UNIVERSIDADE FEDERAL DE SERGIPE
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

EFICÁCIA DA CRIOTERAPIA NA REDUÇÃO DA DOR, EDEMA E TRISMO APÓS CIRURGIA DE TERCEIROS MOLARES: REVISÃO SISTEMÁTICA E META-ANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS

Aracaju
Janeiro / 2019

EDMUNDO MARQUES DO NASCIMENTO JUNIOR

EFICÁCIA DA CRIOTERAPIA NA REDUÇÃO DA DOR, EDEMA E TRISMO APÓS CIRURGIA DE TERCEIROS MOLARES: REVISÃO SISTEMÁTICA E META-ANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS

Dissertação apresentada ao Programa de Pós-graduação em Odontologia da Universidade Federal de Sergipe, para obtenção do título de Mestre em Odontologia.

Orientador: Prof. Dr. Paulo Ricardo S. Martins Filho

Aracaju

Janeiro / 2019

FICHA CATALOGRÁFICA ELABORADA PELA BIBLIOTECA BISAU
UNIVERSIDADE FEDERAL DE SERGIPE

N244e

Nascimento Junior, Edmundo Marques do
Eficácia da crioterapia na redução da dor, edema e trismo após cirurgia de terceiros molares: revisão sistemática e meta-análise de ensaios clínicos randomizados / Edmundo Marques do Nascimento Junior ; orientador Paulo Ricardo S. Martins Filho. – Aracaju, 2018.
42 f. : il.

Dissertação (mestrado em Odontologia) – Universidade Federal de Sergipe, 2018.

1. Crioterapia. 2. Cirurgia bucal. 3. Dor. 4. Edema. 5. Trismo. I. Martins Filho, Paulo Ricardo S., orient. II. Título.

CDU 616.314

CRB-5: SE-001850/O

Especialmente a **Deus**, por me dar forças, paciência e determinação nessa etapa tão importante de minha formação profissional.

Aos meus amores **Letícia e Kamilla**, grandes inspirações, por suportarem minha ausência, pela paciência e boa vontade, e por todo o apoio em todos os momentos.

Ao meus pais, **Telma e Edmundo**, exemplos de vida, de superação, os maiores responsáveis pela pessoa e profissional que me tornei.

AGRADECIMENTOS

Ao querido amigo e professor **Paulo Ricardo Saquete Martins Filho**, meu orientador, por toda paciência, ajuda e oportunidades ao longo de todo o curso. Muito obrigado por confiar e acreditar em mim. Foi uma experiência inacreditável !

A **todos os professores do Programa de Pós-Graduação em Odontologia**, pelo excelente conteúdo ministrado. Apesar de toda dificuldade, vocês fizeram a diferença.

Aos professores **André Luís Faria e Silva** e **Liane Maciel de Almeida Souza**, especialmente, pelas oportunidades que me deram em suas linhas de pesquisa. Foi um enorme prazer ajuda-los e aprender com vocês.

Ao amigo e professor **Bernardo Brasileiro**, que me aceitou como estagiário docente e sempre esteve disponível para ajudar.

Aos **amigos do mestrado**, pela convivência harmoniosa e alegre. Meus sinceros agradecimentos.

A **Maíra**, secretária do PRODONTO, por toda paciência e ajuda ao longo do curso.

Ao querido amigo **Thiago Santana**, que inicialmente me incentivou a participar da seleção dessa pós-graduação. Muito obrigado pela força e orientação inicial.

Ao meu eterno mestre e amigo, o Prof. **Paulo José Medeiros**, que sempre me incentivou, apoiou e ajudou, não apenas no tempo em que estive na Universidade do Estado do Rio de Janeiro, mas também por todo o tempo até os dias de hoje.

RESUMO

A remoção de terceiros molares é um procedimento rotineiro em cirurgia buco-maxilo-facial e está normalmente relacionado a complicações como dor, edema e trismo no pós-operatório, interferindo na qualidade de vida dos pacientes. O controle da inflamação pós-operatória se torna, então, de fundamental importância e tem sido realizado de diversas maneiras, sendo a crioterapia bastante comum como coadjuvante. A literatura carece de evidências sobre a eficácia da crioterapia no controle da dor, edema e trismo após a remoção de terceiros molares. O objetivo desse estudo foi investigar essa eficácia, através de uma revisão sistemática e meta-análise de ensaios clínicos randomizados (ECRs). Uma pesquisa foi realizada no PubMed, Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS, Science Direct, Google Scholar, OpenThesis e ClinicalTrials.gov, até junho de 2018. As palavras-chave incluíram *cryotherapy*, *third molars* e *wisdom teeth*. Os critérios de elegibilidade foram: (1) população: pacientes submetidos à remoção de terceiros molares; (2) intervenção e controles: utilização de crioterapia *versus* não utilização de crioterapia; (3) desfechos: o desfecho primário foi dor pós-operatória e os desfechos secundários foram edema e trismo; (4) tipo de estudo: ECRs. Dois revisores extraíram os dados e avaliaram a qualidade dos estudos de acordo com as diretrizes da Cochrane para ECRs. Os efeitos do tratamento foram definidos como diferença de média ponderada (WMD) ou diferença média padronizada (SMD) e intervalos de confiança de 95% (IC) foram estabelecidos. A força da evidência foi analisada usando o sistema de classificação GRADE (Grading of Recommendations Assessment, Development, and Evaluation). Para calcular os tamanhos de efeito, médias e desvios padrão (DP) foram obtidos para cada grupo de estudo e desfechos de interesse. Seis ECRs foram incluídos na meta-análise. Diferenças na intensidade da dor foram encontradas no segundo (WMD -0,72, IC 95% -1,45 a 0,01, p = 0,05, I^2 = 0%) e terceiro (WMD -0,36, IC 95% -0,59 a -0,13, p = 0,002, I^2 = 0%) dias de pós-operatório. Nenhuma evidência foi encontrada de que a crioterapia foi eficaz na redução do trismo e edema após a cirurgia de terceiros molares. Apesar da melhora nos níveis de dor quando utilizada a crioterapia, a qualidade da evidência foi considerada baixa.

Palavras-Chaves: Crioterapia; cirurgia bucal; dor; edema; trismo.

ABSTRACT

Third molars removal is a routine procedure in oral and maxillofacial surgery and is usually related to postoperative complications such as pain, edema and trismus, interfering in patients' quality of life. Controling postoperative inflammation then becomes important and has been performed in several ways, with cryotherapy being quite common as a supporting method. There is a lack of evidence on the efficacy of cryotherapy to control pain, edema and trismus after third molars removal. The aim of this study was to investigate this efficacy through a systematic review and meta-analysis of randomized clinical trials (RCTs). We searched PubMed, Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Google Scholar and OpenThesis to select RCTs from inception to June 2018. The search string included *cryotherapy*, *third molars*, and *wisdom teeth*. The eligibility criteria were: (1) population: patients submitted to removal of impacted third molars; (2) intervention and control: postoperative cryotherapy *versus* no cold therapy; (3) outcomes: primary outcome was postoperative pain and secondary outcomes were facial swelling and trismus; (4) study type: RCTs. Eligible studies must had reported at least one of the outcomes of interest. Two reviewers selected studies, extracted data and assessed study quality according to Cochrane guidelines for RCTs. We used either the weighted mean difference (WMD) or the standardized mean difference (SMD) as effect measures and a 95% confidence intervals (CI). The strength of evidence was measured using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating system. To calculate the effect sizes, means and standard deviations (SD) were obtained for each study group and outcome of interest. Six RCTs were included in the meta-analysis. Differences in pain intensity were found in the second (WMD -0.72, 95% CI 1.45 to 0.01, p = 0.05, I2 = 0%) and third (WMD -0.36, 95% CI % -0.59 to -0.13, p = 0.002, I2 = 0%) postoperative days. No evidence was found that cryotherapy was effective in reducing trismus and edema after third molar surgery. Despite the improvement in pain levels when cryotherapy was used, the quality of the evidence was considered low.

Keywords. Cryotherapy; oral surgery, pain, edema, trismus.

SUMÁRIO

1 INTRODUÇÃO

A remoção dos terceiros molares está frequentemente associada a complicações pós-operatórias, como dor, edema e trismo (LAUREANO FILHO et al., 2005; DE SANTANA-SANTOS et al., 2013; ALTIPARMAK et al., 2018). Essas complicações surgem da resposta inflamatória, que é uma consequência direta e imediata do procedimento cirúrgico, e podem causar limitação de função, e comprometimento da qualidade de vida dos pacientes (MCGRATH et al., 2003; GROSSI et al., 2007).

Muitos métodos têm sido utilizados no controle das complicações relacionadas à remoção de terceiros molares e incluem a administração de enzimas proteolíticas (AL-KHATEEB & NUSAIR, 2008; SINGH et al., 2016), drenos cirúrgicos (CERQUEIRA et al., 2004; KOYUNCU et al., 2015), crioterapia (LAUREANO FILHO et al., 2005; ZANDI et al., 2016), medicamentos anti-inflamatórios e analgésicos (BAMGBOSE et al., 2006; BUYUKKURT et al., 2006; MAJID & MAHMOOD, 2011; ATKINSON et al., 2015; ZERENER et al., 2015) e laser de baixa intensidade (FERRANTE et al., 2013). Os anti-inflamatórios não-esteroidais (AINEs) são amplamente utilizados para controlar a dor e a inflamação, mas estão associados a efeitos colaterais gastrointestinais e eventos aterotrombóticos (KEARNEY et al., 2006; BAIGENT et al., 2013). O uso de corticosteroides, que atuam nos mediadores da inflamação responsáveis pelo exsudato vascular e edema, tem aumentado nos últimos anos, raramente resultando em efeitos colaterais de curto prazo (HERRERA-BRIONES et al., 2013; NGEOW & LIM, 2016).

A aplicação do gelo para fins terapêuticos é um método simples, de baixo custo e de fácil aplicação, tradicionalmente utilizado como coadjuvante no controle do edema e desconforto após procedimentos cirúrgicos intraorais (FOROUZANFAR et al., 2008). A crioterapia inclui diversas técnicas, como compressa de gelo, massagem com gelo, embalagens de gel congelado, gelo em saco plástico ou em um pano (GREENSTEIN, 2007) e aplicação de compressa fria a uma temperatura regulada através de máscara facial (GLASS et al., 2016). A aplicação do gelo reduz a temperatura da pele, levando à vasoconstrição e diminuição do metabolismo tecidual, permeabilidade microvascular e velocidade de condução nervosa (DEAL et al., 2002; ALGAFLY; GEORGE, 2007; BLOCK, 2010), proporcionando benefícios fisiológicos aos pacientes submetidos à remoção de terceiros molares.

Embora a vasoconstrição induzida pelo gelo pareça ser benéfica na redução da dor, edema e trismo após a cirurgia de terceiro molar, resultados conflitantes são encontrados na literatura (FORSGREN et al., 1985; LAUREANO FILHO et al., 2005; ZANDI; AMINI; KESHAVARZ, 2016; ALTIPARMAK et al., 2018), tornando a evidência de eficácia da crioterapia incerta.

2 OBJETIVO

Avaliar, através de uma revisão sistemática e meta-análise de ensaios clínicos randomizados, a eficácia da crioterapia no controle da dor, edema e trismo após a remoção dos terceiros molares.

3 MATERIAL E MÉTODOS

Esta revisão sistemática e meta-análise foi conduzida de acordo com o modelo PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (MOHER et al., 2010) e suplementada pelo Manual da Cochrane Collaboration (HIGGINS et al., 2011). A aprovação do Comitê de Ética em Pesquisa e o consentimento informado não foram necessários.

3.1 ESTRATÉGIA DE BUSCA

Foram utilizadas as bases de dados eletrônicas PubMed, Web of Science, SCOPUS, Science Direct, Cochrane Central Register of Controlled Trials (CENTRAL), e a base de dados internacional para ensaios clínicos (www.clinicaltrials.gov) até junho de 2018. A literatura cinza foi incluída através de buscas no Google Acadêmico e no site OpenThesis (www.openthesis.org). Os primeiros 100 resultados do Google Acadêmico foram verificados. Nossa busca foi restrita a estudos na íntegra, em sua versão completa, sem restrições de idioma. A lista de referências de todos os estudos elegíveis foi manualmente analisada para identificação de estudos adicionais a serem incluídos.

A estratégia de busca foi estruturada da seguinte forma: (ice OR cryotherapy OR cold OR cooling OR hilotherapy OR hilotherm) AND (third molar OR third molars OR wisdom tooth OR wisdom teeth). Não foram realizados filtros durante a busca, para ampliar o número de artigos elegíveis.

3.2 CRITÉRIOS DE ELEGIBILIDADE E SELEÇÃO DOS ESTUDOS

Dois revisores, de forma independente, analisaram os resultados e identificaram os estudos relevantes com base em seus títulos e resumos. Os estudos relevantes foram lidos na íntegra e selecionados de acordo com os seguintes critérios de elegibilidade:

População: pacientes submetidos a cirurgias para remoção de terceiros molares.

Grupo de Intervenção e Controle: uso pós-operatório de crioterapia *versus* não utilização de crioterapia.

Desfecho: o desfecho primário foi dor, medida através de escala visual analógica (EVA), e os desfechos secundários foram edema e trismo. Trismo foi definido como limitação de abertura bucal e deveria ser demonstrado na forma de diferença entre a máxima distância interincisal, antes e depois da cirurgia.

Desenho do Estudo: ensaios clínicos randomizados (ECRs).

Os estudos incluídos deviam trazer ao menos um dos desfechos de interesse. Estudos que não informaram os dados do desfecho (média e desvio padrão) foram excluídos. Discordâncias entre os dois revisores foram resolvidas em consenso ou por um terceiro revisor.

3.3 EXTRAÇÃO DOS DADOS E AVALIAÇÃO DO RISCO DE VIÉS

Usando uma folha padronizada de coleta de dados (Apêndice A), foram extraídas as seguintes informações: autores, ano de publicação, tipo do estudo, características demográficas dos participantes do estudo, medicações pré- e pós-operatórias, método de crioterapia, período de acompanhamento pós-operatório e as medidas dos desfechos.

O risco de viés foi avaliado de acordo com as diretrizes da Cochrane para ensaios clínicos. Foram analisados sete domínios de avaliação: geração de sequência aleatória e ocultação de alocação (viés de seleção), cegamento dos participantes e profissionais (viés de performance), cegamento de avaliação do desfecho (viés de detecção), desfechos incompletos (viés de atrito), relato de desfecho seletivo (viés de relato), e outras fontes potenciais de viés. O risco de viés foi avaliado como sendo baixo, incerto ou alto de acordo com critérios estabelecidos (HIGGINS et al., 2011). A extração dos dados e o risco de viés foram realizadas por dois revisores independentes e as discordâncias foram resolvidas em consenso ou por um terceiro revisor.

3.4 MEDIDAS DE TRATAMENTO E SÍNTESE DE DADOS

Como os desfechos primários e secundários foram apresentados como dados contínuos, usamos a diferença de média ponderada (WMD) ou a diferença de média padronizada (SMD) como medidas de efeito. WMD foi calculado quando a medida de desfecho em todos os ECRs foi determinada usando a mesma escala, e SMD quando os resultados foram medidos usando diferentes escalas. Para calcular WMD ou SMD, médias e desvios padrão (SD) foram obtidos de cada grupo de estudo e resultado de interesse. O

tamanho do efeito foi determinado pelo cálculo da estatística *d* de Cohen (COCHRAN, 1954). Um valor de 0,2 foi considerado um efeito pequeno, um valor de 0,5 um efeito médio e um valor de 0,8 um efeito grande. Um tamanho de efeito negativo indicou que a crioterapia foi eficaz na redução da dor, edema e trismo. O trismo e o edema foram analisados com base na diferença em relação ao pré-operatório (HIGGINS et al., [s.d.]) e as diferenças entre os grupos para cada tempo de acompanhamento foram meta-analisadas pelo método da variância genérica.

Gráficos *forest plot* foram usados para apresentar graficamente os tamanhos de efeito e os intervalos de confiança de 95% (IC). Um $p < 0,05$ bicaudal foi usado para determinar a significância estatística. A heterogeneidade foi avaliada pelo teste Q de Cochran (COCHRAN, 1954) e quantificada pelo índice I^2 (HIGGINS & THOMPSON, 2002). Índices menores do que 25% indicaram baixa heterogeneidade entre os estudos, entre 25 e 75% moderada heterogeneidade e acima de 75% alta heterogeneidade (HIGGINS & THOMPSON, 2002). Na presente meta-análise, as estimativas reunidas e o IC de 95% correspondente foram calculados com base no modelo de efeitos aleatórios, utilizando o método Der Simonian-Laird. Uma análise de subgrupo foi realizada de acordo com o tempo de acompanhamento.

Embora os *funnel plots* possam ser ferramentas úteis na investigação de efeitos de estudos pequenos em meta-análises, eles têm poder limitado para detectar tais efeitos quando há poucos estudos (SIMMONDS, 2015). Portanto, como tivemos um pequeno número de estudos incluídos nos subgrupos, não realizamos a análise de viés de publicação. A análise de sensibilidade "*leave-one-out*" foi realizada omitindo-se um estudo de cada vez e examinando a influência de cada estudo individual no tamanho do efeito combinado (STERNE et al., 2001). As análises foram conduzidas usando o Review Manager 5.3 (Cochrane IMS, Copenhagen, Dinamarca).

3.5 QUALIDADE DA EVIDÊNCIA

Nós classificamos a qualidade da evidência para o efeito da crioterapia no desfecho primário como alta, moderada, baixa ou muito baixa, usando o sistema de classificação GRADE (GUYATT et al., 2008a, 2008b).

4 RESULTADOS

Cryotherapy in reducing pain, trismus and facial swelling after third molar surgery

Systematic review and meta-analysis of randomized clinical trials

Edmundo Marques do Nascimento-Júnior, DDS; Gustavo Marques Sobral dos Santos, DDS; Mário Luis Tavares Mendes, MSc; Maximiliano Cenci, PhD; Marcos Britto Correa, PhD; Tatiana Pereira-Cenci, PhD; Paulo Ricardo Saquete Martins-Filho, PhD.

There was no funding source for this systematic review.

Corresponding author: Prof. Paulo Ricardo Saquete Martins-Filho. Universidade Federal de Sergipe, Hospital Universitário, Laboratório de Patologia Investigativa. Rua Cláudio Batista, s/n. Bairro Sanatório. Aracaju, Sergipe, Brasil. CEP: 49060-100. Email: martins-filho@ufs.br

Abstract

Background. The aim of this systematic review and meta-analysis was to verify the effects of cryotherapy on pain, trismus and facial swelling in patients submitted to third molar surgery.

Types of Studies Reviewed. The authors searched for randomized clinical trials (RCTs) in PubMed, Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Google Scholar and OpenThesis. Eligibility criteria were: (1) *population:* patients submitted to removal of impacted third molars; (2) *intervention and comparison:* postoperative cryotherapy *versus* no cold therapy; (3) *outcomes*: primary outcome was postoperative pain and secondary outcomes were facial swelling and trismus. Eligible studies must have reported at least one of the outcomes of interest. After extracting data and assessing quality, the authors performed the meta-analyses.

Results. The authors included 6 studies in the quantitative synthesis analysis. Differences in pain intensity were found on postoperative day 2 (weighted mean difference [WMD] -0.72, confidence interval [CI] 95% -1.45 to 0.01, P = 0.05) and postoperative day 3 (WMD -0.36, CI 95% -0.59 to -0.13, P = 0.002). No evidence was found that cryotherapy was effective in reducing trismus and facial swelling. The quality of evidence was graded as low.

Conclusions and Practical Implications. Current evidence suggests that cryotherapy may have a small benefit in reducing pain after third molar surgery but is not effective on facial swelling and trismus. Due to the lack of standardization of cold application, effective evidence-based treatment protocols for cryotherapy after third molar surgery still need to be established.

Key Words. Cryotherapy; third molar; oral surgery, postoperative pain.

Introduction

Third molar removal is a routine procedure for maxillofacial surgeons and is often associated to postoperative complications such as pain, swelling and trismus.[1] These complications are thought to arise from inflammatory response which is a direct and immediate consequence of the surgical procedure, and may limit patients' daily functions in the recovery phase and compromise their quality of life.[2]

Several methods have been used for controlling postoperative morbidities related to third molar removal and include the administration of proteolytic enzymes[4,5], tube drains[6,7], , low-level laser therapy[8], and anti-inflammatory and analgesic drugs.[9–13] Although non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to control postoperative pain and inflammation, there is evidence of increased risk of gastrointestinal side effects and cardiovascular events.[14,15] In oral and maxillofacial surgery, cryotherapy is a popular non-pharmacological intervention used in the management of immediate postoperative inflammatory complications[16–18] and is defined as the application of substances that remove heat from the body for therapeutic purposes.[19]

Cryotherapy includes numerous techniques to induce heat abstraction such as ice pack, ice massage, frozen gel packs, ice chips in a plastic bag or in a washcloth[20], and application of cold compression at a regulated temperature through a face mask cold compression therapy.[21] Cold application reduces the skin temperature leading to vasoconstriction of blood vessels and decrease of tissue metabolism, microvascular permeability and nerve conduction velocity[22–24], which

would provide physiological benefits for patients submitted to third molars removal including decreased bleeding, muscles spasms, inflammation and pain.

Although cryotherapy is largely used in oral and maxillofacial surgery, the scientific evidence of the efficacy of such therapy is anecdotal, since not only randomized trials but even well-designed clinical studies are limited. However, the knowledge of possible beneficial effects of cold-induced vasoconstriction on reducing postoperative complications has allowed the empirical use of such therapy. Because of conflicting results presented in the literature[18,25–27] we conducted a systematic review and meta-analysis to verify the effects of cryotherapy on pain, trismus and facial swelling in patients submitted to third molar surgery.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[28] and supplemented by guidance from the Cochrane Collaboration Handbook for Systematic Reviews of Interventions.[29] Institutional review board approval and informed consent were not required for this systematic review and meta-analysis.

Eligibility criteria

The following elements were used to define eligibility criteria: (1) *population:* patients submitted to removal of impacted third molars; (2) *intervention and comparison:* postoperative cryotherapy *versus* no cold therapy; (3) *outcomes*: primary outcome was postoperative pain measured by the visual analogue scale (VAS) and secondary outcomes were facial swelling and trismus; (4) *study type:*

randomized clinical trials (RCTs). Eligible studies must report at least one of the outcomes of interest.

Search Strategy

Searches for RCTs were performed in PubMed, Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to June 30, 2018. A gray-literature search included Google Scholar and OpenThesis. The first 100 results of the Google Scholar search were analyzed. The search was limited to studies published in full-text versions, without language restriction. The reference lists of all eligible studies and reviews were scanned to identify additional studies for inclusion. The structured search strategy used the following terms: (ice OR cryotherapy OR cold OR cooling OR hilotherapy OR hilotherm) AND (third molar OR third molars OR wisdom tooth OR wisdom teeth). To expand the number of eligible articles, no filters were used in the search.

Study Selection

Two reviewers (E.M.N.-J. and M.L.T.M.) independently screened the search results and identified studies that were potentially relevant based on their title and abstract. Relevant studies were read in full text and selected according to eligibility criteria. Disagreements between the two reviewers were resolved by consensus or by a third reviewer (P.R.S.M.-F.).

Data Extraction and Risk of Bias Assessment

Using a standardized data extraction sheet, the following information from the studies were extracted: demographic characteristics of study participants, preoperative and postoperative medication, method of cryotherapy, duration of follow-up, and outcome data.

Risk of bias was assessed according to the Cochrane guidelines for RCTs. Seven domains were assessed for evaluation: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. Risk of bias was rated as low, unclear, or high according to established criteria[29]. Data extraction and risk of bias assessment were performed by two independent reviewers (E.M.N.-J. and M.L.T.M.), and disagreements were resolved by consensus or by a third reviewer (P.R.S.M.-F.).

Data Synthesis

Because primary and secondary outcomes were presented as continuous data, we used either the weighted mean difference (WMD) or the standardized mean difference (SMD) as effect measures. WMD was calculated when the outcome measure in all RCTs was determined using the same scale, and SMD when outcomes were measured using different scales. To calculate WMD or SMD, means and standard deviations (SD) were obtained for each study group and outcome of interest. Effect size was determined by calculating Cohen's *d* statistic[30]. A value of 0.2 was considered a small effect, a value of 0.5 a medium effect, and a value of 0.8 a large effect. A negative effect size indicated that cryotherapy was beneficial in reducing pain, facial swelling and trismus. Trismus and facial swelling were analyzed

based on change-from-baseline measures[31] and the differences between groups for each follow-up time were meta-analyzed using the generic inverse-variance method.

A forest plot was used to present the effect sizes and the 95% confidence interval (CI). A 2-tailed P value < 0.05 was used to determine significance. Statistical heterogeneity was assessed using the Cochran Q test[30] and quantified by the I^2 index.[32] A subgroup analysis was performed according to the follow-up time. The statistical power for the random-effects meta-analysis of primary outcome was calculated using the summary effect size, average number of participants per group, total number of effect sizes, and study heterogeneity.[33]

Although funnel plots may be useful tools in investigating small study effects in meta-analyses, they have limited power to detect such effects when there are few studies.[34] Therefore, because we had a small number of included studies within the subgroups, we did not perform funnel plot analysis. “Leave-one-out” sensitivity analysis was conducted by omitting one study at a time and examining the influence of each individual study on the pooled effect size. Meta-analyses were conducted using the Review Manager, version 5.3 (Cochrane IMS, Copenhagen, Denmark). Statistical power was analyzed using R statistical language.

Grading the Strength of Evidence

We graded the strength of evidence for the effect of cryotherapy on primary outcome as high, moderate, low or very low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating system. In the GRADE system, RCTs begin as high-quality evidence but may be lowered by 1 or more of 5

categories of limitations: risk of bias, inconsistency (heterogeneity), indirectness of evidence, imprecision, and publication bias.[35,36]

Results

Data Sources

Search strategy yielded 5,763 potentially relevant studies. After screening titles and abstracts, 12 full-text articles were assessed for eligibility and 6 RCTs [16,18,25–27,37] were included in the meta-analysis. A flow diagram of the study selection process and specific reasons for exclusion are detailed in Figure 1.

Study Characteristics

Four studies[18,25–27] were described as split-mouth or cross-over RCTS and 2 studies[16,37] as conventional parallel-group design. The total number of patients included was 231 and most of them were young adults. Only healthy subjects who required surgical removal of mandibular third molars were included. In 5 studies[16,18,25–27], patients were submitted to third molar removal under local anesthesia.

Details of anti-inflammatory regimen were reported in 5 studies and included postoperative administration of ibuprofen[16,27,37], flurbiprofen[25] or nimesulide.[18] The use of analgesics as rescue medication was described in 3 studies.[18,26,37] In 4 studies, patients used antimicrobial therapy with chlorhexidine gluconate 0.2% mouthwash for one week.[18,25,27,37] Application of ice packs on the operated side of the face was performed during the first 24h[16,25–27,37] or 48h[18] following surgery.

All studies evaluated postoperative pain as an outcome of interest and used a visual analogue scale (VAS) for measurements. Trismus and facial swelling were described in 5 studies.[18,25–27,37] Trismus was measured using maximum mouth opening (MMO) which was described as the maximum distance between the incisal edges of the upper and lower incisors. In 3 studies[25,26,37], mouth opening ability was recorded as a follow-up measurement. In the remaining studies[26,27], the magnitude of trismus was calculated by subtracting each of the postoperative inter-incisal distances from the preoperative measurement. Facial swelling was measured using different linear distances: from the gonion to the lateral canthus of the eye and from the tragus to the labial commissure[27]; from the gonion to the tragus and from the gonion to pogonion[18]; or from the tragus to the labial commissure.[25] To calculate the degree of swelling, preoperative facial size was subtracted from the postoperative measurements. The method of measuring facial swelling was not detailed in 2 studies.[26,37] The main characteristics of RCTs are presented in Table 1.

Risk of Bias

eFigure 1 provides a risk of bias summary for each included RCT. Most RCTs had unclear risk of selection and reporting bias. For the domain of blinding of participants and personnel, all RCTs were rated as having high risk of bias. Three studies [18,25,27] had a low risk of detection bias.

Data Synthesis and subgroup analysis

Postoperative pain

Four RCTs[16,25,27,37] included in this meta-analysis provided sufficient data for pain evaluation during the first postoperative week. Pain in patients using cryotherapy was lower when compared to the control group. Differences in pain intensity were found on postoperative day 2 (POD2) (WMD -0.72, CI 95% -1.45 to 0.01, P = 0.05, I^2 = 0%) and postoperative day 3 (POD3) (WMD -0.36, CI 95% -0.59 to -0.13, P = 0.002, I^2 = 0%), but the effect sizes were small to moderate (POD2, *d* = -0.34; POD3, *d* = -0.60) (Figure 2). For the primary outcome, the power of meta-analysis to detect a moderate effect size was 75%.

Trismus and facial swelling

Four RCTs included in this meta-analysis provided enough data to analyze the effects of cryotherapy on trismus and facial swelling. No evidence was found that cryotherapy was effective in reducing trismus (Figure 3) and facial swelling (Figure 4) following third molar surgery.

Strength of evidence

We graded the efficacy of cryotherapy in reducing pain following third molar removal as low quality of evidence as per the GRADE criteria (Table 2).

Discussion

Third molar removal is a common procedure in the routine of oral and maxillofacial surgeons and is often related to postoperative inflammatory complications, leading to a reduction in patients' quality of life in the recovery phase.

During the immediate postoperative period, several endogenous substances are produced, in particular, histamine, bradykinin and prostanoids (prostaglandins, prostacyclin, thromboxane and the leukotrienes), which are involved in the development of pain, edema and trismus associated with inflammation.[38]

Patients who have undergone third molars removal usually experience their most severe pain during the first 24 hours after extraction.[39] Nociceptive pain is caused by the stimulation of peripheral of A-delta and C-polymodal pain receptors and can be aggravated for variable periods of time after surgery.[40–42] Postoperative symptoms after surgical removal of third molars can be adequately controlled with the use of NSAIDs but the application of cryotherapy in the first 24 hours postoperatively has been used traditionally as an additional method to prevent or reduce acute postoperative pain due to the thermal effects on nerve fibers membranes.

Clinical practice and physiological rationale strongly suggest a potential interest of cryotherapy as a coadjuvant therapy in third molar surgery. During the cryotherapy, the decrease of skin temperature leads to increase in pain threshold, but an optimal temperature of the target tissue has not been defined. Studies have reported that a skin surface temperature of 13.6°C results in local analgesia and 12.5°C reflects a 10% reduction in nerve conduction velocity.[43,44] Therefore, a therapeutic skin surface temperature is accepted ranging from 10°C to 15°C[20], which allows comfort of the patient during cryotherapy and increases patient compliance with the treatment[45]. Cooling the skin at lower temperatures may activate A- and C-fibers sensitive to innocuous cooling and cold-sensitive nociceptors.[46,47]

This meta-analysis evaluated the efficacy of cryotherapy in reducing postoperative complications after third molars removal and showed a decrease of pain intensity for patients receiving cryotherapy compared to the control group during

the second and third days after surgery, but the magnitude of the effect was small to moderate. These results should be interpreted with caution because the effect estimates may have been influenced by a range of factors including the size and shape of ice packs, length of therapeutic intervals and duration of ice application, tissue thickness, and method of cryotherapy. Although cryotherapy was performed during the first 24h after surgery, controversy was found regarding the means of cold application (bilateral facial ice pack[37], thermo-gel wrapped in a disposable towel[25], ice cubes placed in a sealed plastic bag and wrapped in a cloth[27], and ice pack in a plastic bag[16]) and length of therapy (continuous[16,37] *versus* intermittent cold application with different resting periods[25,27]). The choice of cryotherapy modality and cold application intervals should be an important part of clinical decision making, but the evidence from head-to-head trials comparing cooling techniques after third molar surgery is scarce and a pragmatic recommendation for a specific prescription is limited.[48] Notably, in this systematic review most patients received postoperative NSAIDs making it impossible to analyze the specific clinical effects of local cryotherapy by itself. However, despite the results of this meta-analysis and poor quality of evidence of physiological benefits of cryotherapy after third molar surgery, pain relief is a subjective experience and could be explained in part by placebo effect. Moreover, the difficulty of blinding the subjects in the trials may lead to a high risk of performance bias, reducing the quality of the results.

Although cryotherapy appears to slightly reduce pain after third molars removal, our results showed no additional benefits in reducing trismus and facial swelling. Cryotherapy provides rapid cooling of superficial tissues, but it has been showed that skin surface temperature is a weak predictor of intramuscular temperature during cryotherapy[43] and that the amount of adipose tissue over the

application site is a significant factor in the extent of intramuscular temperature change.[49] In addition, because deeper tissues gradually decrease in temperature, as heat is transferred via conduction to rewarm the superficial skin surface close to the cold application[50], the short-term treatment duration of cryotherapy used for controlling facial swelling and trismus after third molar surgery may not be sufficient. However, it may not be practical to recommend that a patient applies cold therapy after oral surgery beyond a night rest.[20]

Conclusions

Current evidence suggests that cryotherapy may have a small additional benefit in reducing pain after third molar surgery and it is not effective on facial swelling and trismus. Furthermore, several devices and modalities of cold application exist, and which is the most effective after surgery remains uncertain. Considering the limitations of the present study and low quality of available evidence, further high-quality RCTs are needed to confirm these findings and effective evidence-based treatment protocols for cryotherapy after third molar surgery still need to be established.

References

1. de Santana-Santos T, de Souza-Santos A-A-S, Martins-Filho P-R-S, da Silva L-C-F, de Oliveira E Silva E-D, Gomes A-C-A. Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. *Med Oral Patol Oral Cir Bucal*. 2013;18(1):e65-70.
2. McGrath C, Comfort MB, Lo ECM, Luo Y. Changes in life quality following third molar surgery--the immediate postoperative period. *Br Dent J*.

2003;194(5):265-8; discussion 261.

3. Grossi GB, Maiorana C, Garramone RA, et al. Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. *J Oral Maxillofac Surg*. 2007;65(11):2218-2226.

4. Al-Khateeb TH, Nusair Y. Effect of the proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. *Int J Oral Maxillofac Surg*. 2008;37(3):264-268.

5. Singh T, More V, Fatima U, Karpe T, Aleem MA, Prameela J. Effect of proteolytic enzyme bromelain on pain and swelling after removal of third molars. *J Int Soc Prev Community Dent*. 2016;6(Suppl 3):S197-S204.

6. Cerqueira PRF, Vasconcelos BC do E, Bessa-Nogueira RV. Comparative study of the effect of a tube drain in impacted lower third molar surgery. *J oral Maxillofac Surg*. 2004;62(1):57-61.

7. Koyuncu BÖ, Zeytinoğlu M, Tetik A, Gomel MM. Effect of tube drainage compared with conventional suturing on postoperative discomfort after extraction of impacted mandibular third molars. *Br J Oral Maxillofac Surg*. 2015;53(1):63-67.

8. Ferrante M, Petrini M, Trentini P, Perfetti G, Spoto G. Effect of low-level laser therapy after extraction of impacted lower third molars. *Lasers Med Sci*. 2013;28(3):845-849.

9. Buyukkurt MC, Gungormus M, Kaya O. The Effect of a Single Dose Prednisolone With and Without Diclofenac on Pain, Trismus, and Swelling After Removal of Mandibular Third Molars. *J Oral Maxillofac Surg*. 2006;64(12):1761-1766.

10. Zerener T, Aydintug YS, Sencimen M, et al. Clinical comparison of submucosal injection of dexamethasone and triamcinolone acetonide on postoperative discomfort after third molar surgery. *Quintessence Int*. 2015;46(4):317-326.

11. Atkinson HC, Currie J, Moodie J, et al. Combination paracetamol and ibuprofen for pain relief after oral surgery: a dose ranging study. *Eur J Clin Pharmacol*. 2015;71(5):579-587.

12. Majid OW, Mahmood WK. Effect of submucosal and intramuscular dexamethasone on postoperative sequelae after third molar surgery: Comparative study. *Br J Oral Maxillofac Surg*. 2011;49(8):647-652.

13. Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, Ogunlewe MO. Prospective, randomized, open-label, pilot clinical trial comparing the effects of dexamethasone coadministered with diclofenac potassium or acetaminophen and diclofenac potassium monotherapy after third-molar extraction in adults. *Curr Ther Res - Clin Exp*. 2006;67(4):229-240.

14. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332(7553):1302-1308.

15. Baigent C, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779.

16. Forouzanfar T, Sabelis A, Ausems S, Baart JA, Effect IVDW. Clinical paper Oral surgery Effect of ice compression on pain after mandibular third molar surgery : a single-blind , randomized controlled trial. 2008:824-830.

17. Zandi M, Amini P, Effectiveness AK. Effectiveness of cold therapy in reducing pain , trismus , and oedema after impacted mandibular third molar surgery : a randomized , self-controlled , clinical trial. *Int J Oral Maxillofac Surg*. 2015;(October):3-8.

18. Laureano Filho JR, de Oliveira e Silva ED, Batista CI, Gouveia FM V. The influence of cryotherapy on reduction of swelling, pain and trismus after third-molar extraction: a preliminary study. *J Am Dent Assoc*. 2005;136(6):774-778.

19. Nadler SF, Weingand K, Kruse RJ. The physiologic basis and clinical applications of cryotherapy and thermotherapy for the pain practitioner. *Pain Physician*. 2004;7(3):395-399.

20. Greenstein G. Therapeutic efficacy of cold therapy after intraoral surgical procedures: a literature review. *J Periodontol*. 2007;78(5):790-800.

21. Glass GE, Waterhouse N, Shakib K. Hilotherapy for the management of perioperative pain and swelling in facial surgery: a systematic review and meta-analysis. *Br J Oral Maxillofac Surg*. 2016;54(8):851-856.

22. Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. *Br J Sports Med*. 2007;41(6):365-369.

23. Deal DN, Tipton J, Rosencrance E, Curl WW, Smith TL. Ice reduces edema. A study of microvascular permeability in rats. *J bone Jt Surg*. 2002;84-A(9):1573-1578.

24. Block JE. Cold and compression in the management of musculoskeletal injuries and orthopedic operative procedures: a narrative review. *Open access J Sport Med*. 2010;1:105-113.

25. Altiparmak N, Bayram B, Diker N, Araz K. Efficacy of Ice Pack Therapy After Impacted Third Molar Surgery : A Randomized Controlled Clinical Trial. *Turkiye Klin J Dent Sci*. 2018;24(1):19-25.

26. Forsgren H, Heimdahl A, Johansson B, Krekmanov L. Effect of application of cold dressings on the postoperative course in oral surgery. *Int J Oral Surg*. 1985;14(3):223-228.

27. Zandi M, Amini P, Keshavarz A. Effectiveness of cold therapy in reducing pain, trismus, and oedema after impacted mandibular third molar surgery: A randomized, self-controlled, observer-blind, split-mouth clinical trial. *Int J Oral Maxillofac Surg*. 2016;45(1):118-123.

28. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341.

29. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

30. Cochran WG. The Combination of Estimates from Different Experiments. *Biometrics*. 1954;10(1):101.

31. Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of

Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

32. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.

33. Valentine JC, Pigott TD, Rothstein HR. How Many Studies Do You Need? *J Educ Behav Stat*. 2010;35(2):215-247.

34. Simmonds M. Quantifying the risk of error when interpreting funnel plots. *Syst Rev*. 2015;4:24.

35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.

36. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is “quality of evidence” and why is it important to clinicians? *BMJ*. 2008;336(7651):995-998.

37. Westhuijzen AJ Van Der, Becker PJ, Morkel J, Roelse JAA. A randomized observer blind comparison of bilateral facial ice pack therapy with no ice therapy following third molar surgery. 2005:281-286.

38. Seymour RA. Use of Analgesics in Postoperative Dental Pain: A Review. *J R Soc Med*. 1984;77(11):949-954.

39. Peñarrocha M, Sanchis JM, Sáez U, Gay C, Bagán J V. Oral hygiene and postoperative pain after mandibular third molar surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;92(3):260-264.

40. Song J, Kim H, Park E, et al. Pre-emptive ice cube cryotherapy for reducing pain from local anaesthetic injections for simple lacerations: a randomised controlled trial. *Emerg Med J*. 2018;35(2):103-107.

41. Renton T. An update on pain. *Br Dent J*. 2008;204(6):335-338.

42. Ong CKS, Seymour R a. Pathogenesis of postoperative oral surgical pain. *Anesth Prog*. 2003;50(1):5-17.

43. Bugaj R. The cooling, analgesic, and rewarming effects of ice massage on

localized skin. *Phys Ther*. 1975;55(1):11-19.

44. Jutte LS, Merrick MA, Ingersoll CD, Edwards JE. The relationship between intramuscular temperature, skin temperature, and adipose thickness during cryotherapy and rewarming. *Arch Phys Med Rehabil*. 2001;82(6):845-850.

45. Kennet J, Hardaker N, Hobbs S, Selfe J. Cooling efficiency of 4 common cryotherapeutic agents. *J Athl Train*. 2007;42(3):343-348.

46. Schepers RJ, Ringkamp M. Thermoreceptors and thermosensitive afferents. *Neurosci Biobehav Rev*. 2010;34(2):177-184.

47. Cain DM, Khasabov SG, Simone DA. Response properties of mechanoreceptors and nociceptors in mouse glabrous skin: an in vivo study. *J Neurophysiol*. 2001;85(4):1561-1574.

48. Rana M, Gellrich NC, Ghassemi A, Gerressen M, Riediger D, Modabber A. Three-dimensional evaluation of postoperative swelling after third molar surgery using 2 different cooling therapy methods: A randomized observer-blind prospective study. *J Oral Maxillofac Surg*. 2011;69(8):2092-2098.

49. Myrer WJ, Myrer KA, Measom GJ, Fellingham GW, Evers SL. Muscle Temperature Is Affected by Overlying Adipose When Cryotherapy Is Administered. *J Athl Train*. 2001;36(1):32-36.

50. Enwemeka CS, Allen C, Avila P, Bina J, Konrade J, Munns S. Soft tissue thermodynamics before, during, and after cold pack therapy. *Med Sci Sports Exerc*. 2002;34(1):45-50.

Figure legends

Figure 1. Flowchart of data collection.

Figure 2. Efficacy of cryotherapy on pain within the first postoperative week.

Figure 3. Efficacy of cryotherapy on trismus within the first postoperative week.

Figure 4. Efficacy of cryotherapy on facial swelling within the first postoperative week.

Supplementary data

eFigure 1. Risk of bias assessment. Footnote: (+) low risk of bias; (-) high risk of bias; (?) unclear risk of bias.

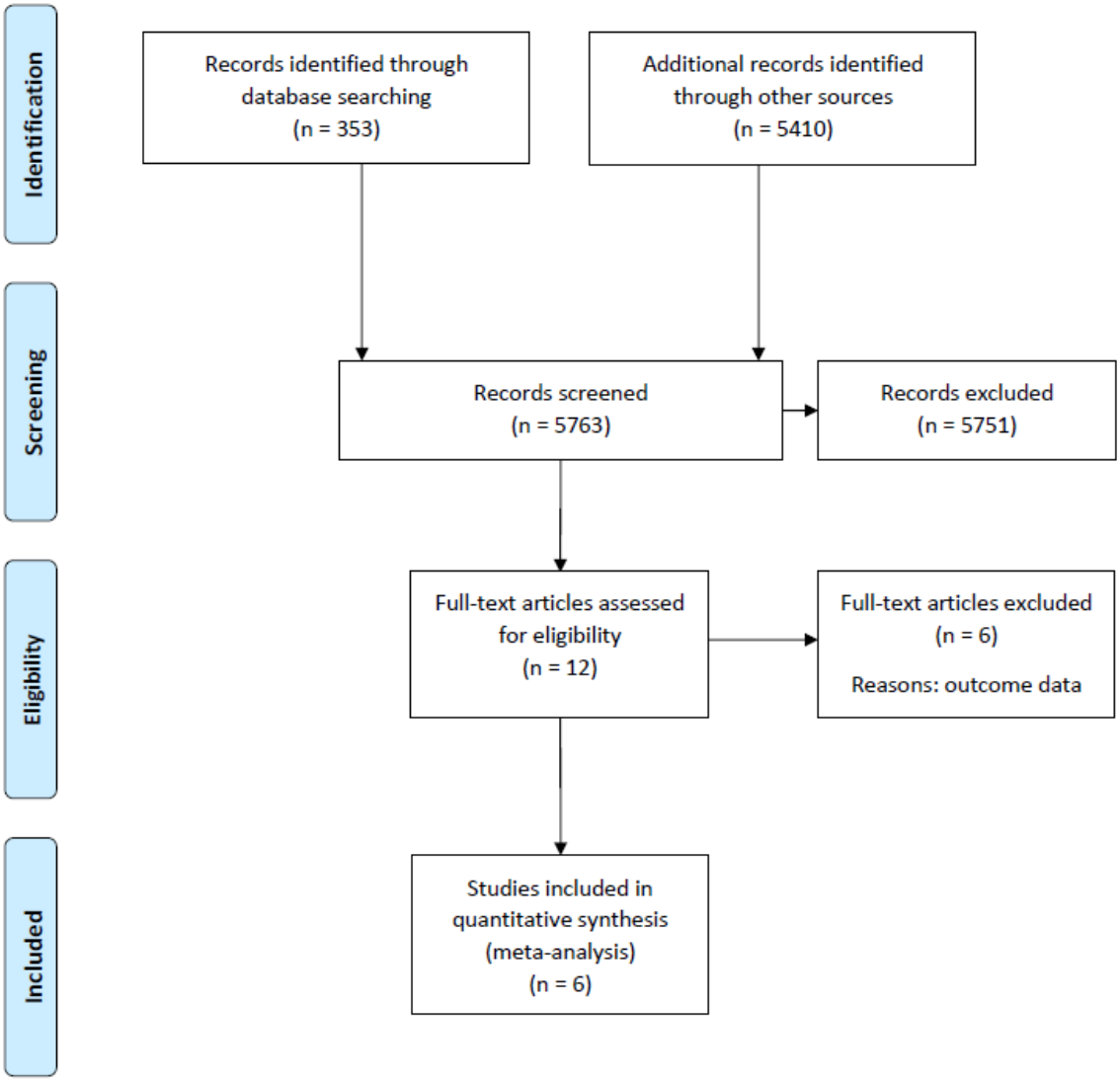

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 353)
Additional records identified through other sources (n = 5410)
Records screened (n = 5763)
Records excluded (n = 5751)
Full-text articles assessed for eligibility (n = 12)
Full-text articles excluded (n = 6)
Reasons: outcome data
Studies included in quantitative synthesis (meta-analysis) (n = 6)

Figure 1

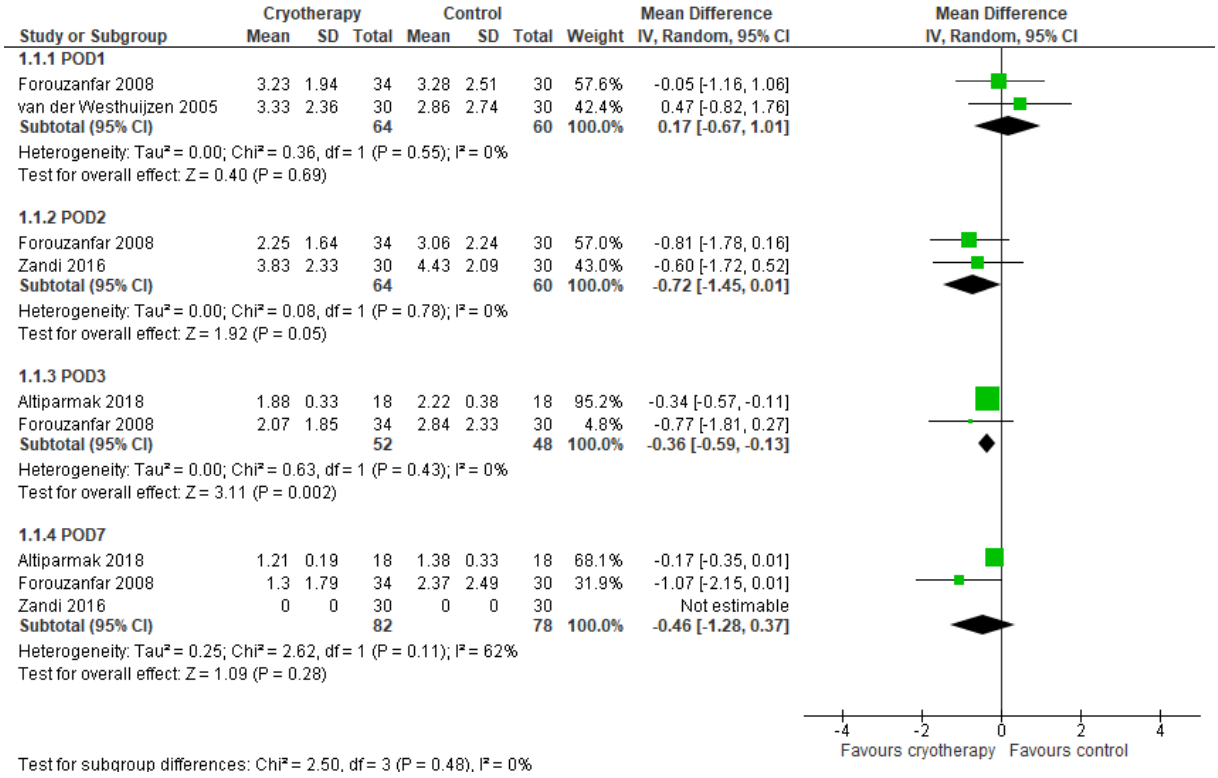


Figure 2

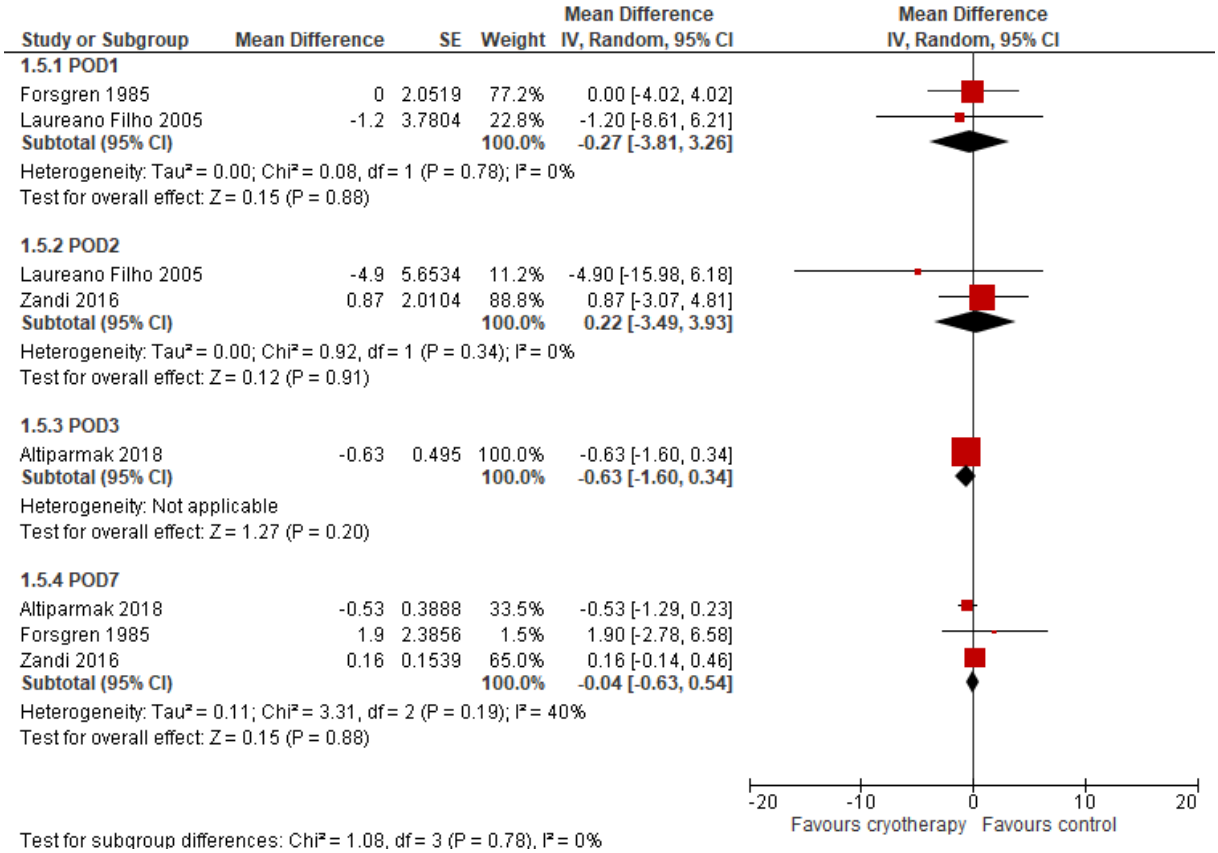


Figure 3

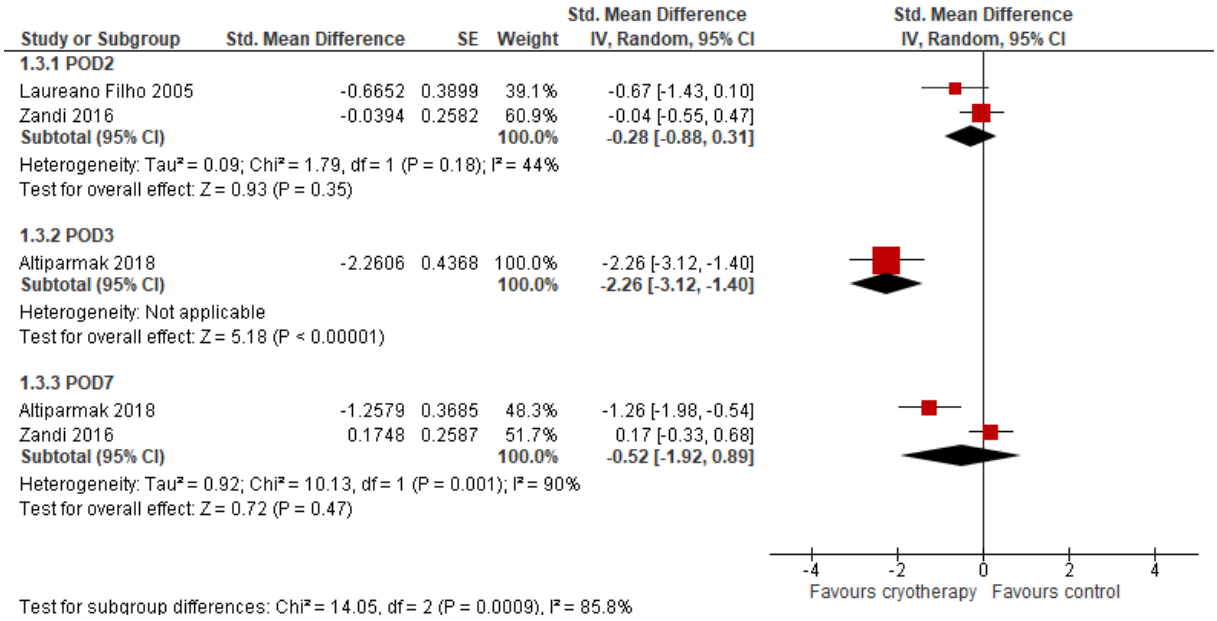
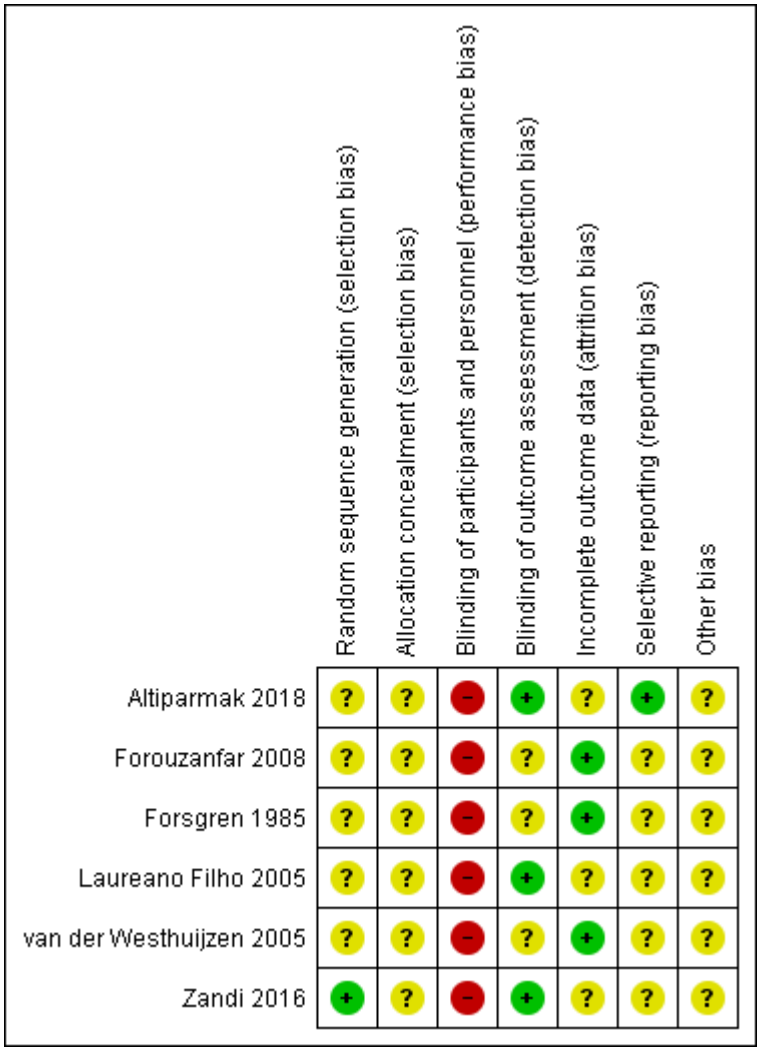


Figure 4



eFigure 1

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	n	Design	Population	Cold therapy	Postoperative medication	Follow-up visits	Key findings		
								Pain	Trismus	Swelling
Forsgren et al.	1985	45	Cross-over RCT	Bilateral impacted third molar	Application of cold pack immediately after surgery for every 15 min for 2h	Paracetamol as a rescue medication	1st, 2nd and 7th days	There were no significant differences in pain assessment between cold therapy and control groups	There were no significant differences in MMO between cold therapy and control groups	There were no significant differences in swelling between cold therapy and control groups
Laureano Filho et al.	2005	14	Cross-over RCT	Bilateral impacted third molar	Application of cold pack for 30 min every one and one-half hours for 48h	Nimesulide 100mg, every 12 h, and paracetamol 750mg, every 6h	1st, 2nd and 7th days	The increase in pain was smaller on the treated side than on the control side	There were no significant differences in MMO between cold therapy and control groups	There were significant differences in two of the five points that were used to measure the swelling
van der Westhuijzen et al.	2005	60	Parallel RCT	Bilateral impacted third molar	A facial ice pack was used continuously during the first 24h following surgery	Ibuprofen 200mg, paracetamol 250mg, and codeine 10mg prior to the surgery and every 6h for the first 24h	1st day	There were no significant differences in pain assessment between cold therapy and control groups	There were no significant differences in MMO between cold therapy and control groups	There were no significant differences in swelling between cold therapy and control groups
Forouzanfar et al.	2008	64	Parallel RCT	Unilateral impacted third molar	Compression with ice pack for 45 min immediately after surgery	Ibuprofen 600mg, every 8h	1st, 2nd, 3th and 7th days	The VAS scores demonstrated a significant pain decrease after cold therapy	Not evaluated	Not evaluated
Zandi et al.	2016	30	Split-mouth RCT	Bilateral impacted third molar	Application of ice packs for periods of 20 min followed by resting periods of 20 min during the first 24h after surgery	Ibuprofen 400mg, every 8h, for 2 days	2nd and 7th days	There were no significant differences in pain assessment between cold therapy and control groups	There were no significant differences in MMO between cold therapy and control groups	There were no significant differences in swelling between cold therapy and control groups
Altiparmak et al.	2018	18	Split-mouth RCT	Bilateral impacted third molar	Thermo-gel was applied for 5 minutes at a time followed by 5 minutes of resting during the first 24h after surgery	Flurbiprofen 100mg, every 12h, for 5 days	3th and 7th days	The increase in pain was smaller on the treated side than on the control side in the 3rd postoperative day	There were no significant differences in MMO between cold therapy and control groups	There were no significant differences in swelling between cold therapy and control groups

MMO, maximum mouth opening.

Table 2. GRADE evidence profile for efficacy of cold therapy to reduce postoperative pain after third molar surgery.

Outcome	Mean difference (95%CI)	Number of studies (participants)	Certainty of the evidence (GRADE)[£]	Recommendation
Postoperative pain	POD2: -0.72 (-1.45 to 0.01) POD3: -0.36 (-0.59 to -0.13)	4 RCTs (172)	⊕⊕◯◯ LOW	Cold therapy probably reduces postoperative pain slightly following third molar removal

POD, postoperative day; CI, confidence interval.

[£] risk of bias: serious; inconsistency: not serious; indirectness: not serious; imprecision: imprecision: serious; publication bias: not evaluated; large effect: no; plausible confounding: no; dose response gradient: no.

5 CONSIDERAÇÕES FINAIS

Os dados avaliados nesta meta-análise sugerem a eficácia do uso da crioterapia no controle da dor após cirurgia de remoção de terceiros molares. Nenhuma evidência demonstrou que a crioterapia foi eficaz na redução do trismo e edema. No entanto, devido ao fato de a qualidade da evidência ter sido considerada baixa, mais estudos clínicos controlados são necessários para confirmar nossos achados.

6 COMUNICADO A IMPRENSA (PRESS RELEASE)

A EFICÁCIA DO GELO NO CONTROLE DA DOR, INCHAÇO E DIFICULDADE DE ABERTURA DA BOCA APÓS CIRURGIAS DE REMOÇÃO DE TERCEIROS MOLARES

As cirurgias de remoção de terceiros molares, mais conhecidos como dentes sisos, ou dentes do juízo, são procedimentos bastante comuns no consultório dentista especialista em cirurgia. Normalmente, os pacientes procuram atendimento por recomendação do seu ortodontista, dentista especialista em aparelho dentário, ou após episódios de incômodo na área relacionada a esses dentes.

Rotineiramente, o uso de compressas de gelo é prescrito para controlar dor, inchaço e limitação da abertura da boca no pós-operatório. No entanto, a ciência mostra que não existem comprovações de sua eficácia.

O objetivo do nosso trabalho foi fazer um levantamento de todos os estudos disponíveis sobre o assunto, para analisá-los e poder saber, de fato, se a técnica funciona. Nosso trabalho mostrou que houve uma redução da dor quando os pacientes usavam compressas de gelo, em comparação com aqueles que não usavam. Não encontramos comprovação de que o gelo melhora a abertura bucal e o inchaço.

Apesar de nossos achados, precisamos que mais estudos sejam realizados para sabermos se, de fato, o uso do gelo é eficaz no controle desses três sintomas, para esse tipo de cirurgia dental.

Contatos: Edmundo Marques (dredmundomarques@gmail.com) e Paulo Saquete (martins-filho@ufs.br). Universidade Federal de Sergipe, Hospital Universitário, Laboratório de Patologia Investigativa. Rua Cláudio Batista, s/n. Bairro Sanatório. Aracaju, Sergipe, Brasil. CEP: 49060-100.

REFERÊNCIAS

Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. Br J Sports Med. 2007 Jun;41(6):365–9.

Al-Khateeb TH, Nusair Y. Effect of the proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. Int J Oral Maxillofac Surg [Internet]. 2008 Mar;37(3):264–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18272344

Altiparmak N, Bayram B, Diker N, Araz K. Efficacy of Ice Pack Therapy After Impacted Third Molar Surgery : A Randomized Controlled Clinical Trial. Turkiye Klin J Dent Sci. 2018;24(1):19–25.

Atkinson HC, Currie J, Moodie J, Carson S, Evans S, Worthington JP, et al. Combination paracetamol and ibuprofen for pain relief after oral surgery: a dose ranging study. Eur J Clin Pharmacol [Internet]. 2015 May;71(5):579–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25778933

Baigent C, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. Lancet [Internet]. 2013;382(9894):769–79. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60900-9

Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, Ogunlewe MO. Prospective, randomized, open-label, pilot clinical trial comparing the effects of dexamethasone coadministered with diclofenac potassium or acetaminophen and diclofenac potassium monotherapy after third-molar extraction in adults. Curr Ther Res - Clin Exp. 2006;67(4):229–40.

Block JE. Cold and compression in the management of musculoskeletal injuries and orthopedic operative procedures: a narrative review. Open access J Sport Med. 2010 Jul;1:105–13.

Buyukkurt MC, Gungormus M, Kaya O. The Effect of a Single Dose Prednisolone With and Without Diclofenac on Pain, Trismus, and Swelling After Removal of Mandibular Third Molars. J Oral Maxillofac Surg. 2006;64(12):1761–6.

Cerqueira PRF, Vasconcelos BC do E, Bessa-Nogueira RV. Comparative study of the effect of a tube drain in impacted lower third molar surgery. J oral Maxillofac Surg. 2004 Jan;62(1):57–61.

Cochran WG. The Combination of Estimates from Different Experiments. Biometrics [Internet]. 1954 Mar;10(1):101. Available from: http://www.jstor.org/stable/3001666?origin=crossref

de Santana-Santos T, de Souza-Santos A-A-S, Martins-Filho P-R-S, da Silva L-C-F, de Oliveira E Silva E-D, Gomes A-C-A. Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. Med Oral Patol Oral

Cir Bucal. 2013 Jan;18(1):e65-70.

Deal DN, Tipton J, Rosencrance E, Curl WW, Smith TL. Ice reduces edema. A study of microvascular permeability in rats. J bone Jt Surg. 2002 Sep;84–A(9):1573–8.

Ferrante M, Petrini M, Trentini P, Perfetti G, Spoto G. Effect of low-level laser therapy after extraction of impacted lower third molars. Lasers Med Sci. 2013 May;28(3):845–9.

Forouzanfar T, Sabelis A, Ausems S, Baart JA, van der Waal I. Effect of ice compression on pain after mandibular third molar surgery: a single-blind, randomized controlled trial. Int J Oral Maxillofac Surg. 2008;37(9):824–30.

Forsgren H, Heimdahl A, Johansson B, Krekmanov L. Effect of application of cold dressings on the postoperative course in oral surgery. Int J Oral Surg. 1985;14(3):223–8.

Glass GE, Waterhouse N, Shakib K. Hilotherapy for the management of perioperative pain and swelling in facial surgery: a systematic review and meta-analysis. Br J Oral Maxillofac Surg [Internet]. 2016;54(8):851–6. Available from: http://dx.doi.org/10.1016/j.bjoms.2016.07.003

Greenstein G. Therapeutic efficacy of cold therapy after intraoral surgical procedures: a literature review. J Periodontol [Internet]. 2007 May;78(5):790–800. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17470011

Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Beretta M, Farronato D, et al. Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. J Oral Maxillofac Surg [Internet]. 2007 Nov;65(11):2218–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17954317

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008b May;336(7651):995–8.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008a Apr;336(7650):924–6.

Herrera-Briones FJ, Prados Sánchez E, Reyes Botella C, Vallecillo Capilla M. Update on the use of corticosteroids in third molar surgery: systematic review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2013 Nov;116(5):e342-51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22902498

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ [Internet]. 2011 Oct 18;343:d5928. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22008217

Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med [Internet]. 2002 Jun 15;21(11):1539–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12111919

Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C, et al. Do selective

cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ [Internet]. 2006;332(7553):1302–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16740558%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1473048

Koyuncu BÖ, Zeytinoğlu M, Tetik A, Gomel MM. Effect of tube drainage compared with conventional suturing on postoperative discomfort after extraction of impacted mandibular third molars. Br J Oral Maxillofac Surg. 2015 Jan;53(1):63–7.

Laureano Filho JR, de Oliveira e Silva ED, Batista CI, Gouveia FM V. The influence of cryotherapy on reduction of swelling, pain and trismus after third-molar extraction: a preliminary study. J Am Dent Assoc [Internet]. 2005 Jun;136(6):774–8; quiz 807. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16022042

Majid OW, Mahmood WK. Effect of submucosal and intramuscular dexamethasone on postoperative sequelae after third molar surgery: Comparative study. Br J Oral Maxillofac Surg. 2011;49(8):647–52.

McGrath C, Comfort MB, Lo ECM, Luo Y. Changes in life quality following third molar surgery--the immediate postoperative period. Br Dent J [Internet]. 2003 Mar 8;194(5):265–8; discussion 261. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12658303

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg [Internet]. 2010;8(5):336–41. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1743919110000403

Ngeow WC, Lim D. Do Corticosteroids Still Have a Role in the Management of Third Molar Surgery? Adv Ther [Internet]. 2016 Jul;33(7):1105–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27287853

Simmonds M. Quantifying the risk of error when interpreting funnel plots. Syst Rev. 2015 Dec;4(1):24.

Singh T, More V, Fatima U, Karpe T, Aleem MA, Prameela J. Effect of proteolytic enzyme bromelain on pain and swelling after removal of third molars. J Int Soc Prev Community Dent. 2016 Dec;6(Suppl 3):S197–204.

Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ [Internet]. 2001 Jul 14;323(7304):101–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11451790

Zandi M, Amini P, Keshavarz A. Effectiveness of cold therapy in reducing pain, trismus, and oedema after impacted mandibular third molar surgery: A randomized, self-controlled, observer-blind, split-mouth clinical trial. Int J Oral Maxillofac Surg [Internet]. 2016;45(1):118–23. Available from: http://dx.doi.org/10.1016/j.ijom.2015.10.021

Zerener T, Aydintug YS, Sencimen M, Bayar GR, Yazici M, Altug HA, et al. Clinical comparison of submucosal injection of dexamethasone and triamcinolone acetonide on postoperative discomfort after third molar surgery. Quintessence Int [Internet]. 2015 Apr;46(4):317–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25529005

APÊNDICE A

FORMULÁRIO DE COLETA DE DADOS

Autor/Ano	
Local do Estudo	
Tipo de estudo	
Cegamento	Descrição:
Objetivos	
Hipótese	
Critérios de Inclusão	
Critérios de Exclusão	
Variáveis estudadas	
Média Idade	
Amostra por sexo	
Método da crioterapia	
Grupo controle	
Medicação pré-operatória	
Medicação pós-operatória	
Período de acompanhamento	
Grupo 1 (teste)/nº pacientes	
Grupo 2 (controle)/ nº pacientes	
Outras considerações	
Niveis de dor / dia de PO	
Niveis de edema / dia de PO	
Niveis de trismo / dia de PO	
Complicações Pós-Operatórias	
Análise estatística	
Total de Pacientes	
Perdas de pacientes	Descrição:
Limitações	
Conclusões	