INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Comparative efficacy and safety of pharmacological interventions to reduce inflammatory complications after mandibular third molar surgery: a systematic review and network meta-analysis protocol

Canellas, JV[1]; Ritto, FG[2]; Tiwana, PS[3].

Review question / Objective: **This systematic review aims to compare the effects of different drugs to reduce postoperative inflammatory complications (pain, edema, and trismus) after mandibular third molar surgery by applying a frequentist network meta-analysis approach. To this end, the proposed study will answer the following questions: 1) Among diverse drugs currently available, which postoperative pharmacological regimen is the most efficient to reduce pain after mandibular third molar surgery? 2) Is the pre-emptive analgesia effective in reducing pain immediately after the mandibular third molar surgery? In this case, 3) Which preoperative pharmacological regimen is the most efficient? 4) Among diverse corticosteroids currently available, what is the best option to control the edema induced by the surgery? 5) What is the optimal dose and route of administration of corticosteroids prior to mandibular third molar surgery to control the pain/ edema induced by the surgery?**
Condition being studied: **Inflammatory complications after mandibular third molar surgery (Pain, edema, and trismus).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 July 2021 and was last updated on 22 July 2021 (registration number INPLASY202170069).

INTRODUCTION

Review question / Objective: **This systematic review aims to compare the effects of different drugs to reduce postoperative inflammatory complications (pain, edema, and trismus) after mandibular third molar surgery by applying a frequentist network meta-analysis approach. To this end, the proposed study will answer the following questions: 1) Among diverse drugs currently available,**

which postoperative pharmacological regimen is the most efficient to reduce pain after mandibular third molar surgery? 2) Is the pre-emptive analgesia effective in reducing pain immediately after the mandibular third molar surgery? In this case, 3) Which preoperative pharmacological regimen is the most efficient? 4) Among diverse corticosteroids currently available, what is the best option to control the edema induced by the surgery? 5) What is the optimal dose and route of administration of corticosteroids prior to mandibular third molar surgery to control the pain/ edema induced by the surgery?

Rationale: Mandibular third molar surgery is one of the most common surgeries performed in dentistry. Numerous clinical trials have investigated various pharmacological agents to reduce inflammatory complications following the surgery; However, there is a large amount of studies and sometimes describing contradictory results, making it difficult for surgeons to decide which pharmacological agent, dose, and administration route are truly effective. Therefore, the prescription of these pharmacological agents should be performed based in the best available evidence.

Condition being studied: Inflammatory complications after mandibular third molar surgery (Pain, edema, and trismus).

METHODS

Search strategy: 1) MEDLINE via PubMed ((((((((((acute pain[MeSH Terms]) OR (pain[MeSH Terms])) OR (pain management[MeSH Terms])) OR (pain)) OR (edema[MeSH Terms])) OR ("facial swelling")) OR (edema)) OR (swelling)) AND ((((((((((molar, third[MeSH Terms]) OR (tooth, unerupted[MeSH Terms])) OR (tooth, impacted[MeSH Terms])) OR (tooth extraction[MeSH Terms])) OR ("wisdom tooth")) OR ("wisdom teeth")) OR ("3rd molar")) OR ("third molar")) OR (third-molar))) AND ((((((((((Randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title])) OR "Clinical Trials as Topic"[Mesh:NoExp])) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms])). 2) Cochrane Database (molar, third[MeSH Terms]) OR (tooth, unerupted[MeSH Terms]) OR (tooth, impacted[MeSH Terms]) OR (tooth extraction[MeSH Terms]) OR ("wisdom tooth") OR ("wisdom teeth") OR ("3rd molar") OR ("third molar") OR (third-molar) AND (acute pain[MeSH Terms]) OR (pain[MeSH Terms]) OR (pain management[MeSH Terms]) OR (pain) OR (edema[MeSH Terms]) OR ("facial swelling") OR (edema) OR (swelling) AND (Randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized [Title/Abstract]) OR placebo [Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title]) OR "Clinical Trials as Topic"[Mesh: NoExp]). 3) EMBASE third molar'/exp OR 'unerupted tooth'/exp OR 'tooth impaction'/exp OR 'tooth extraction'/exp OR 'wisdom tooth' OR 'wisdom teeth' OR '3rd molar' OR 'third molar' AND 'pain'/exp OR 'analgesia'/exp OR 'edema'/exp OR 'facial swelling'/exp OR swelling OR edema OR pain AND 'randomized controlled trial'/exp AND topic OR 'controlled clinical trial' OR randomized:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR 'clinical trial topic' OR randomization.

Participant or population: We will include studies investigating health humans (American Society of Anesthesiologists - ASA I or II) who had been submitted to mandibular third molar surgery. No restrictions regarding age, gender, or ethnicity will be applied.

Intervention: Pharmacological agents used preoperatively or postoperatively to reduce inflammatory complications after mandibular third molar surgery.

Comparator: In this frequentist network meta-analysis each pharmacological agent will be compared with each other and placebo will be the reference.

Study designs to be included: We will include only randomized controlled trials (RCTs).

Eligibility criteria: Studies will be selected according to the PICOS criteria (Participant, intervention, comparator, outcomes, and study design) outlined in the referred sections. We will exclude studies testing homeopathic medications. Similarly, studies testing topical agents will be excluded. No restriction of country, publications status, setting, or language will be applied.

Information sources: We will search the following electronic bibliographic databases: EMBASE, MEDLINE via PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL). We will use the PICOS strategy for research question construction and evidence search. The reference lists of the articles identified will be cross-checked. Furthermore, and studies from the 'grey literature' will be screened through the following trial registry platform: ClinicalTrials.gov (www.clinicaltrials.gov). A comprehensive manual search will be done in the relevant journals of Dentistry. We will contact study correspondent authors to clarify any doubts. Finally, the reference lists of the included studies will be checked to identify additional potential primary studies.

Main outcome(s): 1) Postoperative pain intensity measured in the first week by the Visual Analog Scale or any other validated scale; 2) Edema assessed by the extra oral facial measurements or any other validated method in the first week.

Additional outcome(s): 1) Trismus measured by recording the interincisal opening in the first week; 2) The number of analgesic consumed in the first week; 3) Adverse effects; 4) Assessment of Quality of life.

Data management: Two review authors will independently search the databases and, upon retrieving study titles and abstracts, identify RCTs to be screened for final selection. The review authors will independently screen the full texts of these included RCTs. Any discrepancies will be solved by discussion. The frequentist network meta-analysis will be performed using R software version 3.6.2 or if available a later version. Network Meta-analysis will be performed using Frequentist Methods (netmeta package) for the Mac OS X computer system. The references will be imported into EndNote X9 software (Thompson Reuters, Philadelphia, PA, USA) where duplicates will be automatically removed.

Quality assessment / Risk of bias analysis: Two review authors will independently assess the risk of bias. Any discrepancies will be solved by discussion. Study quality in terms of sequence generation, allocation concealment, blinding, the completeness of outcome data, selective reporting and other biases will be assessed with the Cochrane Collaboration risk of bias tool.

Strategy of data synthesis: A pairwise meta-analysis for direct evidence and a network meta-analysis for direct and indirect evidence of eligible comparisons will be accomplished. The effect size measure for continuous outcomes will be the standardized mean difference (SMD) because we expect that the studies use different scales of overall pain intensity. We will pool the results using a random-effects meta-analysis. Heterogeneity will be assessed using both the $\chi 2$ test and the I2 statistic. We will consider an I2 value greater than 50% indicative of substantial heterogeneity. In addition to the heterogeneity assessment using the I2 statistic. We will investigate the assumption of transitivity and similarity based on clinical and methodological characteristics. Inconsistency will be assessed by comparing direct and indirect evidence. The net heat plot will be used to show the contribution of each design to the network estimate and the extent of inconsistency due to each design. We will also assess evidence of publication bias. Intention-To-treat (ITT) data will be used whenever available. To rank the various pharmacological interventions for each

outcome, we will use the P-scores which are equivalent to SUCRA values.

Subgroup analysis: None planned.

Sensitivity analysis: None planned.

Language: No language restriction will be imposed.

Country(ies) involved: USA.

Keywords: third molar; pain; swelling; trismus; pre-emptive effect; systematic review; network meta-analysis.

Dissemination plans: The results of this systematic review will be disseminated through peer reviewed journal.

Contributions of each author:

Author 1 - João Vitor dos Santos Canellas - Performed all preliminary searches, formal screening of search results against eligibility criteria, data extraction, risk of bias assessment, qualitative data analysis and quantitative data analysis, statistical expertise, drafting of manuscript.
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Author 2 - Fabio Gambôa Ritto - Formal screening of search results against eligibility criteria, data extraction, risk of bias assessment, provides feedback and corrections on the final manuscript.
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Author 3 - Paul S. Tiwana - The author oversees the progress of the review, provides feedback and corrections on the protocol and approves the final manuscript.