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Protocol: Intra-alveolar adjunctive therapies for reducing postoperative complications after mandibular third molar surgery: a systematic review with planned network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 April 2026 and was last updated on 3 April 2026.

INTRODUCTION

Review question / Objective The objective of this study is to compare five intra-alveolar adjunctive therapies (platelet-rich fibrin, ozone, hyaluronic acid, chlorhexidine, and absorbable collagen sponge) for reducing postoperative complications following mandibular third molar surgery using a network meta-analysis of randomized controlled trials. This study aims to evaluate the relative effectiveness and strength of the available evidence supporting each intervention, thereby guiding clinical decision-making toward safer and more effective practices. Additionally, it seeks to identify gaps in the literature to inform the design of future randomized clinical trials in this field.

Rationale Mandibular third molar surgery is one of the most frequently performed procedures in oral and maxillofacial surgery. Despite its routine nature, it is commonly associated with

postoperative complications such as pain, edema, trismus, and alveolar osteitis, which can significantly impair patients' short-term recovery and quality of life. Therefore, identifying effective strategies to minimize these complications is essential to optimize postoperative outcomes. In this context, intra-alveolar adjunctive therapies applied transoperatively—directly into the extraction socket during surgery—have been proposed as targeted approaches to modulate local healing and reduce postoperative inflammatory complications. These interventions include platelet-rich fibrin (PRF), ozone, hyaluronic acid, chlorhexidine, and absorbable collagen sponges, all of which act locally at the surgical site. Although these techniques are widely reported in the literature, the growing number of available interventions, combined with heterogeneity in study design and methodological limitations across randomized controlled trials, makes it challenging to establish clear and reliable clinical recommendations. Consequently, clinical decision-

making may vary substantially, and some interventions may be adopted without robust scientific evidence, potentially leading to inconsistent outcomes and unnecessary additional procedures.

To address these challenges, this study will synthesize evidence from randomized controlled trials using a network meta-analysis framework, enabling the simultaneous comparison of multiple intra-alveolar transoperative interventions. This approach allows the estimation of relative treatment effects and the ranking of interventions according to their effectiveness in reducing postoperative complications. In addition, the study will assess the risk of bias and certainty of the evidence to ensure a comprehensive and reliable synthesis.

By identifying the most effective intra-alveolar transoperative strategies and highlighting gaps in the current literature, this study aims to support evidence-based clinical decision-making and inform the design of future high-quality randomized clinical trials in this field.

Condition being studied Postoperative complications (pain, edema, trismus, and alveolar osteitis) following mandibular third molar surgery and their management using intra-alveolar transoperative adjunctive therapies applied directly into the extraction socket.

METHODS

Search strategy The detailed search strategy is provided in the supplementary materials of this protocol.

Participant or population Healthy patients requiring mandibular third molar surgery. No other restrictions on sex, gender, or ethnicity were placed on the population of the study.

Intervention Only intra-alveolar adjunctive interventions administered transoperatively, directly into the extraction socket during mandibular third molar surgery, will be considered. Eligible interventions include platelet-rich fibrin (PRF), ozone, hyaluronic acid, chlorhexidine, and absorbable collagen sponge. Studies evaluating systemic therapies, non-local interventions, or postoperative applications not delivered intra-alveolarly at the time of surgery will be excluded.

Comparator Eligible intra-alveolar adjunctive interventions will be compared against each other through a network meta-analysis framework, using the no-treatment control group (natural blood clot) as the common reference comparator. Studies

directly comparing two or more eligible interventions will also be included and incorporated into the network.

Study designs to be included Studies in humans, including only randomized clinical trials.

Eligibility criteria Studies will be selected based on the predefined PICOS criteria (Participants, Interventions, Comparators, Outcomes, and Study design) described in the corresponding sections. Eligible studies will include randomized controlled trials conducted in humans that evaluate intra-alveolar adjunctive interventions administered transoperatively during mandibular third molar surgery. Studies without accessible full text will be excluded. Trials investigating systemic interventions (e.g., pharmacological regimens), non-local therapies, or interventions not delivered intra-alveolarly at the time of surgery will be excluded.

Information sources We will search the following electronic bibliographic databases: EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. The reference lists of the articles identified will be cross-checked. Furthermore, studies from the 'grey literature' will be screened through the following trial registry platforms: Current Controlled Trials (<http://www.controlled-trials.com>), ClinicalTrials.gov (<http://www.clinicaltrials.gov>), and EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/ctr-search/search>). A manual search will be done in the relevant journals of dentistry. If necessary, the searches will be re-run just before the final analyses, and further studies will be retrieved for inclusion.

Main outcome(s) The primary outcomes are postoperative pain, edema, trismus, and alveolar osteitis, assessed using any validated measurement tools during the postoperative period. Pain may be measured using scales such as the visual analogue scale (VAS) or numerical rating scale (NRS); edema through linear or volumetric measurements; trismus by maximum mouth opening; and alveolar osteitis based on clinical diagnosis criteria. Data will be extracted at predefined time points (e.g., postoperative days 1, 3, and 7), prioritizing the most commonly reported time points across studies.

Additional outcome(s) None.

Data management The studies will be imported into Endnote 2025 software (Clarivate, Philadelphia, PA, USA), where duplicates will be

automatically removed. All analyses will be performed using the software R (the latest available version for Mac OS X computer system). The package "netmeta" will be used to run network meta-analysis. This package is available from the Comprehensive R Archive Network (CRAN).

Quality assessment / Risk of bias analysis Risk of Bias 2 (ROB2) tool according to the methods described by the Cochrane Collaboration. The assessment of evidence quality will be measured using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which allows the evaluation of the following five domains: (i) risk of bias, (ii) inconsistency, (iii) indirectness, (iv) imprecision, and (v) overall quality of evidence.

Strategy of data synthesis A frequentist network meta-analysis will be performed using direct and indirect evidence from eligible comparisons. We will provide a quantitative and narrative synthesis to summarize the level of evidence of different methods to reduce postoperative complications following mandibular third molar surgery. We will provide summaries of intervention effects for each study by calculating standardized mean differences or mean differences in continuous outcomes, and odds ratios or risk ratios in dichotomous outcomes. We will pool the results using a random-effects model, given the expected clinical and methodological heterogeneity across studies. Heterogeneity will be assessed using both the τ^2 test and the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. The heterogeneity within designs and between designs will be analyzed. Additionally, the assumption of transitivity and similarity based on clinical and methodological characteristics will be assessed. Global inconsistency will be assessed using the design-by-treatment interaction model, and local inconsistency will be explored using the Net Heat Plot. Publication bias will be assessed using comparison-adjusted funnel plots when sufficient studies are available. The overall ranking of different interventions will be determined by calculating the Surface Under the Cumulative Ranking curve (SUCRA) values. In addition to the network meta-analysis, conventional pairwise meta-analyses will be conducted for each intervention compared with the no-treatment control group when sufficient data are available. These analyses will be used to compare direct evidence with network estimates and to assess the consistency and robustness of the findings. Although the included interventions differ in their

mechanisms of action, they are considered clinically comparable within the network because all are intra-alveolar adjunctive therapies administered transoperatively into the extraction socket during mandibular third molar surgery, with the objective of reducing postoperative inflammatory complications. The transitivity assumption will be assessed by examining the distribution of potential effect modifiers across treatment comparisons, including patient characteristics, surgical difficulty, baseline risk, perioperative cointerventions, intervention delivery characteristics, and outcome assessment time points. If major clinical or methodological intransitivity is identified, its impact will be explored through sensitivity or exploratory analyses whenever feasible.

Subgroup analysis Subgroup analyses may be conducted based on key clinical or methodological variables, such as surgical difficulty, use of perioperative cointerventions (e.g., corticosteroids or antibiotics), risk of bias, and outcome assessment time points, if sufficient data are available.

Sensitivity analysis Trials with major imbalances in perioperative cointerventions across study arms will be carefully examined, and their impact on network assumptions will be explored in sensitivity analyses whenever feasible.

Language restriction Studies published in any language will be selected.

Country(ies) involved Brazil, United States.

Keywords third molar; postoperative complications; local interventions; pain; swelling; alveolar osteitis; systematic review; Platelet-rich fibrin; ozone; hyaluronic acid; chlorhexidine; and absorbable collagen sponge.

Dissemination plans The findings of this systematic review will be disseminated through different approaches to reach a broad audience of researchers, clinicians, and stakeholders. It will be submitted for publication in a high-impact, international peer-reviewed journal specializing in oral and maxillofacial surgery. Additionally, the results will be presented at relevant national and international scientific conferences to facilitate discussion and collaboration within the scientific community.

List of included authors

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