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Evaluation of postoperative complications after mandibular third molar surgery with the use of platelet-rich fibrin: a systematic review and meta-analysis

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Abstract. The current literature was reviewed to analyze the effects of platelet-rich fibrin (PRF) on postoperative complications after mandibular third molar surgery (pain, alveolar osteitis, swelling, and bone healing). A comprehensive literature search was performed up to 2016 in the PubMed/MEDLINE, Cochrane Library, LILACS, and ScienceDirect databases and the grey literature. Additional records were identified through manual and reference searches. The full-text articles of potentially relevant studies were reviewed; only randomized clinical trials were included. Two review authors assessed the risk of bias independently. A total of 1430 publications were evaluated, of which seven were selected for qualitative analysis and two for quantitative analysis. A meta-analysis was performed only for alveolar osteitis, due to the considerable heterogeneity among studies for the other outcome variables. There were 485 extractions (243 test, 242 control) in 280 patients. PRF appeared to accelerate healing in mandibular third molar surgery, reducing postoperative pain and swelling. Quantitative analysis showed a decrease in prevalence of alveolar osteitis (odds ratio 0.31, 95% confidence interval 0.13–0.77, $Z = 2.54$, $P = 0.01$). Although more clinical trials of a better design and with larger samples are necessary to allow definitive conclusions to be drawn, PRF is a potentially useful biomaterial.

Key words: third molar surgery; platelet-rich fibrin; pain; swelling; bone healing; alveolar osteitis; systematic review.

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Mandibular third molar surgery is one of the most common procedures performed in dentistry. In cases where the teeth are deeply impacted and covered by a large quantity of bone, surgery can be very difficult, leading to increased tissue manipulation, a longer operation time, and consequently more postoperative discomfort[1]. Postoperative complications include pain, swelling, infection, alveolar osteitis (dry socket), and haemorrhage[2]. Oral and maxillofacial surgeons always seek to improve their surgical technique, in order to reduce these complications after surgery.

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate, developed by Choukroun et al. in France[3]. This biomaterial is autologous and has many clinical applications. It is produced without the addition of anticoagulant and with no gelling agent, through the immediate centrifugation of blood after collection[3–8]. The theory is that the use of platelet concentrates improves healing by slow release of growth factors and cytokines that are derived from the blood platelets and leukocytes[7]. Furthermore, another important characteristic of this biomaterial is the fibrin matrix, which is produced by natural polymerization[9]. The unique architecture of the fibrin matrix together with its leukocyte content may have a potential healing effect, reducing the morbidity associated with surgery. One of the main advantages of PRF over the first-generation platelet concentrate – platelet-rich plasma (PRP) – is the complex and resilient structure of the fibrin matrix; this matrix holds a significant quantity of cytokines within its structure, which are released slowly during healing[10].

The use of PRF as a surgical adjuvant has been proposed for several types of procedure. Applications reported in the literature include the treatment of bony defects, maxillary sinus augmentation, dental implant surgery, periodontal tissue engineering, post-extraction socket healing, and third molar surgery, all with promising results[11–16]. With regard to mandibular third molar surgery specifically, some authors have described the beneficial effects of PRF in reducing pain and alveolar osteitis after surgery[13,17]. However, the true effect of PRF on potential post-surgical complications is unclear.

The objective of this systematic review was to answer the following focused question: Is there a difference in postoperative complications (pain, alveolar osteitis, swelling, and bone healing impairment) when PRF is used in mandibular third molar surgery?

Materials and methods

This study was registered in the PROSPERO database (number CRD42016043438). The PRISMA statement guidelines for systematic reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were followed to summarize the evidence accurately and reliably[18]. The risk of bias was assessed using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials[19]. The PICOS strategy was followed: (P) patients or population: adolescents and/or adults requiring the extraction of a mandibular third molar; (I) intervention: placement of autologous PRF in the alveolar socket following extraction; (O) outcomes: the evaluation of pain, prevalence of alveolar osteitis, and facial swelling within the initial 7 days after mandibular third molar surgery, and evaluation of bone healing with a minimum follow-up of 4 weeks after mandibular third molar surgery; (S) study design: studies in humans, including only randomized controlled clinical trials (RCT). No term was used in the comparator or control group (C), because PRF was compared with the absence of socket treatment.

Studies that included participants aged <17 years or >60 years, studies in which anticoagulants were used to prepare PRF, and studies in which additional therapeutic procedures were used were excluded. Articles that did not describe a randomization process in the methodology were also excluded. Additionally, non-controlled clinical trials, quasi-randomized studies, editorial letters, historical reviews, in vitro studies, cohort studies, and observational and descriptive studies were also excluded.

An electronic search of the MEDLINE/PubMed database, Cochrane Library, Latin American and Caribbean Health Sciences Literature database (LILACS), and ScienceDirect database was conducted from their respective dates of inception to August 2016. Medical subject heading (MeSH) terms and free text words were used in the search. The MEDLINE/PubMed search strategy was: Molar, Third [MeSH Terms] OR Tooth Extraction [MeSH Terms] OR Surgery, Oral[MeSH Terms] OR Oral Surgical Procedures [MeSH Terms] OR Tooth Socket[MeSH Terms] OR Tooth, Impacted[MeSH Terms] OR molar OR third OR third molar OR wisdom tooth OR tooth OR teeth OR dental AND Blood Platelets[MeSH Terms] OR Platelet-Rich Plasma[MeSH Terms] OR Fibrin/therapeutic use[MeSH Terms] OR platelet rich fibrin OR platelet concentrate OR Choukroun's PRF OR PRF AND Pain[MeSH Terms] OR Edema[MeSH Terms] OR Dry Socket[MeSH Terms] OR Wound Healing[MeSH Terms] OR Bone Regeneration[MeSH Terms] OR pain OR swelling OR alveolitis OR bone OR complications OR healing. This strategy was adapted for the other database searches. The titles and abstracts of the resulting articles were checked, and the full-text article was obtained for those that the authors considered relevant.

The reference lists of the articles identified were cross-checked for unidentified published material. Furthermore, studies from the 'grey literature' were 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). The Brazilian database of theses and dissertations (Banco de Teses and Dissertações – CAPES) was checked for unpublished material. A manual search was done in the relevant journals: *British Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery*, *International Journal of Oral and Maxillofacial Surgery*, *Clinical Oral Investigations*, *Journal of Dentistry*, *Journal of Cranio-Maxillo-Facial Surgery*, and *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. No language restriction was applied in the search process.

The screening process was performed by two of the review authors independently (JVC and FGR); any disagreements between the two reviewers during the selection process were resolved through additional discussion with the senior reviewer (PJM). The primary outcome evaluated was the amount of pain after mandibular third molar surgery. The secondary outcomes evaluated were the prevalence of alveolar osteitis, amount of facial swelling, and bone healing after mandibular third molar surgery. The review authors also independently assessed the risk of bias using the Cochrane Collaboration tool. Sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias were analyzed by the authors. Similarly any disagreement between the two reviewers was resolved by discussion with the senior reviewer.

A meta-analysis was performed for the quantitative variable 'alveolar osteitis'.