



Universidade Federal de Uberlândia
Faculdade de Odontologia
Programa de Pós-Graduação em Odontologia



Vinícius Lima de Almeida

**Desempenho de concentrados sanguíneos no controle dos sinais e sintomas
inflamatórios após a exodontia dos terceiros molares inferiores**

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia, como requisito parcial para obtenção do Título de Mestre em Odontologia na Área de Concentração de Clínica Odontológica Integrada.

Uberlândia

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DEDICATÓRIA

Aos meus pais (Neusa Lima Almeida e José Vilobaldo de Almeida Filho), a minha irmã (Vivian Cristine Lima de Almeida), a minha esposa (Alessandra Gondim Fernandes Lima, a minha filha (Eloah Fernandes Lima de Almeida) e aos meus avós (Maria José Costa de Almeida e José Vilobaldo de Almeida), dedico este trabalho por todo incentivo e apoio ao longo de toda a pós-graduação.

De modo especial dedico não só a presente pesquisa, mas toda a minha trajetória à minha mãe (Neusa Lima Almeida) e aos meus amados avós, Maria Rosa da Santos Lima (in memoriam) e João da Costa Lima (in memoriam).

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Resumo

O presente estudo visa resumir as evidências disponíveis e responder à seguinte pergunta: “O que se sabe sobre o desempenho de concentrados sanguíneos no manejo das sequelas após a exodontia dos terceiros molares inferiores em relação às evidências disponíveis em revisões sistemáticas?”. Uma busca eletrônica foi feita nas bases de dados Cochrane Library, Embase, LILACS, MEDLINE (*via* PubMed), SciELO, Scopus e Web of Science. Além disso, as bases EASY e MedRxiv também foram utilizadas para capturar parcialmente a “literatura cinza”. Foram incluídas revisões sistemáticas, com ou sem meta-análise, que investigaram o desempenho de concentrados sanguíneos no controle das sequelas após a exodontia dos terceiros molares inferiores. Quatro desfechos foram analisados: dor, edema, abertura bucal e osteíte alveolar. A qualidade metodológica das revisões sistemáticas incluídas foi avaliada por meio da ferramenta AMSTAR 2, e o risco de viés foi avaliado usando a ferramenta ROBIS. Dentre os 388 registros encontrados, 13 revisões sistemáticas foram elegíveis para o presente estudo. No geral, as revisões sistemáticas avaliaram 57 estudos primários publicados de 2007 a 2021, sendo que houve 30 sobreposições de estudos selecionados entre as revisões sistemáticas. De acordo com o AMSTAR-2, nenhuma revisão sistemática incluída apresentou alta ou moderada qualidade metodológica. Segundo o ROBIS, apenas uma revisão sistemática foi julgada com baixo risco e as demais com alto risco de viés. Esta overview apresenta limitações de alta heterogeneidade e risco de viés nas revisões sistemáticas incluídas e em seus estudos primários, o que dificulta a consolidação de evidências precisas. Contudo, ainda há o benefício de enfatizar a cautela na interpretação de dados para a tomada de decisões clínicas sobre o uso de concentrados sanguíneos, visto que foi possível identificar, por meio de uma análise minuciosa, falhas metodológicas relevantes em revisões sistemáticas aparentemente robustas sobre o tema. Fatores biológicos pertinentes aos concentrados sanguíneos mostram-se promissores na otimização do processo de reparo tecidual, mas resultados inconclusivos tanto em ensaios clínicos randomizados quanto em revisões sistemáticas são obtidos no que diz respeito a eficácia desses produtos no controle das sequelas após a exodontia do terceiro molar inferior.

Palavras-Chave: Dente Serotino; L-PRF; Dor; Edema; Trismo; Alveolite.

Abstract

The present study aims to summarize the available evidence and answer the following question: What is the current knowledge on the performance of blood concentrates in handling sequelae after lower third molar extractions with the evidence available in systematic reviews? An electronic search was made in the Cochrane Library, Embase, LILACS, MEDLINE (via PubMed), SciELO, Scopus, and Web of Science databases. The EASY and MedRxiv databases were also used to capture the "grey literature." The study included systematic reviews with or without meta-analyses that investigated the performance of blood concentrates in controlling sequelae after lower third molar extractions. Four outcomes were analyzed: pain, edema, mouth opening, and alveolar osteitis. The AMSTAR-2 tool evaluated the methodological quality of the included systematic reviews, and ROBIS assessed the risk of bias. Among the 388 results, 13 systematic reviews were eligible for the present study. Overall, these reviews evaluated 57 primary studies published from 2007 to 2021, with 30 overlaps of studies selected for the systematic reviews. According to the AMSTAR-2, none of the included systematic reviews presented high or moderate methodological quality. The ROBIS tool showed only one systematic review with a low risk, and the others had a high risk of bias. The limitations of this overview are high heterogeneity and risk of bias in the included systematic reviews and their primary studies, complicating the establishment of correct evidence. However, it is worth noting that the data must be carefully interpreted for clinical decision-making on blood concentrate use, as a detailed analysis showed relevant methodological flaws in apparently robust systematic reviews on the topic. Biological factors pertinent to blood concentrates are promising for optimizing tissue repair, and randomized clinical trials and systematic reviews show inconclusive results regarding the efficacy of these products in controlling sequelae after lower third molar extraction.

Keywords: Third Molar; Pain; Edema; Trismus; Alveolitis.

Introdução & Referencial teórico

INTRODUÇÃO E REFERÊNCIAL TEÓRICO

A remoção de terceiros molares é um procedimento de rotina na clínica odontológica e está frequentemente associada a complicações pós-operatórias, tais como dor, edema e trismo¹. Essas complicações decorrem de uma resposta inflamatória exacerbada, que é consequência direta do procedimento cirúrgico, limita funções diárias do paciente e compromete sua qualidade de vida durante a recuperação². Esse resultado pode estar relacionado à maior complexidade e, por vezes, necessidade de técnicas cirúrgicas mais invasivas para remoção desses elementos dentais³.

O reparo tecidual é um processo complexo que visa restabelecer a integridade e a função dos tecidos afetados por traumas. Esse processo envolve a interação coordenada entre células e uma ampla variedade de mediadores químicos. Inicia-se no momento do trauma e pode perdurar por períodos de duração variável⁴. O processo de reparo é geralmente dividido em quatro etapas distintas: hemostasia, inflamação, proliferação e remodelação. É importante ressaltar que a fase inflamatória desempenha um papel crucial no período subsequente à cirurgia, estando associada às possíveis complicações pós-operatórias⁵. O estabelecimento de estratégias visando otimizar o processo de reparo tecidual, com o objetivo de restaurar a fisiologia do tecido e minimizar as repercussões no pós-operatório, representa um desafio constante. Tais estratégias buscam melhorar a qualidade de vida do paciente^{3,6}. Diversas terapêuticas são utilizadas para otimizar esse processo, cada uma com suas vantagens e desvantagens. Entre elas, destacam-se o uso de anti-inflamatórios e analgésicos, laserterapia de baixa intensidade⁷, crioterapia⁸, produtos fitoterápicos⁵ e a utilização de produtos derivados do sangue⁹.

A aplicação de produtos derivados do sangue no campo cirúrgico teve início há mais de 40 anos, com a utilização do adesivo de fibrina para otimizar o processo de reparo de feridas^{9,10}. Resultados promissores motivaram à realização de pesquisas cujos resultados levaram ao desenvolvimento dos concentrados sanguíneos, tendo o plasma rico em plaquetas (PRP) como concentrado de primeira geração^{11,12}. Esse derivado sanguíneo contém mais de 95% de plaquetas e níveis elevados de fatores de crescimento plaquetários, tais como o fator de crescimento derivado de plaquetas (PDGF) e o fator de crescimento do endotélio vascular (VEGF), além de fatores de coagulação e citocinas. Esses componentes possuem a capacidade de otimizar o reparo tecidual por meio do estímulo à angiogênese, a proliferação celular e

ativação de células vinculadas ao processo de cicatrização de feridas, como fibroblastos, neutrófilos e células tronco-mesenquimais^{13,14}.

Os benefícios ao processo de cicatrização de feridas levaram à crescente utilização do PRP. No entanto, seu modo de obtenção e manuseio limitaram o seu potencial. Os protocolos para sua obtenção exigem um tempo clínico prolongado, variando de 30 minutos a mais de 1 hora, e a adição de procoagulantes, como a trombina bovina ou cloreto de cálcio, é necessária para a formação de um coágulo¹⁵. Além disso, o PRP apresenta consistência líquida e sua aplicação exige a combinação com outros biomateriais como aloenxertos e xenoenxertos, a fim de permitir sua aplicação. Outro entrave é a liberação rápida e curta de fatores de crescimento presentes no PRP^{16,17}. Em resposta a essas limitações, pesquisas tem sido conduzidas em busca de novos produtos derivados do sangue. Um desses avanços é a fibrina rica em plaquetas (PRF), que devido suas características, é considerado um concentrado sanguíneo de segunda geração, que foi desenvolvida na França em 2001¹⁸.

A fibrina rica em plaquetas, posteriormente renomeada fibrina rica em plaquetas e leucócitos (L-PRF), possui um método mais simples na sua produção. Diferentemente do PRP, não são necessários procoagulantes como a trombina e o cloreto de cálcio, e o protocolo de centrifugação necessita somente um ciclo de 700 g com um período de 12 minutos^{15,19,20}. Após a coleta do sangue em tubos de vidro e aplicação desse protocolo de centrifugação, três camadas são formadas nos tubos: o plasma acelular (camada superior), células vermelhas (camada inferior) e o coágulo de fibrina L-PRF (camada intermediária)¹⁹. A camada intermediária consiste em uma matriz de fibrina tridimensional contendo vários fatores de crescimento tais como o PDGF, VEGF, fator de crescimento transformador beta (TGF-beta), fator de crescimento de insulina (IGF) e o fator de crescimento epidérmico (EGF), além das plaquetas e componentes celulares. Somado ao elevado quantitativo de fatores teciduais, os leucócitos desempenham papel essencial no processo de reparo tecidual, apresentando maior potencial no processo de angiogênese e na formação de tecidos^{20,21}. Dessa forma, o L-PRF contempla mais requisitos para o reparo tecidual, pois proporciona um arcabouço tridimensional de fibrina, atua como um reservatório de citocinas e fatores de crescimento de liberação lenta (10 a 14 dias) e possui células como macrófagos e neutrófilos, além de fragmentos celulares como plaquetas²².

O L-PRF tem apresentado resultados clínicos promissores nas diversas áreas da medicina e odontologia^{23,24}. Com objetivo de beneficiar cada vez mais o processo de reparo tecidual, pesquisas foram realizadas com o intuito de analisar a influência de protocolos de

centrifugação na arquitetura da matriz de fibrina, na distribuição celular ao longo dessa matriz e na capacidade de liberação de fatores de crescimento²⁵. Surgiu, então, o conceito de centrifugação de baixa velocidade, que, combinado com diferentes tempos de centrifugação, resultou no desenvolvimento de concentrados sanguíneos conhecidos como fibrina rica em plaquetas avançado (A-PRF) e fibrina rica em plaquetas avançado plus (A-PRF+)^{22,26}. Estudos *in vitro* demonstraram que essa nova geração de concentrados sanguíneos possuem uma matriz tridimensional de fibrina mais porosa, distribuição celular homogênea e com maior concentração e possibilidade de liberação de fatores de crescimento^{27,28}. Essa liberação aumentada de fatores teciduais pode tornar essa matriz superior ao L-PRF em algumas situações clínicas²⁸.

Com o objetivo de aplicar os possíveis benefícios dessa terapêutica em prol de um pós-operatório mais confortável, autores utilizaram esses concentrados sanguíneos em alvéolos de terceiros molares inferiores, após a exodontia e, analisaram seu papel no controle dos sinais e sintomas inflamatórios^{29,30,31,32}. Apesar de resultados promissores serem esperados no manejo da dor, do edema e do trismo, a literatura científica tem apresentado discrepâncias nesse sentido, com estudos reportando achados conflitantes.

Os resultados do estudo de Ogundipe et al. (2011)²⁹, mostraram que a aplicação tópica de PRP nos alvéolos após a exodontia do terceiro molar inferior proporcionou menor escore médio de dor pós-operatória, enquanto não houve diferença estatisticamente significativa na redução do edema e trismo quando comparado ao grupo controle. Esses resultados mostram-se contraditórios com o estudo de Gandevivala et al. (2017)³¹, no qual a aplicação tópica de PRP proporcionou redução estatisticamente significativa do edema, enquanto não houve diferença estatisticamente entre os lados teste e controle com relação a dor.

A literatura também se mostra contraditória quanto ao papel do L-PRF no controle dos sinais e sintomas inflamatórios. Os resultados do estudo de Kumar et al. (2016)³³, determinam que o grupo teste experimentou redução estatisticamente significativa no escore de dor durante o primeiro, segundo e sétimo dia pós-operatório. Embora Asutay et al. (2017)³⁴, afirmem que esse concentrado sanguíneo tenha um efeito positivo no reparo tecidual, os resultados desse estudo mostraram não haver diferença estatisticamente significativa com relação a dor, edema e trismo, quando comparado ao grupo controle, após a exodontia do terceiro molar inferior.

O A-PRF parece ser mais consistente no manejo da dor. Caymaz e Uyanic (2019)³⁵, realizaram uma comparação desse concentrado sanguíneo com o L-PRF após a exodontia do

terceiro molar inferior e foi observado que houve diferença estatisticamente significativa para o controle a dor a favor do A-PRF, com este último levando aos menores escores para dor durante os três primeiros dias de pós-operatório, apesar de não haver diferença estatisticamente significativa na redução do edema e do trismo. Além da redução estatisticamente significativa da dor no terceiro dia de pós-operatório, os resultados do estudo de Gupta e Agarwal (2021)³⁶, também mostraram que o A-PRF proporcionou redução estatisticamente significativa no edema e no trismo após a exodontia do terceiro molar inferior quando comparado ao grupo controle.

Devido a existência de estudos publicados com resultados contraditórios em relação aos benefícios do uso de concentrados sanguíneos após a exodontia dos terceiros molares inferiores, e com o objetivo de fornecer embasamento para a tomada de decisão baseada em evidências, foram realizadas revisões sistemáticas da literatura. Até o momento, foram identificadas 13 revisões sistemáticas sobre a temática, as quais também apresentam resultados contraditórios em relação a indicação e aos reais benefícios da utilização de concentrados sanguíneos após a exodontia dos terceiros molares inferiores^{28,30,37,38,39,40,41,42,43,44,45,46,47}. Portanto, faz-se necessário a realização de uma overview para analisar os fatores que contribuem para resultados contraditórios e, assim, determinar a necessidade de novas revisões sistemáticas ou a condução de novos estudos clínicos com padronização adequada a fim de possibilitar futuras revisões sistemáticas com maior poder de embasamento para a tomada de decisão clínica.

Capítulo 1

Desempenho de concentrados sanguíneos no controle dos sinais e sintomas inflamatórios após a exodontia dos terceiros molares inferiores: overview

RESUMO

Objectives: To summarize the available evidence and answer the following question: What is the current knowledge on the performance of blood concentrates in handling sequelae after lower third molar extractions with the evidence available in systematic reviews?

Material and Methods: An electronic search was made in the Cochrane Library, Embase, LILACS, MEDLINE (via PubMed), SciELO, Scopus, and Web of Science databases. The EASY and MedRxiv databases were also used to capture the "grey literature." The study included systematic reviews with or without meta-analyses that investigated the performance of blood concentrates in controlling sequelae after lower third molar extractions. Four outcomes were analyzed: pain, edema, mouth opening, and alveolar osteitis. The AMSTAR-2 tool evaluated the methodological quality of the included systematic reviews, and ROBIS assessed the risk of bias.

Results: Among 388 studies, 13 systematic reviews were eligible for the present study. Overall, these reviews evaluated 57 primary studies published from 2007 to 2021, and with 30 overlaps of studies selected for the systematic reviews. According to the AMSTAR-2, none of the included systematic reviews presented high or moderate methodological quality. The ROBIS tool showed only one systematic review with a low risk, and the others had a high risk of bias.

Discussion: The limitations of this overview are high heterogeneity and risk of bias in the included systematic reviews and their primary studies, complicating the establishment of correct evidence. However, it is worth noting that the data for clinical decision-making on blood concentrate use should be carefully interpreted, as a detailed analysis showed relevant methodological flaws in apparently robust systematic reviews on the topic. Biological factors pertinent to blood concentrates are promising for optimizing tissue repair, and randomized clinical trials and systematic reviews show inconclusive results regarding the efficacy of these products in controlling sequelae after lower third molar extraction.

Palavras-chave: Dente Serotino; L-PRF; Dor; Edema; Trismo; Alveolite.

INTRODUCTION

Lower third molar extractions may be associated with sequelae, such as pain, edema, mouth-opening difficulties, and alveolar osteitis, which harm patients' postoperative quality of life^{1,2}. Several therapeutic approaches have been indicated to control these inflammatory signs and symptoms, including drug therapy, cryotherapy, low-level laser therapy, and blood concentrates^{2,3,4,5,6,7}.

Blood concentrates originate from autologous blood and primarily consist of platelets, fibrin, leukocytes, and growth factors⁸. Platelet-rich plasma (PRP) is the first-generation blood concentrate, presenting disadvantages such as the need for more than one step for production and anti- and procoagulant addition^{9,10,11}. Studies developed new blood products, such as platelet-rich fibrin (PRF), which was later renamed to leukocyte-and platelet-rich fibrin (L-PRF)¹². New centrifugation protocols were developed from L-PRF, resulting in advanced leukocyte-and platelet-rich fibrin (A-PRF), advanced leukocyte-and platelet-rich fibrin plus (A-PRF+), and concentrated growth factor (CGF)^{10,11,12,13}.

Blood concentrates are fibrin-based biomaterials containing cells, matrix proteins, pro- and anti-inflammatory mediators, and growth factors, showing positive performance in handling postoperative sequelae, such as pain, edema, trismus, and alveolar osteitis^{14,15}. Thus, inflammatory response modulation occurs, optimizing primary hemostasis, chemotaxis, angiogenesis, and mitogenesis of endothelial cells¹⁵.

Systematic reviews in the literature have analyzed the effect of blood concentrates on postoperative sequelae management, such as pain, edema, mouth opening degree, and alveolar osteitis, showing conflicting results and several recommendations for randomized clinical trials with larger samples and more homogeneous methodologies^{16,17,18,19}. Moreover, these reviews' overall synthesis and assessment have not been performed. Therefore, this overview summarized the available evidence and answered the following question: What is the current knowledge on the performance of blood concentrates in handling sequelae after lower third molar extractions with the evidence available in systematic reviews?

MATERIAL AND METHODS

Protocol registration

The protocol of this review was created according to the PRISMA–P²⁰ guidelines and registered *a priori* in the PROSPERO database (CRD42023405301) (<https://www.crd.york.ac.uk/prospero/>). The overview was conducted according to the JBI Manual for Evidence Synthesis²¹ and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations²².

Eligibility criteria

The study included systematic reviews with or without meta-analyses that investigated the performance of blood concentrates in controlling sequelae after lower third molar extractions. Four outcomes were analyzed: pain, edema, mouth opening, and alveolar osteitis.

The included studies were considered systematic reviews if they corresponded to the following description: Use of explicit and systematic methods selected to minimize biases, thus providing more reliable findings that allow conclusions and decision-making²³. There were no restrictions on year or language.

The exclusion criteria were 1) randomized clinical trials; 2) studies with different objectives; 3) case reports; 4) animal studies; 5) *in vitro* studies; 6) letters to the editor; 7) observational studies; and 8) systematic reviews with or without meta-analyses and with outcomes not directly related to pain, edema, and mouth opening.

Sources of information, search, and selection of studies

An electronic search was made in the Cochrane Library, Embase, LILACS, MEDLINE (via PubMed), SciELO, Scopus, and Web of Science databases. The EASY and MedRxiv databases were also used to capture the "grey literature." A search strategy was formulated for each database, respecting their respective syntax rules and using the DeCS (Health Science Descriptors), MeSH (Medical Subject Headings), and Emtree (Embase Subject Headings) descriptors with the Boolean operators AND/OR to maximize the search. Table 1 describes the search strategy for each database.

The search results were exported to EndNote Web™ software (Thomson Reuters, Toronto, Canada) for identifying and removing duplicates. Next, they were exported to Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar), which analyzed the titles and abstracts using the described eligibility criteria. Subsequently, the full texts of the preliminary eligible studies were obtained and evaluated. The "grey literature" results were

simultaneously evaluated with Microsoft Word™ 2010 (Microsoft™ Ltd., Washington, USA). Two eligibility reviewers (VLA and CMM) performed this entire process independently. Divergences were resolved after consulting with a third eligibility reviewer (LRP).

Table 1- Search strategy.

Databases	Search strategies (June 2022)
Primary databases	
Cochrane Library https://www.cochranelibrary.com/	#1 "Molar, Third" OR "Wisdom Tooth" OR "Wisdom Teeth" OR "Third Molar" in All Text #2 "Pain, Postoperative" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Dry Socket" OR "Alveolar Osteitis" OR "Wound Healing" OR "Wound" OR "Healing" OR "Recovery" OR "Morbidity" OR "Outcomes" OR "Efficacy" OR "Comparison" in All Text #3 "Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich" in All Text #1 AND #2 AND #3
Embase https://www.embase.com	('molar, third'/exp OR 'molar, third' OR 'wisdom tooth'/exp OR 'wisdom tooth' OR 'wisdom teeth'/exp OR 'wisdom teeth' OR 'third molar'/exp OR 'third molar') AND ('pain, postoperative'/exp OR 'pain, postoperative' OR 'pain'/exp OR 'pain' OR 'edema'/exp OR 'edema' OR 'swelling'/exp OR 'swelling' OR 'trismus'/exp OR 'trismus' OR 'dry socket'/exp OR 'dry socket' OR 'alveolar osteitis'/exp OR 'alveolar osteitis' OR 'wound healing'/exp OR 'wound healing' OR 'wound'/exp OR 'wound' OR 'healing'/exp OR 'healing' OR 'recovery'/exp OR 'recovery' OR 'morbidity'/exp OR 'morbidity' OR 'outcomes'/exp OR 'outcomes' OR 'efficacy'/exp OR 'efficacy' OR 'comparison'/exp OR 'comparison') AND ('platelet-rich fibrin'/exp OR 'platelet-rich fibrin' OR 'prf' OR 'platelet-rich')
LILACS http://pesquisa.bvsalud.org/	((("Molar, Third" OR "Wisdom Tooth" OR "Wisdom Teeth" OR "Third Molar") AND ("Pain, Postoperative" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Dry Socket" OR "Alveolar Osteitis" OR "Wound Healing" OR "Wound" OR "Healing" OR "Recovery" OR "Morbidity" OR "Outcomes" OR "Efficacy" OR "Comparison") AND ("Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich"))) AND (db:("LILACS"))
MEDLINE (via PubMed) http://www.ncbi.nlm.nih.gov/pubmed	#1 "Molar, Third"[Mesh] OR "Wisdom Tooth"[tw] OR "Wisdom Teeth"[tw] OR "Third Molar"[tw] #2 "Pain, Postoperative"[Mesh] OR "Pain"[Mesh] OR "Edema"[Mesh] OR "Swelling"[tw] OR "Trismus"[Mesh] OR "Dry Socket"[Mesh] OR "Alveolar Osteitis"[tw] OR "Wound Healing"[Mesh] OR "Wound"[tw] OR "Healing"[tw] OR "Recovery"[tw] OR "Morbidity"[Mesh] OR "Outcomes"[tw] OR "Efficacy"[tw] OR "Comparison"[tw] #3 "Platelet-Rich Fibrin"[Mesh] OR "PRF"[tw] OR "Platelet-Rich"[tw] #1 AND #2 AND #3
SciELO https://scielo.org/	((("Molar, Third" OR "Wisdom Tooth" OR "Wisdom Teeth" OR "Third Molar") AND ("Pain, Postoperative" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Dry Socket" OR "Alveolar Osteitis" OR "Wound Healing" OR "Wound" OR "Healing" OR "Recovery" OR "Morbidity" OR "Outcomes" OR "Efficacy" OR "Comparison") AND ("Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich"))
Scopus http://www.scopus.com/	((("Molar, Third" OR "Wisdom Tooth" OR "Wisdom Teeth" OR "Third Molar") AND ("Pain, Postoperative" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Dry Socket" OR "Alveolar Osteitis" OR "Wound Healing" OR "Wound" OR "Healing" OR "Recovery" OR "Morbidity" OR "Outcomes" OR "Efficacy" OR "Comparison") AND ("Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich"))
Web of Science http://apps.webofknowledge.com/	#1 TS= ("Molar, Third" OR "Wisdom Tooth" OR "Wisdom Teeth" OR "Third Molar") #2 TS= ("Pain, Postoperative" OR "Pain" OR "Edema" OR "Swelling" OR "Trismus" OR "Dry Socket" OR "Alveolar Osteitis" OR "Wound Healing" OR "Wound" OR "Healing" OR "Recovery" OR "Morbidity" OR "Outcomes" OR "Efficacy" OR "Comparison") #3 TS= ("Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich") #1 AND #2 AND #3
Grey literature	
EASY https://easy.dans.knaw.nl/	("Third molar" OR "Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich")
MedRxiv https://www.medrxiv.org/	((("Molar, Third" OR "Wisdom Tooth" OR "Wisdom Teeth" OR "Third Molar") AND ("Platelet-Rich Fibrin" OR "PRF" OR "Platelet-Rich"))

Source: Produced by the authors.

Data collection

After selecting the articles, two reviewers (VLA and CMM) extracted the following information: author, year, and journal of the publication; research objective; blood concentrate type; searched databases and search period; primary studies included in the systematic reviews; tools for assessing the risk of bias of studies included in the systematic reviews; and main results and conclusions. To ensure consistency between the reviewers (VLA and CMM) during data extraction, they performed a calibration exercise of jointly extracting information from an eligible study. In case of missing data, the corresponding authors of the eligible studies were contacted via e-mail, with three weekly contact attempts for up to a month.

Critical assessment of individual evidence sources

Three reviewers (VLA, CMM, and LRP) analyzed the methodological quality of the included systematic reviews using the AMSTAR-2 critical assessment tool²⁴. This tool contains 16 questions (seven critical and nine non-critical), which answers were registered as "yes," "partially yes," "no," or "no meta-analysis performed." The methodological quality was considered "high" if the systematic review presented none or one non-critical factor, "moderate" with more than one non-critical factor, "low" with one critical domain with or without non-critical factors, and "critically low" with more than one critical domain with or without non-critical factors.

Risk of individual bias in the studies

Three reviewers (VLA, CMM, and LRP) independently assessed the risk of bias in the included systematic reviews using the ROBIS tool for evaluating the risk of bias in systematic reviews²⁵.

Initially, they analyzed four domains from which biases might have been introduced in a systematic review: (a) eligibility criteria of the study, (b) identification and selection of articles, (c) data collection and study assessment, and (d) synthesis and results. Moreover, each domain has five to six signaling questions with the following possible answers: "yes (Y)," "probably yes (PY)," "probably no (PN)," "no (N)," "not informed (NI)," or "not applicable (NA)." Later, the overall risk of bias was evaluated when interpreting the review findings and whether it considered the identified limitations in any of the described domains.

All reviewers agreed on the decisions about the scoring system and cutoffs before analyzing biases. The authors determined the classification system for the bias within each domain as "low risk" if all signaling questions were scored as Y/PY, "unclear risk" if only one

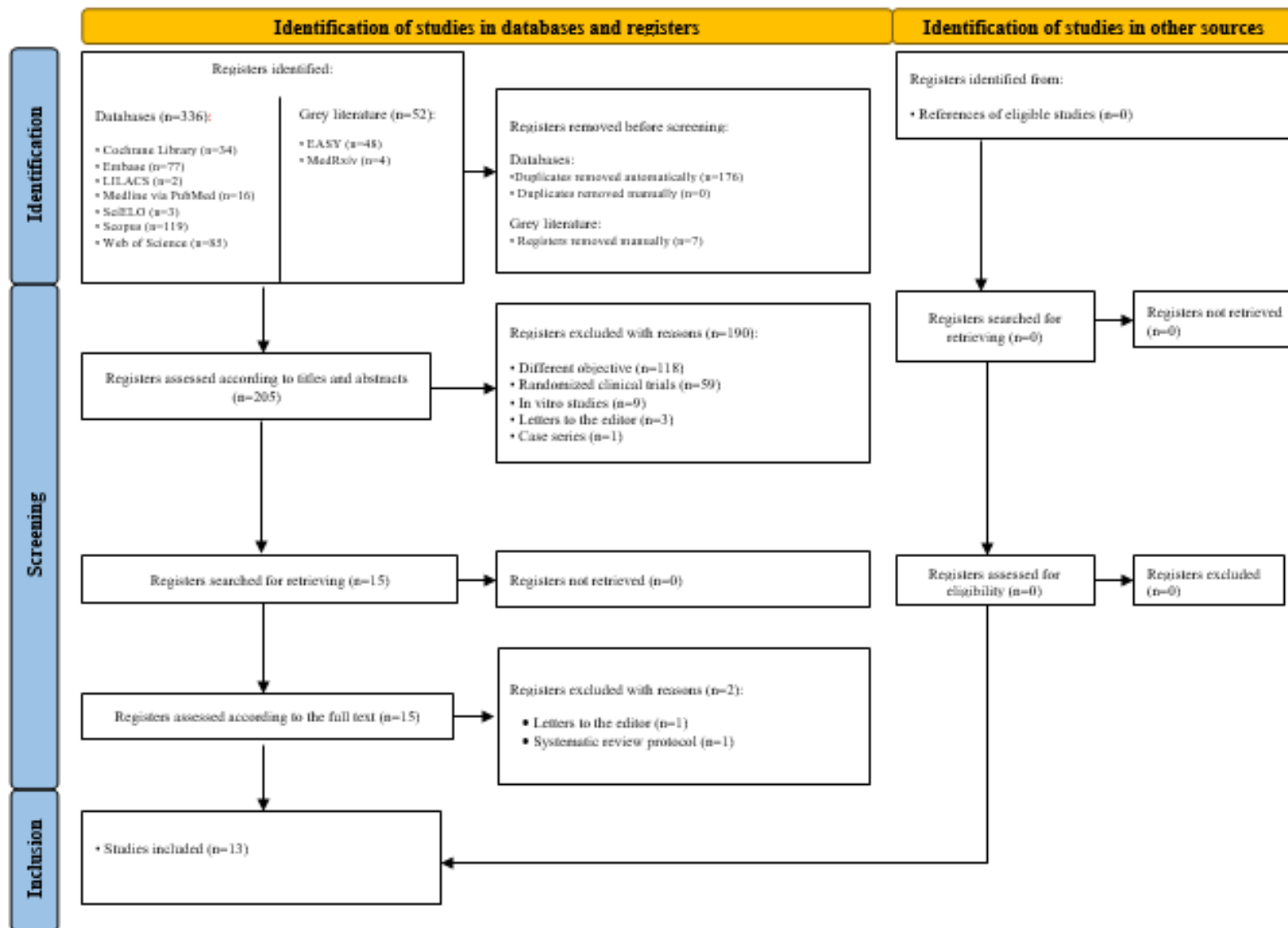
question received PN/N/NI, and "high risk" if more than one question scored PN/N/NI. Moreover, the overall risk of bias regarding each systematic review was characterized as (a) "low" if all four domains had a "low risk" or only one had an "unclear risk," (b) "moderate" if two or more domains had an "unclear risk," and (c) "high" if one or more domains had a "high risk."

RESULTS

Selection of systematic reviews

The study identification process found 388 records. After removing duplicates and reading the titles and abstracts, only 15 studies were fully assessed, of which two were eliminated. The references of the 13 potentially eligible systematic reviews were carefully assessed, but did not locate additional articles. Finally, 13 systematic reviews were selected^{16,17,18,19,26,27,28,29,30,31,32,33,34}. Figure 1 details the study selection in a flowchart.

Figure 1 - Flowchart showing the selection process of the eligible studies.



Source: Produced by authors.

Characteristics of the included systematic reviews

The systematic reviews were published from 2014 to 2022. Only one study was published in Chinese³¹, and the others in English. There were similarities regarding the databases used for searching the articles, and all reviews included MEDLINE (via PubMed). As an additional strategy, six selected systematic reviews^{17,18,26,27,32,34} were manually searched through journals or the list of references of their primary studies. Table 2 describes the main characteristics of the included systematic reviews.

Table 2- Main characteristics of the included systematic reviews.

Author, year Publication journal	Objectives	Blood concentrate	Databases (Research period)	Number of included primary studies		Risk of bias tool
				Qualitative synthesis	Quantitative synthesis	
Barona-Dorado et al., 2014 ¹⁶ Med Oral Patol Oral Cir Bucal	To assess the scientific evidence supporting PRP application in post-extraction sockets of retained lower third molars.	PRP	P: Cochrane Central Register of Controlled Trials; Embase via Ovid; MEDLINE via PubMed; NIH. (June 2013)	3	Meta-analysis was not performed.	Jadad scale
Al-Hamed et al., 2017 ²⁶ J Oral Maxillofac Surg	To assess the effect of PRF on socket healing after the surgical extraction of lower third molars.	PRF	P: Cochrane Central Register of Controlled Trials; PubMed; Scopus. (August/November 2015)	6	- OA (n=1) - RO (n=2) - Trismus (n=2)	Cochrane Collaboration tool
Canellas et al., 2017 ¹⁷ Int J Oral Maxillofac Surg	To assess potential differences in postoperative complications when using PRF in mandibular third molar surgeries.	PRF	P: Cochrane Library; LILACS; MEDLINE via PubMed; ScienceDirect. C: Theses and Dissertations Base - CAPES; Current Controlled Trials; ClinicalTrials.gov; EU Clinical Trials Register. (August 2016)	7	- OA (n=2)	Cochrane Collaboration tool
He et al., 2017 ²⁷ J Oral Maxillofac Surg	To analyze the local PRF application to control postoperative signs and symptoms after extracting an impacted lower third molar.	PRF	P: Cochrane Library; Embase; PubMed; Web of Science. (October 2016)	10	- OA (n=4) - RO (n=2) - Pain (n=6) - Edema (n=3) - Trismus (n=3)	Cochrane Collaboration tool
Canellas et al., 2019 ²⁸ Int J Oral Maxillofac Surg	To assess to which indications PRF has been effective in oral surgical procedures.	PRF	P: Cochrane Library; LILACS; MEDLINE via PubMed; Scopus; Web of Science. C: ClinicalTrials.gov; EU Clinical Trials Register. (September 2017)	30	- Pain (n=6) - Edema (n=3) - EID (n=2) - OA (n=3) - RO (n=2) - ROLS (n=2) - CT (n=2)	Cochrane Collaboration tool
Xiang et al., 2019 ²⁹ BMC Oral Health	To assess whether PRF is effective for patients during lower third molar extractions.	PRF	P: Cochrane Library; Embase; PubMed. (September 2017)	10	- Pain (n=6) - Edema (n=4) - OA (n=3) - RO (n=2) - Trismus (n=4)	Cochrane Collaboration tool
Bao et al., 2021a ³⁰ J Oral Maxillofac Surg	To investigate the use of L-PRF and A-PRF for relieving signs and symptoms after lower third molar extraction.	A-PRF L-PRF	P: Embase; PubMed; SinoMed; Web of Science. (October 2020)	10	- CT (n=4) - Pain (n=6) - OA (n=2)	Cochrane Collaboration tool

Bao et al., 2021b ³¹ West China Journal of Stomatology	To assess the efficacy of PRF in relieving complications after lower third molar extraction.	PRF	P: Embase; PubMed; SinoMed; Web of Science. (February 2020)	21	- CT (n=3) - CA (n=2) - Pain (n=6) - Edema (n=5) - OA (n=3) - RO (n=2) - Trismus (n=2)	Cochrane Collaboration tool
Fujioka-Kobayashi et al., 2021 ¹⁸ J Oral Maxillofac Surg Med Pathol	To investigate the efficacy of PRF in handling lower third molar extractions from randomized clinical trials.	PRF	P: Cochrane Central Register of Controlled Trials; Embase; LILACS; MEDLINE via PubMed; Scopus. C: Grey Literature Report; OpenGrey. (June 2020)	18	- OA (n=5)	RoB 2
Zhu et al., 2021 ³² International Int J Oral Maxillofac Surg	To estimate the effect of PRF on pain, edema, and trismus control after lower third molar extractions.	PRF	P: Cochrane Library; Embase; PubMed; Web of Science. (May 2019)	19	- CT (n=4) - Pain (n=13) - OA (n=6) - Trismus (n=3)	Cochrane Collaboration tool
Ramos et al., 2022 ³³ J Oral Maxillofac Surg	To determine whether different platelet aggregation protocols (PRF/L-PRF and A-PRF) have similar effects on pain, edema, and trismus control.	PRF A-PRF L-PRF	P: Cochrane; Embase; MEDLINE; PubMed; BVS; Web of Science. (April/July 2021)	17	- CT (n=5) - Pain (n=7) - Edema (n=5) - Trismus (n=5)	Cochrane Collaboration tool
Snopek et al., 2022 ³⁴ Oral Surg	To assess double-blind RCTs with a low or moderate risk of bias to explain whether PRF was beneficial for postoperative pain and edema after mandibular third molar surgeries.	PRF	P: Cochrane Library; Embase; MEDLINE via PubMed; Scopus; Web of Science. C: ClinicalTrials.gov; Grey Literature Report; OpenGrey. (June 2020)	6	- Pain (n=3)	Cochrane Collaboration tool
Vintenson et al., 2022 ¹⁹ Int J Oral Maxillofac Surg	To test the hypothesis that there is no difference in postoperative recovery after SRM3 with A-PRF application in the extraction socket compared to alternative biomaterials or natural wound healing.	A-PRF L-PRF	P: Cochrane Library; Embase; MEDLINE via PubMed; Scopus. C: OpenGrey; OpenThesis. (December 2020)	4	- Pain (n=3) - Edema (n=3) - Trismus (n=3)	Cochrane Collaboration tool
Autor, ano Periódico de publicação	Objetivos	Tipo de concentrado sanguíneo	Bases de dados (Data de pesquisa)	n de estudos primários incluídos		Ferramenta de risco de viés
				Síntese qualitativa	Síntese quantitativa	
Barona-Dorado et al., 2014 ¹⁶ Med Oral Patol Oral Cir Bucal	Avaliar as evidências científicas em apoio à aplicação do PRP em alvéolos pós-extração de terceiros molares inferiores retidos.	PRP	P: Cochrane Central Register of Controlled Trials; Embase via Ovid; MEDLINE via PubMed; NIH. (Junho de 2013)	3	Não foi realizada meta-análise.	Escala de Jadad

Al-Hamed et al., 2017 ²⁶ J Oral Maxillofac Surg	Avaliar o efeito da PRF no processo de cicatrização do alvéolo após a extração cirúrgica dos terceiros molares inferiores.	PRF	P: Cochrane Central Register of Controlled Trials; PubMed; Scopus. (Agosto/Novembro de 2015)	6	- OA (n=1) - RO (n=2) - Trismo (n=2)	Cochrane Collaboration tool
Canellas et al., 2017 ¹⁷ Int J Oral Maxillofac Surg	Avaliar se há diferenças nas complicações pós-operatórias quando a PRF é utilizada na cirurgia de terceiros molares mandibulares.	PRF	P: Cochrane Library; LILACS; MEDLINE via PubMed; ScienceDirect. C: Banco de Teses e Dissertações - CAPES; Current Controlled Trials; ClinicalTrials.gov; EU Clinical Trials Register. (Agosto de 2016)	7	- OA (n=2)	Cochrane Collaboration tool
He et al., 2017 ²⁷ J Oral Maxillofac Surg	Analisar a aplicação local de PRF para controlar os sinais e sintomas pós-operatórios após a extração do terceiro molar inferior impactado.	PRF	P: Cochrane Library; Embase; PubMed; Web of Science. (Outubro de 2016)	10	- OA (n=4) - RO (n=2) - Dor (n=6) - Edema (n=3) - Trismo (n=3)	Cochrane Collaboration tool
Canellas et al., 2019 ²⁸ Int J Oral Maxillofac Surg	Avaliar em quais indicações a PRF tem se mostrado eficaz em procedimentos cirúrgicos orais.	PRF	P: Cochrane Library; LILACS; MEDLINE via PubMed; Scopus; Web of Science. C: ClinicalTrials.gov; EU Clinical Trials Register. (Setembro de 2017)	30	- Dor (n=6) - Edema (n=3) - EID (n=2) - OA (n=3) - RO (n=2) - ROLS (n=2)	Cochrane Collaboration tool
Xiang et al., 2019 ²⁹ BMC Oral Health	Avaliar se a PRF é eficaz para pacientes durante a extração de terceiros molares inferiores.	PRF	P: Cochrane Library; Embase; PubMed. (Setembro de 2017)	10	- CT (n=2) - Dor (n=6) - Edema (n=4) - OA (n=3) - RO (n=2) - Trismo (n=4)	Cochrane Collaboration tool
Bao et al., 2021a ³⁰ J Oral Maxillofac Surg	Investigar o uso da L-PRF e da A-PRF no alívio dos sinais e sintomas após a exodontia do terceiro molar inferior.	A-PRF L-PRF	P: Embase; PubMed; SinoMed; Web of Science. (Outubro de 2020)	10	- CT (n=4) - Dor (n=6) - OA (n=2)	Cochrane Collaboration tool
Bao et al., 2021b ³¹ West China Journal of Stomatology	Avaliar a eficácia da PRF no alívio de complicações após a exodontia do terceiro molar inferior.	PRF	P: Embase; PubMed; SinoMed; Web of Science. (Fevereiro de 2020)	21	- CT (n=3) - CA (n=2) - Dor (n=6) - Edema (n=5) - OA (n=3) - RO (n=2) - Trismo (n=2)	Cochrane Collaboration tool
Fujioka-Kobayashi et al., 2021 ¹⁸ J Oral Maxillofac Surg Med Pathol	Investigar a eficácia da PRF no manejo de exodontias de terceiros molares inferiores a partir de ensaios clínicos randomizados.	PRF	P: Cochrane Central Register of Controlled Trials; Embase; LILACS; MEDLINE via PubMed; Scopus. C: Grey Literature Report; OpenGrey. (Junho de 2020)	18	- OA (n=5)	RoB 2

Zhu et al., 2021 ³² International Int J Oral Maxillofac Surg	Estimar o efeito da PRF no controle da dor, edema e trismo após a exodontia de terceiros molares inferiores.	PRF	P: Cochrane Library; Embase; PubMed; Web of Science. (Maio de 2019)	19	- CT (n=4) - Dor (n=13) - OA (n=6) - Trismo (n=3)	Cochrane Collaboration tool
Ramos et al., 2022 ³³ J Oral Maxillofac Surg	Determinar se os diferentes tipos de protocolos de agregação plaquetária, PRF/L-PRF e A-PRF, têm efeitos semelhantes no controle da dor, edema e trismo.	PRF A-PRF L-PRF	P: Cochrane; Embase; MEDLINE; PubMed; BVS; Web of Science. (Abril/Julho de 2021)	17	- CT (n=5) - Dor (n=7) - Edema (n=5) - Trismo (n=5)	Cochrane Collaboration tool
Snopek et al., 2022 ³⁴ Oral Surg	Avaliar ECRs duplo-cegos com baixo ou moderado risco de viés para esclarecer se a PRF teve um efeito benéfico na dor pós-operatória e edema após cirurgia de terceiros molares mandibulares.	PRF	P: Cochrane Library; Embase; MEDLINE via PubMed; Scopus; Web of Science. C: ClinicalTrials.gov; Grey Literature Report; OpenGrey. (Junho de 2020)	6	- Dor (n=3)	Cochrane Collaboration tool
Vintenson et al., 2022 ¹⁹ Int J Oral Maxillofac Surg	Testar a hipótese de não haver diferença na recuperação pós-operatória após SRM3 com a aplicação de A-PRF no alvéolo de extração comparado com biomateriais alternativos ou cicatrização natural de feridas.	A-PRF L-PRF	P: Cochrane Library; Embase; MEDLINE via PubMed; Scopus. C: OpenGrey; OpenThesis. (Dezembro de 2020)	4	- Dor (n=3) - Edema (n=3) - Trismo (n=3)	Cochrane Collaboration tool

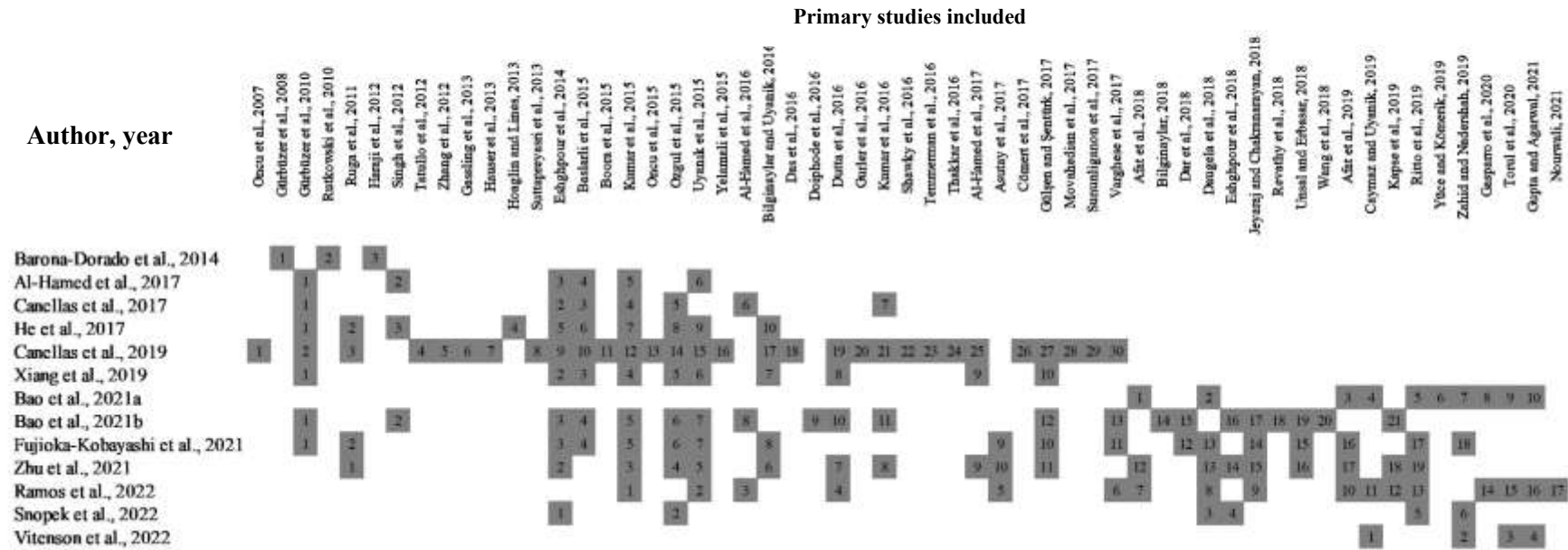
PRP – platelet-rich plasma; PRF – platelet-rich fibrin; A-PRF – Advanced platelet-rich fibrin; L-PRF – Fibrin rich in platelets and leukocytes; P – Main databases; C – Gray literature databases; OA – Alveolar osteitis; RO – Bone repair; EID – Dental Implant Stability; ROLS – Bone repair in maxillary sinus lift; CT – Tissue healing; CA – Consumption of analgesics.

Source: Produced by authors.

Overall, these reviews evaluated 57 primary studies published from 2007 to 2021, with 30 overlaps of studies selected for the systematic reviews. Figure 2 illustrates this overlap of primary studies.

Figure 2 – Overlap of primary studies.

Study Overlay Graph



Sources: Produced by the authors.

Considering the heterogeneity level regarding the designs of primary studies (parallel or split-mouth), samples, measurement methods, and differences in the postoperative assessment of pain, edema, and trismus, three systematic reviews^{16,17,18} could not perform a meta-analysis for these outcomes. Table 3 describes the main results of the systematic reviews.

Table 3- Main outcomes of the included systematic reviews

Author, year	Main results	Main conclusions
Barona-Dorado et al., 2014 ¹⁶	Gürbüz et al., 2008: No statistically significant differences. Rutkowski et al., 2010: PRP showed significantly smaller facial edema and higher bone density. Haraji et al., 2012: PRP showed significantly lower postoperative pain, improved healing, and lower postoperative alveolar osteitis incidence.	The scientific evidence for using PRP in third-molar surgeries is scarce. Hence, randomized clinical trials are required before recommending the clinical application of PRP.
Al-Hamed et al., 2017 ²⁶	PRF showed overall positive results for pain, trismus, edema, periodontal pocket depth, soft tissue healing, and localized osteitis incidence. The meta-analysis could not be performed for all variables. The meta-analyses did not show significant benefits for PRF compared to natural healing sockets.	Considering the limitations of the available evidence, PRF does not seem beneficial for bone consolidation after lower third molar extractions. Further controlled and standardized randomized clinical trials are required to estimate the effect of PRF on socket regeneration.
Canellas et al., 2017 ¹⁷	PRF seemed to accelerate healing in mandibular third molar surgeries, reducing postoperative pain and edema. PRF significantly decreased alveolar osteitis prevalence.	Although further well-designed clinical trials with larger samples are required to allow definitive conclusions, PRF is a potentially useful biomaterial.
He et al., 2017 ²⁷	PRF significantly relieved pain, reduced edema on the third postoperative day, and decreased alveolar osteitis incidence. There were no significant differences in swelling on the first postoperative and bone consolidation day.	The local application of PRF after lower third molar extraction is a valid method to relieve pain and edema at three postoperative days and reduce alveolar osteitis incidence. For patients subjected to complicated surgical extractions, PRF may be recommended for local socket applications.
Canellas et al., 2019 ²⁸	PRF showed significantly better bone regeneration for alveolar cleft reconstruction, decreased alveolar osteitis prevalence, and increased implant stability one week and one month after surgery.	PRF may present improved wound healing when used in oral surgical procedures. The most consistent indications found in this systematic review are (1) to preserve alveolar dimensions after extraction and (2) to reduce alveolitis incidence after lower third molar surgery.
Xiang et al., 2019 ²⁹	PRF relieved pain and edema and reduced alveolar osteitis incidence. There was no statistical difference for trismus and bone and soft tissue healing.	PRF reduces only some postoperative complications but it does not prevent all of them. PRF significantly relieved pain and edema and reduced alveolar osteitis incidence after extracting an impacted lower third molar.
Bao et al., 2021a ³⁰	A-PRF showed a better effect among the three groups for the improvement of postoperative pain on the third and seventh days. L-PRF promoted soft tissue healing on the seventh day compared to the control. However, other comparisons did not show significant differences.	Limited results showed that applying A-PRF after the third molar extraction reduced postoperative pain, and L-PRF promoted soft tissue healing on the seventh postoperative day. However, the positive impact on other postoperative sequelae was not confirmed. Further randomized controlled trials on a large scale and with uniformly standardized measuring methods are required to improve the analyses.
Bao et al., 2021b ³¹	PRF showed significant positive effects on pain, edema, soft tissue healing, trismus, and alveolar osteitis. There was no statistically significant effect on bone healing.	Limited clinical evidence indicates that applying PRF after lower third molar extraction may reduce pain, edema, trismus, and dry socket alveolitis and promote soft tissue healing. However, the effect of PRF on bone healing requires further randomized controlled trials on a large scale and with uniform measuring criteria.

Fujioka-Kobayashi et al., 2021 ¹⁸	PRF significantly reduced the alveolar osteitis rate from 15.9% in the control group to 5.8% in the PRF group, representing an approximated three-fold reduction. PRF showed better results for soft tissue healing.	PRF decreases postoperative pain/morbidity, favors soft tissue healing, and presents lower complication rates of alveolar osteitis incidence. Therefore, PRF represents a feasible auxiliary treatment after lower third molar removal.
Zhu et al., 2021 ³²	PRF significantly reduced alveolar osteitis incidence and postoperative pain (first, third, and seventh days) compared to the controls.	Besides reducing alveolar osteitis incidence and postoperative pain after third molar surgery, it may also improve postoperative healing of soft tissues.
Ramos et al., 2022 ³³	L-PRF showed better pocket depth, insertion level, and pain control (first and third days) but it was not associated with improved soft tissue healing on the seventh day. A-PRF presented lower analgesics intake. L-PRF and A-PRF controlled edema better but not trismus.	Using L-PRF and A-PRF allows better pain and edema control compared to standard PRF protocols but none affected trismus. PRF and L-PRF protocols improved soft tissue healing but not to a statistically significant degree. However, they improved probe depth in the third month after the third molar surgery.
Snopek et al., 2022 ³⁴	PRF favored the reduction of alveolar osteitis frequency and had an uncertain effect on the level of postoperative pain, edema, and wound healing. Pain levels did not show statistical differences.	Considering the low number of included studies, the effect of PRF after lower third molar surgery could not be evaluated. Further studies should focus on a higher methodological quality to produce reliable and comparable study results.
Vintenson et al., 2022 ¹⁹	A-PRF caused significantly lower pain scores than L-PRF and natural wound healing after two, three, and seven days. A-PRF had a significant effect on facial edema and trismus and some positive effects on soft tissue healing.	The included studies were characterized by considerable heterogeneity and confounding variables. Thus, the level of evidence seems inadequate for clinical recommendations according to the focus question.

PRP – platelet-rich plasma; PRF – platelet-rich fibrin; A-PRF – Advanced platelet-rich fibrin; L-PRF – Fibrin rich in platelets and leukocytes.

Source: Produced by the authors.

Critical assessment of individual evidence sources

According to the AMSTAR-2²⁴ analysis, none of the included systematic reviews presented high or moderate methodological quality. Four studies^{17,19,28,34} demonstrated low methodological quality, and the other systematic reviews were critically low^{16,18,26,27,29,30,31,32,33,34}. These results concerned the presence of one or more critical domains with or without non-critical factors. Table 4 summarizes the responses of each systematic review to the AMSTAR-2²⁴ questionnaire.

Tabela 4- Avaliação crítica de fontes individuais de evidência das revisões sistemáticas incluídas.

Author, year	Questions																Methodological quality
	1	2 **	3	4 **	5	6	7 **	8	9 **	10	11	12	13 **	14	15 **	16	
Barona-Dorado et al., 2014 ¹⁶	Y	N	N	PY	N	N	Y	PY	PY	N	NM	NM	Y	Y	NM	N	Critically low
Al-Hamed et al., 2017 ²⁶	N	N	N	PY	N	Y	Y	Y	Y	N	N	N	N	Y	N	Y	Critically low
Canellas et al., 2017 ¹⁷	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	N	Y	Low
He et al., 2017 ²⁷	N	N	N	PY	N	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	Critically low
Canellas et al., 2019 ²⁸	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	N	Y	Low
Xiang et al., 2019 ²⁹	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	N	Y	Critically low
Bao et al., 2021a ³⁰	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	N	Y	Critically low
Bao et al., 2021b ³¹	Y	N	N	PY	N	Y	N	Y	Y	N	Y	N	N	Y	N	Y	Critically low
Fujioka-Kobayashi et al., 2021 ¹⁸	Y	PY	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	Critically low
Zhu et al., 2021 ³²	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	N	N	Y	N	Y	Critically low
Ramos et al., 2022 ³³	Y	Y	N	PY	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	Critically low
Snopek et al., 2022 ³⁴	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Vintenson et al., 2022 ¹⁹	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Low

1 - "Did the research questions and inclusion criteria for the review include the PICO components?"; 2 - "Did the review report contain an explicit statement that the methods were established before performing the review, and the report justify any significant deviations from the protocol?"; 3 - "Did the review authors explain their study design selection for inclusion in the review?"; 4 - "Did the review authors use a comprehensive literature search strategy?"; 5 - "Did the review authors select the studies in pairs?"; 6 - "Did the review authors extract the data in pairs?"; 7 - "Did the review authors provide a list of excluded studies and justify the exclusions?"; 8 - "Did the review authors describe the included studies with adequate details?"; 9 - "Did the review authors use a satisfactory technique to assess the risk of bias (RoB) in individual studies included in the review?"; 10 - "Did the review authors inform the funding sources of the studies included in the review?"; 11 - "In case there was a meta-analysis, did the review authors use adequate methods for the statistical combination of results?"; 12 - "In case there was a meta-analysis, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?"; 13 - "Did the review authors consider RoB in individual studies when interpreting/discussing the review results?"; 14 - "Did the review authors provide a satisfactory explanation and discuss any heterogeneity verified in the review results?"; 15 - "In case there was a quantitative synthesis, did the review authors perform an adequate investigation on the publication bias (small study bias) and discuss its probable impact on the review results?"; 16 - "Did the review authors report any potential sources of conflict of interest, including any funding received for conducting the review?"; Y - Yes; PY - Partially yes; N - No; NM - No meta-analysis performed; ** - Critical domain. Source: Produced by the authors.

Risk of individual bias of the eligible studies

Overall, only one systematic review³⁴ showed a low risk, and the others had a high risk of bias^{16,17,18,19,26,27,28,29,30,31,32,33,34}. There were relevant concerns regarding the risk of bias, including (a) the absence of previous study protocol registration, (b) the absence of a comprehensive electronic search in grey literature databases and with additional strategies, (c) the absence of definite mention of at least two eligibility reviewers in the methodological steps of the systematic review, (d) the absence of sensitivity analyses, (e) primary studies with a high risk of bias, (f) protocol deviations, and (g) data interpretation focused on statistically different results. Table 5 provides more details on the risk of bias assessment.

Table 5- Individual risk of bias of the eligible studies.

Systematic reviews	Phase 2				Phase 3
	1. Eligibility criteria of the study	2. Identification and selection of studies	3. Data collection and study assessment	4. Synthesis and findings	Risk of bias in the review
Barona-Dorado et al., 2014 ¹⁶					
Al-Hamed et al., 2017 ²⁶					
Canellas et al., 2017 ¹⁷			?		
He et al., 2017 ²⁷				?	
Canellas et al., 2019 ²⁸			?		
Xiang et al., 2019 ²⁹			?	?	
Bao et al., 2021a ³⁰			?		
Bao et al., 2021b ³¹			?		
Fujioka-Kobayshi et al., 2021 ¹⁸		?	?		
Zhu et al., 2021 ³²		?	?	?	
Ramos et al., 2022 ³³			?		
Snopek et al., 2022 ³⁴					
Vitenson et al., 2022 ¹⁹		?			

 - Low risk;  - High risk; ? - Undefined.

Source: Produced by the authors.

DISCUSSION

The present overview analyzed the current knowledge on the performance of blood concentrates in handling sequelae after lower third molar extractions with the evidence available in systematic reviews. Considering the surgical nature and complexity, third molar removal may be associated with postoperative sequelae, such as pain, edema, mouth-opening difficulties, and alveolar osteitis². Alveolar healing involves a highly coordinated sequence of biochemical, physiological, cellular, and molecular responses to restore tissue integrity, and blood concentrates have been extensively used to improve tissue repair and optimize the postoperative inflammatory process^{35,36}.

Only one systematic review¹⁶ evaluated platelet-rich plasma (PRP), and the evidence available for using PRP in lower third molar extractions is scarce. Only three primary studies were included^{37,38,39} in the referred systematic review¹⁶, showing conflicting results regarding the efficacy of PRP in controlling pain, mouth opening, and alveolar osteitis. Two of these primary studies^{38,39} did not present methodological flaws in the clinical trials, but there were result interpretation biases. One of the articles³⁹ affirmed that PRP significantly reduced pain levels but did not inform any value (mean and standard deviation). It also did not determine the method for diagnosing alveolar osteitis, and the variables were analyzed jointly between upper and lower third molar sockets. The other study³⁸ did not provide objective data for the analyzed variables and had a small sample. It is worth noting that this included systematic review¹⁶ also presents methodological performance biases. The risk of bias analyzed in the ROBIS tool²⁵ showed that, despite determining the study objective, there was no review question. Moreover, the review neither performed a manual search in the references of the included primary studies nor mentioned the participation of two reviewers during data collection and the risk of bias classification in said studies.

Conflicting results also appeared for the role of leukocyte-and platelet-rich fibrin (L-PRF) in controlling postoperative sequelae after lower third molar removal. Most included systematic reviews presented favorable conclusions regarding the efficacy of blood concentrates^{17,18,27, 29,30,31,32,33}. However, it is worth noting that three of these investigations^{17,30,31} also highlighted outcome limitations and the need for randomized clinical trials with larger samples and a more homogeneous methodology for a higher comparison effect. The risk of bias analysis with the ROBIS tool²⁵ showed that all these reviews present at least a few methodological flaws concerning the lack of reference to a registration protocol^{27,29,30,31,32}, language limitations^{18,29,33}, or the absence of definite mention of at least two eligibility reviewers during the study selection^{27,31}, data extraction¹⁷, and risk of bias

assessment^{27,29,31} of their primary studies. Some methodological flaws, such as the lack of a previous registration protocol, may promote imprecise conclusions, as it is hard to know whether these criteria were established in advance and guided the reviewers' steps during the review or were determined or modified in the review process^{24,25}. Therefore, the findings of the referred systematic reviews must be carefully interpreted, considering the identified methodological limitations, to prevent precipitated or imprecise conclusions.

Some systematic reviews included in the present overview did not present sufficient evidence to indicate the use of PRF after lower third molar extraction^{26,28,34}. The presence of patients with lower third molars at different inclusion/impaction degrees in a single sample might be responsible for introducing biases in clinical trial results²⁶. Moreover, a statistically significant relationship exists between surgical difficulty and postoperative sequelae intensity^{40,41}. It is worth noting that one of these systematic reviews²⁶ presented a high risk of methodological bias due to the lack of reference to previous study protocol registration, the absence of a comprehensive electronic search in grey literature databases, the absence of definite mention of at least two eligibility reviewers during study selection and risk of bias assessment, and the absence of sensitivity analyses. Another systematic review with a high risk of bias²⁸ must be carefully interpreted because, except for one of its primary studies⁴², the others did not present randomized clinical trial registrations, and the statistically insignificant results might have been hidden in the final publication, thus introducing result interpretation biases. Also, the primary studies of one of the included systematic reviews³⁴ were split-mouth double-blind clinical trials, and the statistical methods used in the meta-analysis allowed a reliable interpretation of results. However, due to the methodological heterogeneity for measuring edema and insufficient information on alveolar osteitis, a meta-analysis for postoperative pain was only possible in three randomized clinical trials from the same systematic review³⁴, again showing the limitations of the available evidence.

Our overview showed that A-PRF reduced pain in the first³³, second¹⁹, and third^{19,30} postoperative days. As for trismus and edema, A-PRF promoted a higher reduction only after the third postoperative day¹⁹. These results seem debatable because the release of growth factors through A-PRF occurs for ten days, and the physiological inflammatory response appears immediately after the tissue lesion^{43,44}. Thus, these data should be carefully interpreted because randomized clinical trials presented methodological heterogeneity and potential result interpretation biases¹⁹, as well as methodological flaws for not mentioning the predefined registration protocol³¹, restrictions on publication language¹⁹, or the absence of two reviewers during study selection and data extraction of the primary studies³¹.

Although systematic reviews are the most adequate studies for evidence-based decision-making, accepting their results without a critical assessment may provide improper conclusions²⁴. A critical evaluation should involve deep knowledge of the therapy in question and an understanding of the physical and biological properties of blood concentrates and their indications, advantages, and limitations. Thus, the restrictions of this overview were the high heterogeneity and risk of bias in the included systematic reviews and their primary studies, complicating the establishment of correct evidence. However, it is worth noting that the data for clinical decision-making on blood concentrate use should be carefully interpreted, as a detailed analysis showed relevant methodological flaws in apparently robust systematic reviews on the topic.

CONCLUSION

Biological factors pertinent to blood concentrates are promising for optimizing tissue repair. However, the currently available results from randomized clinical trials and systematic reviews are inconclusive regarding the efficacy of these products in controlling sequelae after lower third molar extraction.

Randomized clinical trials with methodological standardization are first required for considering a systematic review an adequate reference for evidence-based decision-making. Moreover, systematic reviews must be performed according to scientifically established guidelines to minimize risk.

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CONSIDERAÇÕES FINAIS

Ensaio clínico randomizado e revisões sistemáticas da literatura têm sido conduzidos para analisar o efeito dos concentrados sanguíneos como terapia complementar ao controle da dor, edema, trismo e osteíte alveolar após a exodontia do terceiro molar inferior. No entanto, os resultados obtidos até o momento não fornecem evidência científica suficiente para a indicação dessa terapêutica e a presente overview enfrentou desafios inerentes à alta heterogeneidade e ao risco de viés presentes nas revisões sistemáticas incluídas e em seus estudos primários, o que compromete a obtenção de evidências sólidas e confiáveis.

A fim de garantir a robustez e a confiabilidade de uma revisão sistemática como uma fonte de referência para a tomada de decisões fundamentadas em evidências sobre esse tema, é necessário que sejam conduzidos ensaios clínicos randomizados com uma metodologia padronizada. Vale ressaltar que a tomada de decisão não deve se basear exclusivamente nos resultados em análise, uma vez que uma avaliação crítica requer um profundo entendimento da terapia em questão, bem como das propriedades físicas e biológicas dos concentrados sanguíneos.

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