.54 (-2.89 – -2.18) Day 7: -1.73 (-2.25 - -1.22)	In all eligible studies it was observed that ozone therapy was effective in reducing postoperative pain compared to the control group.	⊕⊕ LOW	CRITICAL
Mouth opening (follow up: range 1 days to 7 days)										
3	randomi zed trials	Serious [1]	Serious [2]	not serious	not serious	none	Day 1: 0.87 (-0.44 – 2.18) Day 3: 0.73 (-0.25 – 1.70) Day 7: 0.50 (-0.26 – 1.26)	The results found in the eligible studies were divergent, since in tw o eligible studies there was a difference between the experimental group and the control group and in one study these results were not found.	⊕⊕ LOW	CRITICAL
Edema (follow up: range 1 days to 7 days)										
2	randomi zed trials	Serious [1]	Serious [2]	not serious	not serious	none	Day 1: T-C: 3.11 (0.06 – 6.15) T-P: 0.41 (0.10 – 0.72) Day 3: T-C: 3.53 (-0.38 – 7.45) T-P: 1.01 (-0.46 – 2.48) Day 7: T-C: 0.53 (0.22 – 0.85) T-P: -1.45 (-4.57 – 1.66)	The results found in the eligible studies were divergent, since in two eligible studies there was a difference between the experimental group and the control group and in one study these results were not found.	⊕⊕ LOW	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
[1]Studies have not made it clear about operator and participant blindness; [2] The route of administration of ozone varied among eligible studies.

4 DISCUSSION

Repair is a phenomenon that occurs to reconstruct traumatized tissues and involves cells and numerous chemical mediators. It consists of orderly events initiated at the moment of trauma and lasts for variable periods (*Jing,* 2018). Optimizing and speeding up the repair process to restore tissue physiology is always a challenge. Impacted third molar extraction is one of the most common procedures and is often associated with painful symptomatology, edema and dysfunction, which may be transient or permanent and cause considerable deterioration of the patient's quality of life (*McGraft et al., 2003;Lim et al.,* 2017). The causes are complex and are closely related to the inflammatory process initiated by the surgical act (*Nenman et al.,*1979*; Yuasa 24et al.,* 2004*;Kumar et al.,* 2015*; Elvis and Ekta,* 2011).

The ideal agent to reduce postoperative complications after third molar surgery would alleviate pain, minimize swelling and trismus, promote healing and have no unwanted effects. This systematic review and meta-analysis investigated the efficacy of ozone for pain, swelling and trismus control after impacted mandibular third molar surgery. The results showed a beneficial effect of ozone in relieving pain. However, swelling was greater in patients using ozone therapy than in the control patients, and no statistically significant difference was observed between the two groups with respect to trismus.

Ozone therapy has already been successfully used to reduce pain in several situations: temporomandibular disorders (*Domb,* 2014), gingival grafts (*Tasdemir et al.,* 2016), fibromyalgia (*Tirelli et al.,* 2019), chronic wounds (*Fitzpatrick et al.,* 2018) and back pain (*Doğan et al.,* 2014; *Bocci et al.,* 2015). The action of ozone on pain is related to the capability to control oxidative stress (*Domb,* 2014*; Smith et al.,* 2017*; Tirelli et al.,* 2019). Although this is not the focus of the present work, the molecular mechanisms of ozone action might be of particular importance to understand our results. In a safe and correct dose, ozone represents a nondeleterious acute oxidative stress that induces an antioxidant cellular response, normalizing the existing redox blister in several diseases, with evident contribution to pain control.

The anti-inflammatory effects of ozone have been studied principally in animal models. *In vivo* experiments revealed the inhibition of inflammatory mediators (prostaglandin, interleukin and tumor necrosis factor) and the increase of macrophage and leukocyte activities (*Azarpazhooh et al.,* 2009; *Cho et al.,* 2017). In topical applications, ozone has anti-algic and anti-inflammatory properties, acting as a neurochemical mediator of painful sensations. In addition, it is used as an adjunct in the treatment of chronic pain and promotes inhibition of cyclooxygenase II by causing a reduction in hyperpermeability, edema and pain (*Seidler et al.,* 2008). Some of these effects can justify the improved pain relief after ozone application when compared to conventional postoperatory third molar surgery.

However, this does not clarify the absence of differences in swelling and trismus. Considering that postoperative swelling following third molar surgery is also due to inflammatory processes triggered by manipulation of soft tissues and bone removal (*Feslihan et al.,* 2019), it was expected that the reduction in pain

would come with a reduction in edema. The measurements of edema showed low scores for both groups, indicating acceptable edema control.

Considering that the degree of edema is directly proportional to the complexity of the surgery (*Chuang et al.,* 2008), patients with impacted teeth of a similar difficulty index were chosen, and the operative time was kept comparable to negate intergroup bias in the studies included in this review. Even though these cautions have been used, only two studies that had the same outcome measurement methods were considered to evaluate edema, which represents an important source of bias for this outcome.

The results on swelling can also be linked to the form of ozone used. In dentistry, ozone therapy consists of injections of low concentration ozone gas or topical application of ozonated gel or oil (*Domb,* 2014*; Cho et al.,* 2017). The included studies promote different forms of ozone therapy – injection of ozone gas (*Kazancioglu et al.,* 2014a; *Kazancioglu et al*., 2014b) or topically applied ozone gel (*Sivalingam et al.,* 2017). These differences, combined with the fact that not all studies used a sham group as a control, led us to believe that problems in experimental design contributed to the lack of significant difference.

Trismus is a complication that is directly associated with the surgical time, and the more complex the surgical technique, as in cases where there is a need to perform ostectomy and odontosection, the greater the chance of postoperative complications. It is interesting to note that although improvements were found for both early and late postoperative trismus regardless of therapy, the clinical significance must be assessed. Consequently, the improvements in mouth opening with the use of ozone that were reported in the present systematic review may not amount to a meaningful benefit to the patient. Additionally, the heterogeneity of the included studies may partially be explained by the method for determining maximum mouth opening; for example, whether the measurements were taken when pain was first felt or when the maximum interincisal distance was achieved could influence the results but was not described by any of the authors.

It is also important to consider that pain intensity, degree of inflammation and trismus are usually subjective and show a range of variation among patients. Other factors thought to influence the incidence of complications after third molar removal include age, sex, medical history, oral contraceptives, presence of

pericoronitis, poor oral hygiene, smoking, type of impaction, relationship of third molar to the inferior alveolar nerve, surgical time, surgical technique, surgeon experience, use of perioperative antibiotics, use of topical antiseptics, use of intrasocket medications, and anesthetic technique (C*ho et al.,* 2017). Furthermore, the current meta-analysis also had some limitations. First, the number of studies for some parameter analyses was small, which might lessen the statistical power. Almost all of the included studies presented some positive results. Additionally, two of three studies were developed by the same research group. Hence, one may speculate whether clinical trials on the effect of ozone therapy after third molar surgery have not been conducted or whether the studies with negative results have not been published. Second, the studies exhibited significant heterogeneity. Different study types, scales of measurement, time intervals, and surgical protocols are possible explanations for the heterogeneity. Third, despite the existence of tools to examine publication bias, the small number of studies precluded any attempt to carry out statistical and visual evaluations of publication bias. Egger's test, which would provide a statistical assessment of publication bias, is discouraged when the number of estimates is smaller than 20, and visual interpretation of a funnel plot could misrepresent the actual findings. Finally, one should bear in mind the methodological issues found in the study (*Kazancioglu et al.,* 2014a). As these limitations might have undermined the authors' findings, the results from our meta-analyses should be carefully considered in the clinical setting. This is further supported by the GRADE assessment, which classified the quality of the evidence as "low" for all three outcomes due to the combination of methodological issues and high heterogeneity among studies. In fact, our results provide evidence on the need for well-designed clinical trials to assess the real effect of ozone therapy on postoperative outcomes after third molar surgery. The strengths of this review should also be highlighted. This is the first systematic literature review on the use of ozone therapy in impacted third lower molar removal surgery. Moreover, the extensive search in different databases, without a restriction on the year and language of publication, and the use of "gray literature", considerably minimizes the risk of study selection bias. The use of GRADE and "The Joanna Briggs Institute Critical Appraisal Tools for Use in JBI Systematic Reviews" to assess the quality of evidence and the methodological quality of the studies, respectively,

demonstrates the rigor with which the data from the eligible studies were collected.

5 CONCLUSION

Current studies on the subject have a low level of evidence and divergent results. Although the use of ozone therapy to reduce postoperative pain was promising, in relation to edema and trismus, ozone therapy was not considered effective. Thus, further randomized clinical trials are needed. Given the limited evidence, dentists should carefully evaluate the addition of this therapy after impacted lower third molar surgery.

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