Postoperative oral drug regimen to control the inflammatory complications in mandibular third molar surgery: a systematic review and network meta-analysis protocol

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ABSTRACT

Objective: This network meta-analysis aims to rank the best postoperative drug regimen to control inflammatory complications related to mandibular third molar surgery.

Introduction: Many studies of oral drugs have been proposed to control postoperative inflammatory complications after third molar surgeries with inconclusive results. A systematic review with network meta-analysis in this field may clarify the best therapeutic protocol for practice in dentistry.

Inclusion criteria: This review will consider randomized clinical trials that included healthy adult patients or those who had treated and controlled systemic diseases; asymptomatic patients who were free of acute infection or inflammation at the surgical site immediately before third molar surgery; and patients submitted to surgical removal of one lower third molar at a time in which they have received oral anti-inflammatory and/or analgesics in the postoperative moment. The outcomes are pain, edema, trismus, and adverse effects.

Methods: Sources of published studies, unpublished studies, and gray literature will be searched without time or language restrictions. Titles and abstracts of all search results will be screened by two independent reviewers. The full text of potentially relevant studies will be assessed. Methodological quality of the included studies will be performed using the JBI checklist for experimental studies. Data related to specific details about the population, study methods, interventions, and outcomes will be extracted from the included studies. The findings will be presented in a narrative form and polled in network meta-analysis, when possible.

Systematic review registration number: PROSPERO CRD42020196692

Keywords: analgesics; systematic review; third molar; tooth extraction


Introduction

The surgical extraction of mandibular third molars is one of the most common dentoalveolar surgeries.¹ This surgery can cause tissue and cellular disturbances, resulting in the production and release of biochemical mediators involved in the inflammatory process, such as histamine, bradykinin, and prostaglandins.² Therefore, this procedure is often followed by postoperative complications, including pain, trismus, and swelling, affecting the patients’ quality of life.¹³⁴

The literature shows different randomized clinical trials (RCTs) evaluating anti-inflammatory drugs administered after third molar removal to avoid deviations from normal healing.⁵⁻⁹ Thus, systematic reviews of RCTs have been conducted to indicate an effective postoperative therapeutic protocol in this surgical procedure. In this sense, studies comparing non-steroidal anti-inflammatory drugs (NSAIDs) with other therapeutic protocols in third molar extractions showed that NSAIDs are likely to be
an effective pharmacologic class of analgesics.\textsuperscript{10-13} Another systematic review concluded that paracetamol is a safe and effective drug for the management of postoperative pain in mandibular third molar surgery.\textsuperscript{14} However, we found evidence that ibuprofen has superior analgesic efficacy when compared to paracetamol in lower wisdom teeth extractions.\textsuperscript{15}

Different therapeutic protocols available for postoperative pain control after third molar surgery were compared in a narrative systematic review suggesting that there is strong evidence for the use of paracetamol and ibuprofen to control postoperative pain.\textsuperscript{16} An important limitation was the inclusion of patients undergoing different therapeutic strategies. No data were pooled in the statistical meta-analysis in this study.

Although some systematic reviews were published to assess the efficacy and safety of oral drugs to control inflammatory parameters in post–third molar surgeries, only traditional meta-analyses were performed.\textsuperscript{10,14,15} Typically, a direct meta-analysis allows only pairwise comparisons, thus, in the absence of direct comparisons, the potential benefit of a given anti-inflammatory drug remains unknown. Moreover, pain was the only outcome evaluated by most of these previous studies. In general, swelling and trismus are also recognized as important complications related to surgical procedures.\textsuperscript{4}

Thus, to compare different anti-inflammatory drugs concerning the most important inflammatory outcomes (pain, edema, trismus, and adverse effects), a new systematic review with network meta-analysis (NMA) of the existing therapeutic protocols within mandibular third molar surgery is necessary. The pooled data of RCTs in statistical NMA provide the best evidence regarding the effectiveness of therapeutic strategies and the comparative advantages of treatments in a rank according to their anti-inflammatory performance.\textsuperscript{17}

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted, and no current or in-progress systematic reviews on the topic were identified. The aim of this systematic review is to compare the effects of all oral anti-inflammatory and analgesic drugs administered in the postoperative period of mandibular third molar surgeries in controlling pain, edema, trismus, and with few adverse effects, and to rank the different drugs or coadministration based on their performance with a network meta-analysis.

**Review question**

What is the best postoperative drug regimen in lower third molar surgeries to control pain, edema, and trismus and with few adverse effects?

**Inclusion criteria**

**Population**

Patients will be included in this systematic review if they met the following inclusion criteria:

- healthy patients (without any comorbidities) or patients who had treated and controlled systemic diseases who are 18 years or older;
- asymptomatic and free of pain, swelling, or acute infection or inflammation at the surgical site immediately before mandibular third molar surgery;
- underwent surgical removal of one mandibular third molar at a time (semi- or fully impacted), in which they have received oral drugs (anti-inflammatory and/or analgesics) in the postoperative moment. The definition of “postoperative” is the period after completion of the surgical procedure. It can be given immediately after the surgical procedure or can it be hours or days after the surgery.

Trials in which patients have received drugs (anti-inflammatory, analgesics, anxiolytic, or antibiotics) pre-emptively or have undergone recent local surgical procedures (less than 30 days) will be excluded.

**Intervention**

The intervention is postoperative oral drugs (anti-inflammatory and/or analgesics) in which only one drug or coadministration has been used. There will be no limits regarding dosage or pharmaceutical form. Studies will be excluded if the postoperatively administered substances are either herbal homeopathic medications, topic anti-inflammatory and/or analgesics, or prescription pre-emptive anti-inflammatory and/or analgesics.

**Comparators**

The comparators are placebo or other postoperative oral drugs (anti-inflammatory and/or analgesics) in which only one drug or coadministration was used,
or the same drug with different doses was used in the intervention group.

**Outcomes**
The primary outcome will be pain during the first seven days assessed using VAS scale or the analgesic intake. The secondary outcomes will be edema evaluated through measurement made between reference points on face; trismus evaluated by measuring the distance between the edges of the upper and lower right central incisors at maximum opening of the jaw during the first seven days; and adverse effects.

**Types of studies**
This review will consider RCTs (parallel group or split-mouth design) comparing anti-inflammatory and/or analgesic drugs with other anti-inflammatory and/or analgesic drugs, with the same methods investigated as intervention in different dosages, or with placebo group. In the split-mouth design, a mouth is divided into two or more experimental segments that are randomly assigned to different intervention. This review will consider studies reporting the primary outcome (pain in the first seven days after surgery) and/or the secondary outcomes (edema and/or trismus in the first seven days, adverse effects).

Studies of experimental pain, studies where pain relief is not assessed by the patient’s report, duplicate studies, studies with a design not compatible with the review objective, trials not connected by interventions, and those that did not clarify the methods used in the study will be excluded. Conference abstracts, letters to editors, and case reports will also be excluded. No restrictions of date of publication or language will be applied.

**Methods**
This systematic review protocol is reported in line with JBI methodology for systematic reviews of effectiveness evidence. The systematic review protocol was registered in PROSPERO (CRD4202019 6692).

**Search strategy**
The search strategy will aim to locate both published and unpublished primary studies. An initial limited search of MEDLINE (via PubMed), Cochrane Database of Systematic Reviews, Dentistry & Oral Sciences Source, and PROSPERO was undertaken to locate existing or ongoing reviews on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy. The keywords and combinations of the following search terms were included: “analgesics,” “analgesic drugs,” “anodynes,” “analgesic agents,” “antinociceptive agents,” “anti-inflammatory agents,” “anti-inflammatoryatories,” “third molar,” and “wisdom tooth.” The search strategy, including all identified keywords and index terms, will be adapted for each included information source (Appendix I). The reference list of all studies selected for critical appraisal will be screened for additional studies.

**Information sources**
The sources to be searched include the Cochrane Register of Controlled Trials (CENTRAL) in the Cochrane Register of Studies (via Cochrane Library), Virtual Health Library (VHL; via bvsalud.org), MEDLINE (via PubMed), Web of Science, and Embase (via embase.com). ClinicalTrials.gov will be assessed to identify potential ongoing studies. The search for unpublished/gray literature will include Google Scholar and OpenGrey.

**Study selection**
Following the search, all identified citations will be collated and uploaded into EndNote v.X8 (Clarivate Analytics, PA, USA), and duplicates will be removed. Titles and abstracts will then be screened by four independent reviewers (GMS, RAM, IAF, and KNAS) for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full, and their citation details will be imported into EndNote. The full text of selected citations will be assessed in detail against the inclusion criteria by two pairs of independent reviewers (GMS and RAM; IAF and KNAS). Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or by a third reviewer (SGMF). The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.
**Assessment of methodological quality**

Eligible studies will be critically appraised by two independent reviewers (GMS and RAM) at the study level using standardized critical appraisal instruments from JBI. Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (IAF). The results of the critical appraisal will be reported in narrative form and in a table. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). Included studies will be stratified by methodological quality.

**Data extraction**

Data will be extracted from studies included in the review by two independent reviewers (GMS and RAM) using the standardized JBI data extraction tool. The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (IAF). Authors of papers will be contacted to request missing or additional data, where required.

The following information will be extracted from each included study:

- **Outcome**: amount of pain, edema and trismus during the first seven post-operative days, rescue analgesic intake, and adverse effects attributable to anti-inflammatory and analgesic drugs (e.g., dizziness, nausea, vomiting, disorientation, and seizures).
- **Characteristics of the studies**: author(s), year of publication, country, study design (parallel group or split-mouth design), eligibility criteria, sample size (patients and/or teeth extracted), intervention, and control groups.
- **Characteristics of the participants**: gender, age, third molar side (right or left) and third molar classification (Pell and Gregory and/or Winter classification).
- **Characteristics of the interventions**: anesthetic used (type and quantity), intervention drug (dosage), pharmaceutical form (tablet, capsule, solution, suspension, emulsion), timing of administration, and posology.

**Data synthesis**

Studies will be pooled with traditional statistical meta-analysis for each pairwise comparison using the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia), when possible. Effect sizes will be expressed as either relative risk (RR; for dichotomous data) or weighted (or standardized) mean differences (for continuous data), and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard $\chi^2$ and $I^2$ tests. Statistical analyses will be performed using random effects meta-analysis if $I^2 \geq 30\%$ and fixed effects models if $I^2 < 30\%$. Moreover, a careful evaluation of clinical and methodological heterogeneity across the studies will provide information to make sure that the network maintains transitivity. Thus, a table of trial characteristics that may act as effect modifiers will be compiled from the data collected. Potential effect modifiers include pharmaceutical form (tablet, capsule, solution, suspension, emulsion), timing of administration, and posology.

Where possible, network meta-analysis will be conducted using a Frequentist approach to simultaneously compare multiple treatments via a common comparator. First, a network of treatment comparisons combining both direct and indirect evidence in a single model will be performed. To verify whether the information of both sources between direct and indirect evidence are similar enough to be combined (consistency assumptions), we will examine the regression coefficient of the inconsistency model for each study design and then test the linearity of the regression coefficients for all models. The $p$-value $> 0.05$ and $\tau^2 = 0$ support consistency in the analysis. To explore statistical heterogeneity, sensitivity analyses will be conducted to assess the influence of the effect modifiers in the network. The ranking probabilities will be estimated based on the frequentist analogue of the SUCRA (surface under the cumulative ranking) curve. Publication bias will be checked using funnel plots and Egger and Begg tests as long as more than 10 studies are included in the meta-analysis. All analyses will be implemented using the “meta” and “netmeta” packages of the R statistical software v.3.6.2 (Lucent Technologies, NJ, USA).

A narrative summary will be provided if statistical analysis is not possible.
Assessing certainty in the findings
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence for specific comparison included in the NMA will be followed, and a Summary of Findings (SoF) will be created using GRADEPro GDT (McMaster University, ON, Canada). The direct comparison will start from high certainty of evidence and then determine whether serious or very serious concerns of risk of bias were present. Then, the indirect evidence will be rated down if there were serious concerns of intran- sitivity and so, the certainty of evidence will be rated down if there was concern of imprecision or incoherence for the final NMA estimate. The outcomes reported in the SoF will be pain, edema, and trismus.

Acknowledgments
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) for the scholarships. The Programa de Pós-graduação em Odontologia, Universidade Federal dos Vales do Jequitinhonha e Mucuri, which provided technical support for the development and implementation of this study.

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

References
Appendix I: Search strategy

MEDLINE (PubMed)

Search conducted December 2020

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