Autologous platelet concentrates after third molar extraction: A systematic review

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Abstract

Surgical removal of impacted mandibular third molars is often followed by postoperative sequelae like pain, swelling, trismus, etc. This systematic review explored the benefits of applying different autologous platelet concentrates (APCs) in the extraction socket of third molars. For this systematic review, PubMed, EMBASE, Web of Science, and Scopus have been utilized, initially yielding 544 papers. The search was narrowed to randomized controlled trials (RCTs, *n* = 59) published before 2024, all comparing the outcome of applying APCs in the extraction socket of surgically removed impacted mandibular third molars with unassisted healing (blood clot). Most RCTs primarily assessed the impact of APCs on postoperative sequelae. Some RCTs looked at soft- and hard-tissue healing. Eleven studies used PRP, three PRGF, and 45 L-PRF. A detailed analysis revealed a large heterogeneity between studies rendering a meta-analysis impossible. Moreover, the risk of bias was considered high. In the majority of RCTs, the application of an APC resulted in statistically significant reductions of postoperative sequelae (lower pain intensity, lower consumption of analgesics, less postoperative edema, and a lower incidence of trismus and alveolar osteitis), as well as a faster soft tissue healing, and qualitatively and quantitatively better bone healing. A minority of studies reported significant differences in periodontal parameters distally from the second molar.

1 INTRODUCTION

Third molars, especially those of the lower jaw, are the most frequently impacted teeth with a worldwide prevalence of 24%.[1] Their surgical removal is one of the most common interventions in oral and maxillofacial surgery. It is difficult to find accurate figures for the number of people undergoing third molar extraction(s). However, it is estimated that 10 million third molars are extracted each year in the United States.[2, 3] In the United Kingdom, the National Health Service funds the removal of lower third molars by approximately 152 000 people per year.[4, 5]

Several papers reported an increased incidence of periodontal breakdown or other dental morbidities on the adjacent second molars when third molars are present or impacted.[6-8] A retrospective cohort study on more than 15 000 patients between 16 and 45 years of age, who all had their first surgical extraction of an impacted lower third molar, indicated a direct association between age and various sequelae of the adjacent second molar.[9] The American Association of Oral and Maxillofacial Surgeons therefore advocated surgical extraction of third molars that are associated with disease or at higher risk of developing disease.[10] Moreover, they also suggested removing asymptomatic or pathology-free impacted third molars, prior to the development of pathology, at the time when postsurgical healing is optimal and with a lower risk of complications.[11]

Surgical removal of (impacted or partially impacted) third molars, especially in the mandible, is often followed by postoperative sequelae like pain, swelling, and trismus, and less frequently by temporary or permanent nerve damage (e.g., reduced sensation (hypoesthesia), abnormal sensation (paresthesia), or unpleasant painful sensation (dysesthesia)). The incidence of a surgical site infection (0.2%–5.2%), trismus (0.4%–2%), and alveolitis (0.3–19.1) is considerable.[12] The severity of pain usually peaks within several hours after surgery and may last for several days or more. Facial swelling typically reaches the highest level at around 1- or 2 days post extraction before subsiding over the next days. Trismus, a side effect of the inflammation, can persist for more than a few days. These sequelae may impede patients' everyday function and compromise their quality of life throughout the recovery period.[13, 14]

To control the postoperative inflammatory reactions and reduce the postoperative sequelae, traditional allopathic analgesics are widely used.[15] Today, more often nonpharmacological interventions are considered to enhance pain relief and reduce analgesic use, mitigating the unwanted effects and contra-indications of allopathic medications, especially opioid analgesics. For third molar removal, several complementary methods have been introduced including cryotherapy,[16] the application of hyaluronic acid,[17] low-level laser therapy,[18] ozone therapy,[19] and kinesiotaping,[20] as well as the use of autologous platelet concentrates (APCs).

Autologous platelet concentrates play a crucial role in soft- and hard-tissue healing[21-24] via the release of growth factors (e.g., platelet-derived growth factors (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF)) as well as matrix proteins (e.g., fibronectin and vitronectin), and the high concentration of vital cells (especially leukocytes in the case of L-PRF) and platelets. As such, they facilitate soft- and hard-tissue healing and might reduce the postoperative sequelae, as it has been reported for alveolar ridge preservation,[25] sinus floor elevation,[26] horizontal and vertical bone regeneration,[27] recession coverage,[28] and the regeneration of intra-bony defects around teeth,[29] medication-related osteonecrosis of the jaw,[30] and endo surgery.[31] Even in the treatment of nonhealing chronic wounds such as a diabetic foot, a venous leg ulcer, and a leprosy wound, APCs have been shown to significantly enhance soft tissue regeneration.[32, 33] Moreover, the steady fibrous structure of L-PRF matrices (clots/membranes) provides a supportive 3D scaffold for cytokines and growth factors, which contribute to leukocyte migration, potentially mediating the inhibition of postoperative pain. Finally, the slowly dissolving L-PRF matrices promote the formation of the natural blood clot and protect it. As such the extraction socket is isolated from the outside environment so that exogenous infections are prevented, which will reduce the incidence of alveolar osteitis.

This systematic review intended to verify the impact of applying APCs into the extraction socket after third molar extraction, by analyzing randomized controlled trials (RCTs) compared to unassisted (blood clot) socket healing. Besides soft- and hard-tissue parameters, special attention was given to postoperative sequelae, such as pain, use of analgesics, edema, trismus, alveolitis, and hemostasis.

2 MATERIALS AND METHODS

2.1 Protocol

This systematic review adhered to the PRISMA standard guidelines[34] and the protocol was built using the PRISMA framework.[35] There were no deviations from the initial protocol.

2.2 Focused question

“What is the benefit of applying an APC in the extraction socket of impacted mandibular third molar(s) compared to an unassisted healing?”

2.3 Eligibility criteria and study selection process

The following PICOS approach served as the basis for this review. Two independent authors (S.A.M.S. and J.Y.) carried out the search and screening procedure, starting with an evaluation of abstracts and titles. In the next step, full papers were chosen for examination and compared to the requirements for data extraction. Disagreements between the reviewing authors were resolved through careful discussion. Only research that fulfilled the specified requirements was included:

- Population: systemically healthy humans in need of an impacted mandibular third molar extraction.
- Intervention: Surgical removal of an impacted mandibular third molar(s) followed by the application of an APC (platelet-rich plasma (PRP), plasma rich in growth factor (PRGF), and leukocyte- and platelet-rich fibrin (L-PRF)) as a single biomaterial in the extraction socket (without the use of other biomaterials).
- Comparison: Surgical removal of impacted mandibular third molars with unassisted healing (blood clot only).
- Outcomes: *Primary:* postoperative sequelae, *Secondary:* soft- and hard-tissue healing.
- Study design: randomized controlled trials (RCTs) with a minimum of 10 patients.

2.4 Primary and secondary outcomes

Postoperative sequelae were selected as primary variables including pain, use of analgesics, hemostasis, soft-tissue healing time, and the incidence of alveolitis, edema, and trismus. Radiographic bone fill (RBF), changes in probing pocket depth (PD), and clinical attachment level (CAL) distal to the adjacent second molar were selected as secondary parameters.

2.5 Search strategy

Detailed search strategies followed by manual searching were conducted through the following electronic databases: PubMed (MEDLINE), EMBASE, Web of Science, and Scopus until December 2023 with English set as language restriction.

The search was performed using the following terms: ((3rd molar[Title/Abstract]) OR (third molar[Title/Abstract]) OR (third molars[Title/Abstract]) OR (wisdom tooth[Title/Abstract]) OR (wisdom teeth[Title/Abstract])) AND ((healing[Title/Abstract]) OR (soft tissue healing[Title/Abstract]) OR (socket healing[Title/Abstract]) OR (bone healing[Title/Abstract]) OR (unassisted healing[Title/Abstract]) OR (wound healing[Title/Abstract]) OR (alveolar bone repair[Title/Abstract]) OR (alveolar osteitis[Title/Abstract]) OR (alveolar ridge preservation[Title/Abstract]) OR (bone regeneration[Title/Abstract]) OR (bony regeneration[Title/Abstract]) OR (osseous regeneration[Title/Abstract]) OR (pain[Title/Abstract]) OR (swelling[Title/Abstract]) OR (edema[Title/Abstract]) OR (trismus[Title/Abstract]) OR (alveolitis[Title/Abstract]) OR (osteitis[Title/Abstract]) OR (pocket[Title/Abstract]) OR (clinical attachment[Title/Abstract])) AND ((PRGF[Title/Abstract]) OR (plasma rich in growth factor[Title/Abstract]) OR (PRP[Title/Abstract]) OR (platelet rich plasma[Title/Abstract]) OR (PRF[Title/Abstract]) OR (platelet rich fibrin[Title/Abstract]) OR (L-PRF[Title/Abstract]) OR (leukocytes[Title/Abstract]) OR (leukocytes- and platelet-rich fibrin[Title/Abstract]) OR (platelet rich fibrin[Title/Abstract]) OR (CGF[Title/Abstract]) OR (concentrated growth factor[Title/Abstract]) OR (platelet[Title/Abstract]) OR (platelet concentrate[Title/Abstract]) OR (blood concentrate[Title/Abstract]) OR (autologous platelet[Title/Abstract])).

The reference lists of included papers and systematic review papers were evaluated (cross-referenced) to identify other studies for potential inclusion.

2.6 Data extraction and synthesis

The study data were independently extracted by two reviewers (S.A.M.S. and J.Y). The following data were extracted from the included studies: authors, study design (split-mouth or parallel), follow-up, number of subjects, age (range or mean), gender, number of smokers, number of extracted impacted mandibular third molars, centrifugation protocol (device and settings), surgical technique (mode of APC application (gel/clot/membrane) as well as wound closure (via primary or secondary intention)), as well as the above-mentioned outcome parameters.

To better understand the impact of APCs in the healing of third molar extraction sockets, a distinction was made between: platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), and leukocyte- and platelet-rich fibrin (L-PRF family, including the original L-PRF protocol, as well as advanced PRF (A-PRF), advanced PRF plus (A-PRF+), titanium PRF (T-PRF), horizontal PRF (H-PRF), and concentrated growth factors (CGF)).

2.7 Risk of bias

Two reviewers (J.Y. and M.Q.) undertook an assessment of any risk of bias addressing five domains.

- Domain 1: randomization/allocation, allocation concealment, difference in baseline data caused by patient selection.
- Domain 2: blinding of participants, surgeons, and personnel.
- Domain 3: blinding toward outcome assessment/outcome assessors.

- Domain 4: incomplete outcome data.
- Domain 5: selective outcome reporting.

The reviewers were not blinded to the names of the authors, institutions, journal, or results of a study. Both reviewers performed the risk-of-bias assessment independently, and in case of disagreement, consensus was reached with the assistance of a third review author (S.A.M.S.). Per individual paper, a final risk of bias was estimated using the following protocol:

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria are met.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria are partly met or there was insufficient information to know if they were met.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met as described in the Cochrane Handbook for Systematic Reviews of Interventions.[36]

3 RESULTS

3.1 Literature search

In total, 544 studies were identified using the mentioned search strategy. After the removal of articles that were not relevant to the PICO question (*n* = 338) and were in duplicate (*n* = 143), and papers focusing on maxillary third molars, 59 full-text papers were left for further screening. All those studies were also included in the qualitative analysis, but none of them in the quantitative analysis (Figure 1).

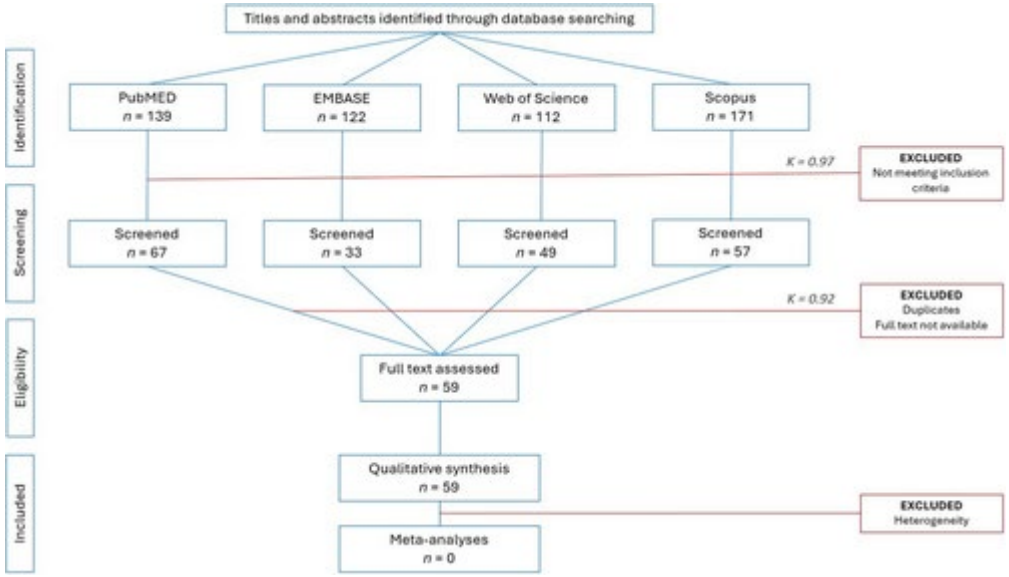


FIGURE 1

[Open in figure viewerPowerPoint]

Flowchart of the search strategy. *K* = Cohen's kappa coefficient for agreement between authors selecting/reviewing the literature.

3.2 PRP versus unassisted healing

Eleven RCTs examined the benefits of applying PRP in comparison to unassisted healing after impacted mandibular third molar extractions.[37-47] Seven out of 11 studies had a split-mouth design, and four were with parallel groups. In all studies, only PRP gel was used to fill the extraction socket. The observation period was between 2 and 6 months (Table 1A).

TABLE 1. Randomized controlled trials on socket healing after third molar extraction comparing unassisted healing (blood clot) with the application of APCs as sole biomaterial. Data, of most relevant parameters, represented in bold indicates statistical significance, with time points in bold and underlined, indicating at which moment they were recorded.

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
(A) PRP							
Sammartino et al. (2005)[46] H	RCT split-mouth 18 weeks H/H/H/S/S	♀= 8/♂= 10 age = 21–26 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	NR 1200 rpm/15’ *batroxobine & 10% gluconate of calcium*	18 C: blood clot 18 T: PRP **gel** to fill	NR	PRP gave: =bone formation *(m 4: no clear data)* **>PD** ↓**** *m **4**: 5.2 vs 1.7 mm* **>CAL** ↑**** *m **4**: 4.5 vs 1.0 mm*
Ogundipe et al. (2011)[45] H	RCT parallel 16 weeks L/S/H/S/S	♀= 35/♂= 25 age = 19–35 0% smokers	1 socket/patient LJ impaction: y healing: Pr	PowerSpin Fx 200 *g*/10’ 160 *g*/10’ *$CaCl_2$ and thrombin*	30 C: blood clot 30 T: PRP **gel** to fill	PRP gave: **<pain** *(d **1**, **3**, **5**, **7**, **14**)* =facial swelling *(d 1, 3, 5, 7, 14)* =trismus *(d 1, 3, 5, 7, 14)*	PRP gave: =bone healing *(w 4, 10, 16)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Célio-Mariano et al. (2012)[38] H	RCT split-mouth 6 months L/H/H/S/S	♀= 8/♂= 7 age = 18–22 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 160 *g*/20’ 400 *g*/15’ *CaCl* $_2$	15 C: blood clot 15 T: PRP $^{gel\ to\ fill}$	NR	PRP gave: **>bone density** *(m **1**, **2**, **3**, 6)* **faster bone healing** *(m **1**, **2**, **3**, 6)*
Kaul et al. (2012)[43] H	RCT split-mouth 6 months H/H/H/S/S	*n* = 25 age = 18–70 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 1000 rpm/10’ 1000 rpm/10’ *CaCl* $_2$	25 C: blood clot 25 T: PRP $^{gel\ to\ fill}$	NR	PRP gave: **<wound dehiscence** *(w **1**)* =bone density **<PD *** *(m **3**, **6**)*
Rao et al. (2013)[42] H	RCT split-mouth 6 months	*n* = 22 age = NR 0% smokers	2 sockets/patient NR	NR 360–400 rpm/20’	22 C: blood clot	NR	PRP gave: =bone regeneration *(m 1, 3, 6)*

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
	S/H/H/S/S		impaction: NR healing: Pr	*calcium gluconate*	22 T: PRP $^{gel\ to\ fill}$		
Dutta et al. (2015)[40] H	RCT parallel 4 months S/H/H/H/S	♀= 31/♂= 29 age = 18–50 0% smokers	1 socket/patient NR impaction: NR healing: Pr	NR 2000 rpm/15’ 3000 rpm/10’ $CaCl_2$	30 C: blood clot 30 T: PRP $^{gel\ to\ fill}$	NR	PRP gave: **better soft tissue healing** *(d **3**, **7**, **14**)* **>lamina dura** *(w **3**, m **2**, **4**)* **>bone density** *(w **3**, m **2**, **4**)* **>trabecular pattern** *(w **3**, m **2**, **4**)*
Dutta et al. (2016)[39] H	RCT parallel 6 months	♀= 13/♂= 27 age = 17–36	1 socket/patient LJ	NR 2000 rpm/15’ 3000 rpm/10’	10 C: blood clot	PRP gave: **<pain** *(d **3**, **7**, **14**)* **<swelling** *(d **3**, **7**, **14**)*	PRP gave: **>soft tissue healing** *(d 3, **7**, **14**)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
	S/S/H/S/S *(2 of 4 arms)*	0% smokers	impaction: # healing: Pr	*$CaCl_2$*	10 T: PRP $^{gel\ to\ fill}$	=dry socket *(d 3: 2 in C; 2 in T)*	**>bone density** *(m 1, 2, **6**)* **>lamina dura** *(m 1, 2, **6**)* **better trabecular pattern** *(m **1, 2, 6**)*
Gandevival a et al. (2017)[41] H	RCT split-mouth 2 months H/H/H/S/S	*n* = 25 age = 16–60 smokers = NR	2 socket/patient LJ impaction: y healing: Pr	NR 1300 rpm/10’ 2000 rpm/10’ *calcium gluconate*	25 C: blood clot 25 T: PRP $^{gel\ to\ fill}$	PRP gave: =pain *(d 1, 3, 7)* **<facial swelling** *(d 1, **3,** 7)*	PRP gave: **<dehiscence rate** *(d **7**)* **>PD** $^{\downarrow}$***** *(m **2**)*
Kumar et al. (2020)[44] H	RCT split-mouth 6 months	♀= 32/♂= 68 age = 21–50 0% smokers	2 sockets/patient LJ impaction: y	NR 2000 rpm/15’ 3000 rpm/10’ *$CaCl_2$*	100 C: blood clot 100 T: PRP $^{gel\ to\ fill}$	PRP gave: **<pain** *(d **1**, **3**, **7**)* **<swelling** *(d **2**, **7**)* **<trismus** *(d **1**, **3**, 7)*	PRP gave: **better soft tissue healing** *(d 3, **7**, **15**)* **>bone density** *(m **3**, **6**)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
	H/H/H/S/S		healing: Pr				**<PD *** *(m **1**, **2**)*
Aftab et al. (2020)[37] H	RCT parallel 4 months S/S/S/H/S	♀= 62/♂= 38 age = 17–42 0% smokers	1 socket/patient LJ impaction: y healing: Pr	NR 1200 rpm/10’ 1000 rpm/10’ *$CaCl_2$ autologous thrombin*	50 C: blood clot 50 T: PRP **gel** to fill	PRP gave: **<pain** *(d **1**, **3**, **5**, **7**, **14**)* **<swelling** *(d **1**, **3**, **5**, **7**, 14)* **<trismus** *(d **1**, **3**, **5**, **7**, **14**)*	PRP gave: **>bone density** *(w **10**, **16**)* **better trabeculae pattern** *(w **10**, **16**)*
Sargaiyan et al. (2022)[47] H	RCT split-mouth 2 months S/S/L/H/S	♀= 8/♂= 7 age = 18–35 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	NR NR *NR*	15 C: blood clot 15 T: PRP **gel** to fill	PRP gave: **<pain** *(d **1**, 3, 7)* =swelling *(d 2, 7)* =dry socket (none)	PRP gave: =soft tissue healing score *(d 1, 3, 7)* =bone density *(m 1)*
(B) PRGF							

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Mozzati et al. (2010)[49] H	RCT split-mouth 7 days L/S/S/S/S	*n* = 16 age = 18–35 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	PRGF system 1800 rpm/8’ *CaCl* $_2$	16 C: blood clot 16 T: PRGF ^{gel} to fill	PRGF gave: **<pain** *(d 1, 2, 3, 4, 5, 6, **7**)* **<swelling** *(d **1**, **2**, **3**, **4**, **5**, **6**, 7)*	PRGF gave: **>IL-1β and IL-6** *(d **7**)* **>IL-10 and TGF-β2** *(d **7**)* **>Coll I and Coll III** *(d **7**)* **>BMP-7** *(d **7**)*
Haraji et al. (2012)[48] H	RCT split-mouth 7 days H/L/L/L/S	n = 40 x̄ age = 22.1 18/40 smokers	2 sockets/patient 20 LJ/20 UJ impaction: # NR	NR 460 *g*/8’ *CaCl* $_2$	40 C: blood clot 40 T: PRGF ^{gel} to fill	PRGF gave: **<pain** *(d **2**, **3**, **4**)* **<dry socket** *(d7: 18 in C; 4 in T)*	PRGF gave: **better healing scores** *(d **3**, **7**)*
O’Sullivan et al. (2022)[50]	RCT parallel	♀= 57/♂= 17 age = 19–39	1 socket/patient	Endoret 580 *g*/8’	38 C: blood clot	PRGF gave: =pain *(d 3, 7)*	PRGF gave: =socket healing index *(d 7)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
L	7 days L/L/L/L/S	23/74 smokers	LJ impaction: y healing: Pr	*$CaCl_2$*	36 T: PRGF ^{gel} to fill	=analgesics *(d 7)* =OHIP-14 *(d 3, 7)* =mouth opening *(d 7)* =dry socket *(d 7: 1 in C, 3 in T)*	
Hoaglin & Lines (2013)[66] H	RCT parallel 7–10 days H/H/H/L/S	♀= 95/♂= 105 age = 14–40+ 10 smokers	2 sockets/patient LJ impaction: # healing: Pr/Se	NR 2700 rpm/10–12’	200 C: blood clot 200 T: 1 L-PRF ^{cl} to fill	L-PRF gave: **<dry socket** *(d 7: 19 in C; 2 in T)*	NR
Eshghpour et al. (2014)[61] L	RCT split-mouth 7 days	♀= 45/♂= 33 x̄ age = 25.1 0% smokers	2 sockets/patient LJ impaction: y	Labofuge 400R 3000 rpm/10’	78 C: blood clot 78 T: 1 L-	L-PRF gave: **<dry socket** *(d7: 16 in C; 7 in T)*	NR

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
	L/L/L/L/L		healing: NR		PRF $^{cl\ to\ fill}$		
Ozgul et al. (2015)[77] S	RCT split-mouth 7 days L/S/S/S/L	♀= 33/♂= 23 age = 18–28 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 3000 rpm/10’	56 C: blood clot 56 T: 1 L-PRF $^{M\ to\ fill}$	L-PRF gave: =pain *(d 1, 3, 7)* **<horizontal swelling** *(d **1**, **3**, 7)* =vertical swelling *(d 1, 3, 7)*	NR
Uyanık et al. (2015)[91] H	RCT split-mouth 7 days H/H/H/L/S *(2 of 4 arms)*	♀= 6/♂= 4 age = 19–31 0% smokers	2 sockets/patient LJ impaction: # healing: Pr	Elektro-mag M415P 400 *g*/10’	10 C: blood clot 10 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(across first **7** d)* **<analgesics** *(in **7** d)* =facial swelling *(d 1, 3, 7)* **<trismus** *(d **1**, 2, 3, 7)*	NR

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Bilginaylar & Uyanik (2016)[55] H	RCT parallel 7 days S/H/L/L/S	♀= 37/♂= 22 age = 18–31 0% smokers	1–2 sockets/pat. LJ impaction: y healing: Pr	Elektro-mag M415P 3000 rpm/10’	C: blood clot: 20 C_1: burs; 20 C_2: piezo T: 1 L-PRF $^{cl\ to\ fill}$ 20 T_1: burs 20 T_2: piezo	L-PRF gave: **<pain T1/T2** *(d **1**, **2**, **3**, 7)* **<analgesics T1/T2** *(d 1, **2**, **3**, 7)* =swelling *(d 1, 2, 3, 7)* =trismus *(d 1, 2, 3, 7)*	NR
Gülşen & Sentürk (2017)[64] H	RCT split-mouth 7 days	♀= 9/♂= 21 age = 17–27 smokers = NR	2 sockets/patient LJ impaction: #	NF200 3000 rpm/10’	30 C: blood clot 30 T: 3 L-	L-PRF gave: = pain *(h 6, 12, d 1, 2, 3, 7)* = swelling *(d 2, 7)*	NR

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
	S/H/H/L/S		healing: Pr		PRF $^{M\ to\ fill}$	= dry socket *(d 7: 3 in C; 0 in T)*	
Asutay et al. (2017)[53] H	RCT split-mouth 7 days S/S/S/L/S	♀= 24/♂= 6 age = 18–29 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 2700 rpm/12’	30 C: blood clot 30 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: = pain *(h 6, 12, d 1, 2, 3, 4, 5, 6, 7)* = swelling *(d 2, 7)* = trismus *(d 2, 7)* = dry socket *(d 7: 3 in C; 1 in T)*	NR
Al-Hamed et al. (2017)[95] H	RCT parallel 7 days S/H/H/L/S	♀= 34/♂= 13 age = 18–48 0% smokers	1/2 sockets/patient LJ impaction: # healing: Pr	NR 3000 rpm/10’	25 C: blood clot 25 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain:** *(d 2, 3, 4, **5**, **6**, **7**)* **<analgesics:** *(d **2**, **3**, 4, 5, **6**, **7**)* **<dry socket** *(d7: 4 in C; 1 in T)*	L-PRF gave: = soft tissue healing scores *(d 7)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Eshghpour et al. (2018)[60] L	RCT split-mouth 7 days L/L/L/L/S *(1 of 2 arms)*	♀= 69/♂= 49 x̄ age: 23.9 0% smokers	2 sockets/patient LJ impaction: # healing: Pr	Labofuge 400R 3000 rpm/10’	118 C: blood clot 118 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<dry socket** *(d 7: 28 in C; 13 in T)*	NR
Afat et al. (2018)[52] S	RCT parallel 7 days S/L/L/L/S *(2 of 3 arms)*	♀= 38/♂= 22 x̄ age = 22 0% smokers	1 socket/patient LJ impaction: +/- healing: Pr	NR 3000 rpm/10’	20 C: blood clot 20 T:1 L-PRF $^{cl\ to\ fill}$ & 1 L-PRF $^{M\ to\ cover}$	L-PRF gave: =pain *(d 0, 1, 2, 3, 4, 5, 6, 7)* =analgesics (*d 0, 1, 2, 3, 4, 5, 6, 7)* **<swelling** *(TPO: d 2, **7**; ACA: d **2**, **7**)* =trismus *(d 2, 7)*	NR

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Daugela et al. (2018)[57] S	RCT split-mouth 14 days L/L/L/S/S	n = 30 x̄ age: 22.8 0% smokers	2 sockets/patient LJ impaction: # healing: Pr	EBA 20 2800 rpm/12’	30 C: blood clot 30 T: 2 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(d **1**, **2**, **3**, **4**, **5**, **6**, **7**)* **<facial swelling** *(d **1**, **3**, 7)* **<dry socket** *(d 7: 4 in C; 0 in T)*	L-PRF gave: **better soft tissue healing** *(d **1**, **3**, **7**, **14**)*
Afat et al. (2019)[51] S	RCT parallel 21 days S/L/L/S/S *(2 of 3 arms)*	♀= 38/♂= 22 x̄ age = 22 0% smokers	1 socket/patient LJ impaction: +/- healing: Pr	NR 3000 rpm/10’	20 C: blood clot 20 T:1 L-PRF $^{cl\ to\ fill}$ & 1 L-PRF $^{M\ to\ cover}$	L-PRF gave: *(up to d 21)* =dry socket *(1 in C; 0 in T)* =bleeding	L-PRF gave: **better soft tissue healing** (*d **7**, **14**, **21***)

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Torul et al. (2020)[88] *(3 arms)* S	RCT parallel 7 days S/L/L/L/S	♀= 52/♂= 23 age = 18–37 0% smokers	1 socket/patient LJ impaction: # healing: Pr	T^1: DUO 198 *g*/14' T^2: Medifuge # settings	C: blood clot (25) 25 T^1: A-PRF cl to fill 25 T^2: CGF cl to fill	both A-PRF/ CGF gave: =pain *(d 2, 7)* =analgesics *(d 2, 7)* =swelling *(d 7)* =trismus *(d 2, 7)*	NR
Koyuncu et al. (2020a)[78] S	RCT split-mouth 7 days S/S/L/L/S	♀= 39/♂= 21 age = 18–35 0% smokers	2 sockets/patient LJ impaction: +/- healing: Pr	Medifuge # settings	60 C: blood clot 60 T: 2 CGF cl to fill	CGF gave: **<pain** *(d **1**, **2**, **3**, **4**, **5**, **6**, **7**)* **<swelling** *(d **3**, **7**)* **<trismus** *(d **3**, **7**)* =dry socket *(d 7: 11 in C: 5 in T)*	CGF gave: **better soft tissue healing** *(d **3**, **7**)*
Koyuncu et al. (2020b)[79]	RCT	♀= 44/♂= 26	2 sockets/patient	Medifuge # settings	70 C: blood clot	CGF gave:	NR

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
S	split-mouth 7 days S/S/L/L/S	age = 18–35 0% smokers	LJ impaction: +/- healing: Pr		70 T: 2 CGF $^{cl\ to\ fill}$	**<dry socket** *(d 3: 8 in C; 0 in T)*	
Nourwali (2021)[75] H	RCT parallel 14 days S/H/H/L/S	*n* = 20 age = 18–40 smokers = NR	1 socket/patient LJ impaction: y healing: Pr	UNICO power 3000 rpm/10’	10 C: blood clot 10 T: 1 L-PRF $^{M\ to\ fill}$	CGF gave: =pain *(h 1, 2, 6, 12, d 1)* **>comfort at night** *(d **1**)* =swelling *(h 12, d1, 2, 3)* **<bleeding** *(**h 1**, 2, 6, 12, 24)*	L-PRF gave: **>soft-tissue healing** *(d **14**)*
Trybek et al. (2021)[89] H	RCT parallel 7 days S/H/H/L/S	♀= 62/♂= 28 age = 18–37 0% smokers	1 socket/patient LJ impaction: y healing: Pr	IntraSpin 708 *g*/12’	45 C: blood clot 45 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(h **6**, **12**, **d 1**, **2**, **3**, 4, 5, 6, 7)* =swelling *(d 1, 2, 7)* **<trismus** *(d **1**, **2**, **7**)*	NR

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
					+ 1 L-PRF [M] to cover	**<body temperature** *(d 1, **2**, 7)*	
Starzyńska et al. (2021)[85] H	RCT parallel 14 days L/H/H/S/S	♀= 65/♂= 35 age = 18–47 0% smokers	1 socket/patient LJ impaction: # healing: Pr	All Centrifuge 1500 rpm/14’	50 C: blood clot 50 T: 4 A-PRF [P] to fill	A-PRF gave: **<**pain *(d **3**, **7**, 14)* **<analgesics** *(d **3**, **7**, 14)* **<swelling** *(d **3**, **7**, 14)* **<trismus** *(d **3**, **7**, 14)* **<bleeding time** ***(first 6 h)*** **>hematoma** *(d **3**, 7, 14)* =dry socket *(d 7: 1 in C, 1 in T)* =body temperature *(d 3, 7, 14)*	NR

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Nowak et al. (2021)[76] S	RCT parallel 14 days L/S/L/L/S	♀= 22/♂= 38 age = 18–40 0% smokers	1 socket/patient LJ impaction: +/- healing: Pr	Duo Quatro 1500 rpm/14’	30 C: blood clot 30 T: 2 L-PRF $^{P\ to\ fill}$ + 2 L-PRF $^{M\ to\ cover}$	L-PRF gave: **<pain** *(across first **7** d)* **<swelling** *(d **7**)* **<trismus** *(d **7**)* **<dry socket** *(d 7: 15 in C; 3 in T)*	L-PRF gave: **lower CRP level** *(d **7**)*
Konuk & Senturk (2022)[70] H	RCT split-mouth 7 days S/H/H/L/S	♀= 22/♂= 8 age = 18–28 43% smokers	2 sockets/patient LJ impaction: y healing: Pr	EBA 20 3000 rpm/10’	30 C: blood clot 30 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: = swelling *(d 1, 2, 7)* = dry socket *(d 7: 0 in C; 0 in T)*	NR
Elayah et al. (2022)[58]	RCT split-mouth	♀= 19/♂= 18 age = 18–38	2 sockets/patient	Trausim DL4015 2300 rpm/13’	37 C: blood clot	CGF gave: **<pain** *(d 1, **3**, **7**)*	CGF gave: **better wound healing index** *(d **7**)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
H	7 days L/H/L/L/S	smokers = NR	LJ impaction: y healing: Pr		37 T: 2 CGF cl to fill	**<less swelling** *(d **1**, **3**, 7)*	
Shruthi et al. (2022)[84] H	RCT parallel 7 days H/H/H/S/S	*n* = 44 age = 18–40 0% smokers	1 socket/patient LJ impaction: y healing: Pr	NR NR	22 C: blood clot 22 T: 2 L-PRF cl to fill	L-PRF gave: **<pain** *(d 1, 3, **7**)* =swelling *(d 1, 3, 7)* **<trismus** *(d 1, **3**, 7)*	NR
Kalyani et al. (2023)[68] H	RCT split-mouth 7 days S/S/L/S/S	*n* = 25 age = 18–45 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 2700 rpm/12’	25 C: blood clot 25 T: 1 L-PRF (NR)	L-PRF gave: **<pain** *(d **1**, 3, **7**)* **<swelling** *(d **1**, **3**, 7)*	L-PRF gave: **better soft-tissue healing index** *(d **7**)*

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
(C) L-PRF (long-term studies)							
Kumar et al. (2015)[71] H	RCT parallel 3 months L/H/H/L/S	*n* = 31 x̄ age = 26 smokers = NR	1 socket/patient LJ impaction: # healing: Pr	NR 3000 rpm/10’	15 C: blood clot 16 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(d **1**)* **<swelling** *(d **1**)* **<interincisal distance** *(d **1**)*	L-PRF gave: = bone density *(m 1, 3)* **>˙*** *(m 1–3: 1.5 vs 0.5 mm)*
Kumar et al. (2016)[72] H	RCT split-mouth 6 months L/H/H/L/S	*n* = 34 age = 18–40 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 3000 rpm/10’	34 C: blood clot 34 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(d **1**, **3**, **7**, 28)* =dry socket *(d7: 1 in C; 0 in T)*	L-PRF gave: = new bone quantity *(m 2, 4, 6)*
Baslarli et al. (2015)[54]	RCT split-mouth	♀= 13/♂= 7 age = 19–34	2 sockets/patient	NR 3000 rpm/10’	20 C: blood clot	L-PRF gave: = dry socket *(d 7: 2 in C; 0 in T)*	L-PRF gave: = scintigram *(m 1, 3)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
H	90 days L/S/S/S/S	0% smokers	LJ, discomfort impaction: +/- healing: Pr		20 T: 1 L-PRF $^{M\ to\ fill}$		= radiopacity *(m 1, 3)* = PD * *(m 1, 3)*
Varghese et al. (2017)[92] L	RCT split-mouth 16 weeks L/L/L/L/S	*n* = 30 age = 18–35 smokers = NR	1/2 sockets/pat. LJ impaction: # healing: Pr	Remi R-23 3000 rpm/10’	30 C: blood clot 30 T: 1 L-PRF $^{cl\ to\ fill}$	NR	L-PRF gave: **better soft tissue healing index** *(m **4**)* **>new bone formation** *(m **4**)* **>% bone fill** *(m 4: 58 vs 47 %)*
Dar et al. (2018)[56] H	RCT split-mouth 3 months H/H/H/S/S	♀= 17/♂= 13 age = 18–50 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	NR 3000 rpm/12’	30 C: blood clot 30 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(d **1**, **3**, **7**, 14)* **<swelling** *(d **1**, **3**, **7**, 14)*	L-PRF gave: **>soft tissue healing** *(d **1**, **3**, **7**, 14)* **better bone healing** (*w **4**, **12***)

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
							>lamina dura formation *(w **4**, 12)* **>bone density** *(w **4**, 12)*
Revathy et al. (2018)[80] H	RCT split-mouth 6 months S/H/H/S/S	♀= 10/♂= 15 age = 18–35 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	NR 3000 rpm/10’	20 C: blood clot (20) 20 T: 1 L-PRF $^{M\ to\ fill}$	L-PRF gave (up to w 3): temporary paraesthesia *(2 in C; 1 in T)*	L-PRF gave: **>bone formation** *(m **1**, **3**, **6**)*
Unsal & Erbasar (2018)[90] H	RCT split-mouth 3 months S/H/S/S/S	♀= 33/♂= 17 age = 15–43 smokers = NR	2 sockets/patient LJ impaction: +/- healing: Pr	NF200 3000 rpm/10’	50 C: blood clot 50 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(h 6, 12, d **1**, 2, 3, d **7**)* <dry socket *(d7: 9 in C; 4 in T)*	L-PRF gave: = PD ***** *(m 3: ≤3 mm)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Jeyaraj et al. (2018)[67] H	RCT parallel 8 weeks S/S/S/H/S	*n* = 60 age = NR smokers = NR	1 socket/patient LJ impaction: # healing: Pr	NR 2700 rpm/12' *or* 3000 rpm/10'	30 C: blood clot 30 T: 2 L-PRF $^{cl\ to\ fill}$	L-PRF gave: =pain *(d 3)* =swelling *(d 3)* =trismus *(d 3)*	L-PRF gave: = bone healing *(m 2)* = PD * *(m 2)*
Ritto et al. (2019)[81] L	RCT split-mouth 3 months L/L/L/L/S	♀= 7/♂= 10 age = 16–29 0% smokers	2 sockets/patient LJ impaction: # healing: Pr	NR 400 *g*/12'	17 C: blood clot 17 T: 2 L-PRF $^{cl\ to\ fill}$	L-PRF gave: =pain *(d 1, 3, 7)*	L-PRF gave: =soft tissue healing index *(m 3)* **>bone density** *(m **3**)* =PD * *(m 3)*
Zahid & Nadershah (2019)[94] H	RCT split-mouth 3 months	♀= 10/♂= 0 x̄ age = 24 0% smokers	2 sockets/patient LJ impaction: y	DUO Quatro 1300 rpm/13'	10 C: blood clot 10 T: 2 A-	A-PRF gave: **<pain** *(across first **7** d)* **<swelling** *(d **7**)*	A-PRF: = soft tissue healing scores *(d 7)* = PD* *(m 1, 3)*

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
	S/S/L/S/S		healing: Pr		PRF $^{M\ to\ fill}$		= CAL* *(m 1, 3)*
Kapse et al. (2019)[69] S	RCT split-mouth 4 months L/S/L/L/S	♀= 17/♂= 13 age = 18–40 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	R-4C DX 2700 rpm/12’	30 C: blood clot 30 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(d **1**, **3**, **7**, **14**)* **<swelling** *(d **1**, **3**, **7**, **14**)*	L-PRF gave: **>bone density** *(w **8**, **16**)* **>lamina dura** *(w **8**, **16**)* **>trabecular pattern** *(w **8**, **16**)*
Yüce & Kömerik (2019)[93] S	RCT parallel 3 months L/S/L/S/S	♀= 22/♂= 18 age = 18–40 0% smokers	1 dry socket/patient LJ impaction: y healing: Se	Duo Quatro 1300 rpm/8’	20 C: curettage + saline (d 1, 3, 5, 7) 20 T: curettage + saline +	A-PRF gave: **<pain** *(d 0, **1**, **3**, **5**, **7**)* **<analgesics for 7 days**	A-PRF gave: **>epithelial healing scores** *(d 0, **7**, **14**)* **>bone density OPTG** *(m 1, **2**, **3**)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
					1 A-PRF $^{cl\ to\ fill}$		
Gupta & Agarwal (2021)[65] H	RCT split-mouth 6 months L/H/L/S/S	♀= 12/♂= 8 age = 18–35 0% smokers	2 sockets/patient LJ impaction: # healing: Pr	NR 1500 rpm/14’	20 C: blood clot 20 T: 1 A-PRF $^{cl\ to\ fill}$	A-PRF gave: **<pain** *(d 1, **3**, **7**)* **<analgesics** *(d 1, **3**, 7)* **<swelling** *(d 1, **3**, 7)* **<trismus** *(d 1, **3**, 7)*	A-PRF gave: **>soft tissue healing score** *(d 1, 3, **7**)* **>bone healing score** *(m **1**, **3**, **6**)*
Sybil et al. (2020)[86] S	RCT split-mouth 6 months L/L/L/S/S	♀= 11/♂= 14 age = 18–55 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	NR 3000 rpm/10’	25 C: blood clot 25 T: 1 L-PRF $^{cl\ to\ fill}$	L-PRF gave: **<pain** *(d **1**, **3**, **7**, m 1)* **<swelling** *(d **1**, **3**, **7**, m 1)*	L-PRF gave: =bone height ***** *(m 3, 6)* **<sulcus bleeding index*** *(m **1**, **3**, **6**)* **>CAL $^{\uparrow}$*** *(m 1, **3**, **6**)*

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
							<plaque index* *(w **1**, m **1**, **3**, **6**)* **<PD *** *(m 3, **6**)*
Gasparro et al. (2020)[63] S	RCT split-mouth 6 months L/L/L/S/S	♀= 8/♂= 10 age = 18–35 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	IntraSpin 408 *g*/12’	18 C: blood clot 18 T: 2 L-PRF ᴹ to fill + 2 L-PRF ᴹ to cover	NR	L-PRF gave: **>CAL ↑*** *(m **6**)* **>PD ↓*** *(m **6**)*
Malhotra et al. (2020)[73] S	RCT split-mouth 4 months	*n* = 50 age = 20–35 smokers = NR	2 sockets/patient LJ	Remi C-854/6 3000 rpm/10’	50 C: blood clot 50 T: 1 L-	L-PRF gave: =pain *(during w 1, m 1, 2)* =swelling *(w 1, m 1, 2)*	L-PRF gave: = wound healing *(w 1, m 1, 2)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
	S/S/L/L/S		impaction: +/- healing: Pr		PRF cl to fill		**>bone density** *(m **1**, **2**, **4**)* **>bone height M2** *(m **1**, **2**, **4**)* =PD * *(w 1, m 1, 2)* =CAL * *(w 1, m 1, 2)*
Sharma et al. (2021)[83] H	RCT split-mouth 6 months S/H/H/S/S	♀= 36/♂= 24 age = 20–40 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	NR 3000 rpm/10’	60 C: blood clot 60 T: 1 L-PRF cl to fill	L-PRF gave: **<pain** *(d 1, **7**, 28)* =dry socket *(d 7: 2 in C; 0 in T)*	L-PRF gave: =bone density *(m 1, 2, 3, 4)*
Njokanma et al. (2022)[74] H	RCT parallel 12 weeks	*n* = 84 age = 18–35 0% smokers	1 socket/patient LJ	Axiom 800B 3000 rpm/10’	42 C: blood clot 42 T: 1 L-	L-PRF gave: **>surgery time** *(32 vs 27 min)*	L-PRF gave: =newly formed bone *(w 1, 4, 8, 12)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
	S/H/H/L/S		impaction: y healing: Pr		PRF cl to fill		=density of RNFB *(w 1, 4, 8, 12)*
Fang et al. (2022)[62] S	RCT parallel 24 weeks S/L/L/S/S	♀= 52/♂= 66 age = 18–50 smokers = NR	1 socket/patients LJ impaction: y healing: Pr	NR Medifuge # settings	60 C: blood clot 58 T: 1 CGF cl to fill	CGF gave: **<pain** *(h **2**, d **1**, **2**)* =swelling *(d 2, 7)* =trismus *(d 2, 7)* =dry socket *(d 7: 3 in C; 0 in T)*	CGF gave: **>mineral bone density** *(m **6**)* **<PD *** *(m **6**)*
Tadic et al. (2023)[87] L	RCT split-mouth 8 weeks L/L/L/L/S	♀= 15/♂= 15 age = 18–40 0% smokers	2 sockets/patient LJ impaction: y healing: Pr	NR 2700 rpm/12’	30 C: blood clot 30 T: 2 L-PRF P to fill	NR	L-PRF gave: =bone density *(w 8, CBCT)* =bone volume gain *(w 8, CBCT)* =PD * *(w 1, 8)*

Article, overall bias	**Study: Design, follow up, bias risk per domain**	**Subjects: gender*, age, % smokers**	**Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se**	**Centrifugation: device, rpm or g/min, coagulation factors**	**Treatment: C = control (BC), T = test (APC)**	**Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding**	**Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)**
Elayah et al. (2023)[59] H	RCT split-mouth 3 months S/H/L/L/S	♀= 14/♂= 16 age = 19–35 smokers = NR	2 sockets/patient LJ impaction: y healing: Pr	Trausim DL4015 2300 rpm/13’	30 C: blood clot 30 T: 2 CGF ^{cl} to fill	NR	CGF gave: **>buccal wall height** *(m **3**)* **>lingual wall height** *(m **3**)* **>alveolar bone width** *(m **3**)* **<socket surface area** *(m **3**)* **>bone density** *(m **3**)* **>PD** $^{\downarrow}$***** *(m **3**)*
Rodrigues et al. (2023)[82] H	RCT split-mouth 90 days	♀= 15/♂= 7 age = 18–28 0% smokers	2 sockets/patient LJ impaction: y	Daiki DT4000 2700 rpm/12’	22 C: blood clot 22 T: 2 L-PRF ^{P} to fill	L-PRF gave: **<pain** *(h 4, **6**, **8**, **16**, d **1**, **2**, **3**)* **<swelling** *(d **3**, 7)*	L-PRF gave: **>wound healing index** *(d **3**, **7**)* **>bone volumes** *(m **3**)*

Article, overall bias	Study: Design, follow up, bias risk per domain	Subjects: gender*, age, % smokers	Extraction info: # sockets, jaw, impacted: Y/N, healing: Pr/Se	Centrifugation: device, rpm or g/min, coagulation factors	Treatment: C = control (BC), T = test (APC)	Primary outcomes: PROs, swelling, pain, trismus, dry socket, bleeding	Secondary outcomes: soft-and hard tissue healing, PD and CAL (2nd molar measures)
	S/H/L/S/S		healing: Pr				**>trabecular thickness** *(m **3**)* =trabecular distance *(m 3)* =grey values *(m 3)* =PD ***** *(d 7, m 3)*

- *Note*: Study: design: RCT, randomized clinical, bias: evaluation of the 5 domains (1st bias arising from the randomization process, 2nd bias because of blinding (patient & personal), 3rd bias because of blinding during outcome assessing, 4th bias due to incomplete data, 5th bias in selection of the reported results); with "H" representing high, "S" some concerns/doubts, and "L" being low; the final overall judgement is presented under the authors name. Subjects: * if gender was not reported, only the number of patients is used. Extraction info: LJ, lower jaw, impacted = position of the 3rd molar (y, impacted; +/-, partially erupted); healing: Pr, primary intention, Se, via secondary intention. Centrifuge: rpm, revolutions per minute, ', minutes, g, g-force; Medifuge # settings, 2700 rpm/2'; 2400 rpm/4'; 2700 rpm/4'; 3000 rpm/3'. Treatment: T, test, C, control, p, patients, in brackets, number of sides or patients, PRP, platelet rich plasma; PRGF, plasma rich in growth factors; L-PRF, leukocyte- and platelet rich fibrin (acronym as mentioned in the paper: A, advanced; CGF, concentrated growth factor); APC matrix: cl, clot; P, plug; M, membrane; application mode: fill, to fill the socket, cover, to cover the socket. Data: ACA, *angulus* mandibulae to lateral *canthus*; CAL, clinical attachment level; CRP, C-reactive protein; NR, not reported; OHIP, oral health impact profile; PD, pocket depth; RNFB, region of newly formed bone; TPO, tragus to pogonion. ↓ = reduction, ↑ = increase, * = for second molar (distally)

3.2.1 Postoperative sequelae

Six papers explored the benefits of an PRP gel application in the extraction socket on postoperative pain, with five reporting lower pain values,[37, 39, 44, 45, 47] and one paper did not observe any impact.[41]

Six papers evaluated the impact of PRP on facial swelling, with four reporting a significant reduction,[37, 39, 41, 44] but two indicating no difference.[45, 47]

Three studies considered the impact on the prevalence of trismus: two favoring PRP,[37, 44] and one failed to find any difference.[45]

The incidence of a dry socket was examined in two papers. No statistically significant differences were found between PRP and unassisted healing.[39, 47]

3.2.2 Soft- and hard-tissue healing

The early soft-tissue healing over the extraction socket was followed in six articles, with five showing a more favorable healing or a lower incidence of wound dehiscence when applying a PRP gel, compared to unassisted healing,[39-41, 43, 44] and one failing to see any difference.[47]

Ten studies evaluated the bone healing of the extraction socket (qualitatively and/or quantitatively), with five reporting faster healing and/or more bone density after using PRP,[37-40, 44] but the five others did not observe any difference.[42, 43, 45-47]

Four papers examined the effect of PRP on the periodontal conditions of the adjacent second molar, all with more favorable results when compared to unassisted healing (more pocket depth reduction and/or clinical attachment gain).[41, 43, 44, 46]

3.3 PRGF versus unassisted healing

Three RCTs examined the benefits of applying PRGF gel (in comparison to unassisted healing), after the extraction of impacted mandibular third molars, two with a split-mouth design, and one with parallel groups[48-50] (Table 1B).

3.3.1 Postoperative sequelae

Two studies reported more favorable outcomes (less pain, less swelling, and/or lower incidence of dry socket) for sockets where PRGF was applied,[48, 49] whereas one paper could not find significant benefits.[50]

3.3.2 Soft- and hard-tissue healing

The impact on soft-tissue healing was not clear, with one paper in favor of PRGF[48] and another one without difference.[50]

3.3.3 Proteins

Mozzati and co-workers[49] analyzed the production of tissue cytokines and other healing factors after third molar extraction. A significant increase in the release of IL-1, IL-6, IL-10, and TGF-ß2, Coll I, Coll III, and BMP-7 at day 7 was observed when swabs from PRGF sites were compared to sites with unassisted healing.

3.4 L-PRF versus unassisted healing

In total, 45 RCTs compared the outcome of applying L-PRF to the extraction socket with unassisted healing after impacted mandibular third molar extraction,[51-95] (Table 1C).

The studies showed a very large heterogeneity, which made it impossible to perform a meta-analysis and very difficult to draw firm conclusions. The most important heterogeneity factors were as follows:

Variety in case selection

- The degree of third molar impaction varied within as well as between studies (completely or partially bony impacted, only soft-tissue impacted).
- Most surgical protocols envisaged healing by primary intention, but in one study healing by secondary intention was allowed.

Variety in study design

- Twenty-nine studies used a split-mouth design, whereas in 16 papers parallel groups were examined.
- The follow-up period ranged from ≤7 days (*n* = 17), to 8–14 days (*n* = 5), to 2–8 weeks (*n* = 3), or longer (*n* = 20).

Variety in L-PRF matrix

- Different centrifugation protocols have been used to prepare the L-PRF: thirty-five studies used a concept similar to the original L-PRF protocol, five applied the A-PRF, and another six used the CGF protocol (one study used both A-PRF and CGF).
- Different types of matrices were used to fill the extraction socket: thirty-four clots, seven membranes, four plugs, and one study did not specify.
- The number of matrices inserted into the extraction socket varied: mostly only one matrix, but in fifteen trials ≥2 matrices were applied.
- In some studies (*n* = 5), L-PRF was also used as a barrier membrane to cover the socket.

Variety in outcome measures

- Several studies only examined postoperative sequelae (*n* = 15), a number only soft- and hard-tissue parameters (*n* = 4), and the majority a combination of both (*n* = 26).

- There was a large variety in recorded parameters, especially how the parameters were measured.

Because of the large variation in time points at which data were collected, we decided to report the outcomes for several time points, with of course differences in the number of studies per time point.

3.4.1 Postoperative sequelae

Postoperative pain

Thirty-two studies compared the pain sensation after impacted mandibular third molar extraction between unassisted healing and the application of L-PRF in the extraction socket.[52, 53, 55-58, 62, 64, 65, 67-69, 71-73, 75-77, 79, 81-86, 88-91, 93-95] The time point at which the postoperative pain was scored, as well as how it was measured (diary, visual analog score, questioned by clinician or scored by the patient) differed between the studies.

The number of studies with a split-mouth design (*n* = 19) reporting a statistically significant reduced pain intensity/duration after the application of L-PRF was: 9 out of 16 at day 1, 9 out of 15 at day 3, and 13 out of 19 at day 7 (the latter including two papers considering the pain across 7 days). When all time points were taken together, 14 out of 19 (73.7 %) papers showed significantly lower pain values in patients treated with L-PRF, for at least one follow-up visit.

The number of studies with parallel groups (*n* = 13) reporting statistically significant beneficial effects with L-PRF was: 5 out of 8 on day 1, 4 out of 8 on day 3, and 5 out of 9 on day 7 (the latter including one paper considering the pain across 7 days). When all time points were taken into consideration, 9 out of 13 papers (69.2 %) demonstrated significantly lower pain values in patients treated with L-PRF, at one or more data points.

Analgesics

Eight articles,[52, 55, 65, 85, 88, 91, 93, 95] evaluated the total analgesic consumption up to day 3 or 7. Two of them with a split-mouth design (both reporting significantly lower consumptions after L-PRF use), and the rest (*n* = 6) with a parallel concept (four of them indicating a reduced use of analgesics in the L-PRF group). All together 75% of the studies reported a reduction in analgesic use.

Postoperative swelling

Twenty-seven papers reported on the impact of L-PRF application on postoperative swelling.[52, 53, 55-58, 62, 64, 65, 67-71, 73, 75-78, 82, 84-86, 88, 89, 91, 94] The time point at which the swelling was recorded, as well as how it was measured (visual analog score, linear measurements in horizontal/vertical direction) differed a lot between the studies.

Of the 16 papers with a split-mouth design, the ratio of studies with statistical superiority of L-PRF (compared to unassisted healing) was 7 out of 10 on day 1, 10 out of 14 on days 2–3, and 5 out of 16 on day 7. Overall, 11 out of 16 papers observed one or more time points where L-PRF significantly

reduced postoperative edema when compared to unassisted healing. This superiority was most obvious at days 2–3, which is in line with the observation that this swelling normally subsides after days 2–3. The corresponding ratios from parallel studies (*n* = 11) were 1 out of 6 on day 1, 2 out of 8 on days 2–3, and 3 out of 8 on day 7, with overall only 4 out of 11 studies reporting a statistical benefit after the application of L-PRF. All together 55.6 % of the studies reported a reduction of the postoperative swelling for at least one time point.

Trismus

Thirteen papers assessed the development of trismus after extraction of an impacted mandibular third molar.[52, 53, 55, 62, 65, 67, 76, 78, 84, 85, 88, 89, 91] The time point at which trismus was recorded, as well as how it was measured, differed a lot between the studies.

From the split-mouth studies (*n* = 4), 1 out of 2 reported a statistically significant lower incidence of trismus on day 1, 2 out of 4 on day 2–3, and 1 out of 4 on day 7, with overall 3 out of the 4 studies presenting at least one time point at which L-PRF could reduce the incidence of trismus compared to unassisted healing. The corresponding data from parallel studies (*n* = 9) were: 1 out of 3 on day 1, 3 out of 8 on days 2–3, and 3 out of 8 on day 7, with 4 out of the 9 studies showing that L-PRF could reduce trismus at one or more follow-up moments. When considering both study designs together, 53.8 % showed a reduction in the incidence of trismus.

Alveolar osteitis (dry socket)

The incidence of alveolar osteitis after the extraction of an impacted mandibular third molar was estimated by 18 papers.[51, 53, 54, 57, 60-62, 64, 66, 70, 72, 76, 78, 79, 83, 85, 90, 95] In all these papers together, 995 unassisted healings were compared to 993 sockets in which L-PRF had been applied, with a respective incidence of a dry socket of 13.1% versus 3.7%, in favor of L-PRF.

Postextraction bleeding (hemostasis)

Three papers examined postextraction hemostasis,[51, 75, 85] with the last two papers reporting statistically significant less postextraction bleeding after L-PRF use.

Fever

Two studies verified the body temperature after the extraction of an impacted mandibular third molar. Trybek and co-workers[89] observed significantly less temperature increase on day 2 (not on day 1 nor on day 7), whereas Starzymska et al.[85] did not observe any difference (days 3 and 7).

Surgical time

Njokanma and co-workers[74] recorded the surgical time and observed a statistically significant increase in surgery time when L-PRF was applied, namely, 32 versus 27 min.

3.4.2 Soft- and hard-tissue healing

Soft-tissue healing extraction socket

Fifteen RCTs followed the soft-tissue/wound healing over the extraction socket of impacted mandibular third molars, exploring the benefits of L-PRF over unassisted healing.[51, 56-58, 65, 68, 73, 75, 78, 81, 82, 92-95] The studies showed some heterogeneity (e.g., parameter used, moment of evaluation). Overall, 12 studies reported data on day 7, with 9 showing a statistically significant faster healing when L-PRF had been applied in the socket. Five papers evaluated the healing after 14 days, and 4 of them indicated a statistically significant improvement with the use of L-PRF.

Bone healing extraction socket

Fifteen papers compared bone healing in terms of density, gray value, radiopacity, and/or bone healing score between sites with unassisted healing and sites where L-PRF has been inserted into the extraction socket of impacted mandibular third molars,[54, 56, 59, 62, 65, 67, 69, 71, 73, 74, 80-83, 87, 93] with only one study with a relatively short follow-up for these parameters.[87] Again, a large variety of parameters (e.g., gray value, scintigram, Hounsfield units) and/or type of radiographs (periapical, orthopantomogram, CBCT) have been used. Ten studies had a split-mouth design, and five a parallel concept. Overall, 7 of the 10 split-mouth studies and 2 of the 5 parallel studies reported a higher bone density at one or more follow-up visits (between 1 and 6 months) when L-PRF had been applied.

The amount of bone formed within the extraction socket of extracted impacted mandibular third molars was assessed in seven papers.[59, 72, 74, 80, 82, 87, 92] Four out of the seven papers observed more bone formation in sockets treated with L-PRF compared to unassisted healing, and the other three showed no difference.[72, 87]

Periodontal parameters adjacent second premolar

Thirteen RCTs measured some periodontal parameters distal of the neighboring second molar after the extraction of the impacted mandibular third molar.[54, 59, 62, 63, 67, 71, 73, 81, 82, 86, 87, 90, 94] Eight papers could not identify significant differences between unassisted healing and the application of L-PRF when pocket probing depths and/or clinical attachment gain were considered, whereas five studies reported more favorable changes for L-PRF.

3.5 Risk of bias

The risk-of-bias assessment for each individual paper, per domain, is illustrated in Figure 2. An overall risk assessment considering all included papers (PRP, PRGF, and L-PRF together) with a proportional distribution (low, unclear, high risk) per domain is highlighted in Figure 3. Unfortunately, the majority (39/59, 66.1%) of studies showed a high risk, primarily because of concerns about blinding, with 14/59 (23.7%) having a moderate risk, and only 6/59 (10.2%) studies with a low risk of bias.



FIGURE 2

Risk of bias for each individual included paper.

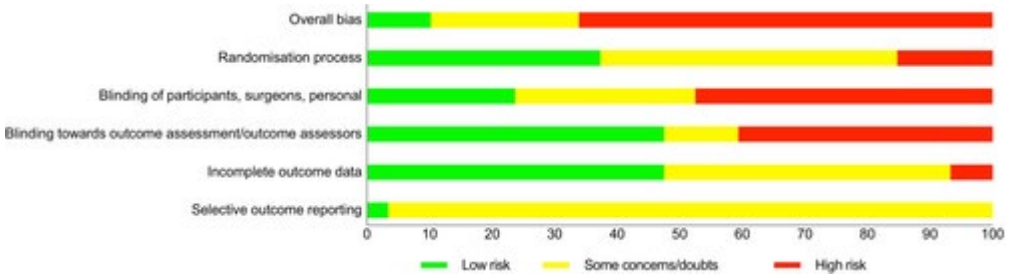


FIGURE 3

Risk of bias graph (review authors' judgments) about each risk of bias item presented as percentages across all included studies.

4 DISCUSSION

APCs including PRP, PRGF, and the L-PRF family (including A-PRF, A-PRF+, CGF, T-PRF, and H-PRF) have the potential to enhance/facilitate soft- and hard-tissue regeneration. Their plethora of capacities including a controlled release of growth factors (e.g., VEGF, PDGF, TGF, and insulin-like growth factor (IGF)) as well as matrix proteins (e.g., fibronectin, vitronectin), an enhanced angiogenesis, an antibacterial and analgesic activity, the promotion of stem cell differentiation toward osteoblasts, and anti-inflammatory activity are explained in four basic science review papers.[21-24] In vitro, APCs can suppress the secretion of pro-inflammatory cytokines (e.g., IL-1β, TNFα, and IL-6[96]), modulate the transition from M1 to M2 (anti-inflammatory phenotype) macrophage polarization,[97] and decrease the inflammatory response of gingival fibroblasts, dendritic cells,[98] and Schwann cells.[99] These are the potential mechanisms of APCs to facilitate wound healing, including soft- and hard-tissue regeneration. The stable fibrine network of the second-generation L-PRF family, housing a higher density of platelets and leukocytes, offers the additional advantage of a slow and continuous release of the above-mentioned important players in early wound healing, forms a fibrous structure conductive to cell attachment, supports the formation of a stable blood clot, and prevents its dissolution.

This systematic review retrieved 15 papers evaluating the effect of APCs on wound healing and postoperative sequelae after the extraction of impacted mandibular third molars. Significantly more papers were available regarding L-PRF compared to PRP and PRGF. None of these studies reported an adverse event after the use of an APC. Several studies included smokers during patient selection, but none of them made a direct comparison between smokers and nonsmokers. However, it seems that the application of APCs in fresh extraction wounds is also beneficial in smokers, especially for soft tissue healing.[25]

Different treatment strategies for the application of APCs were described in the literature. In the majority of the cases, only socket grafting with an APC was performed. Additional socket sealing with a fibrin membrane after grafting with PRP or PRGF or a socket sealing with L-PRF membrane after grafting with L-PRF was used less frequently. L-PRF was used either in clot or membrane/plug form.

4.1 APCs and postoperative swelling

The overall ratio of papers reporting a statistically significant reduction in postoperative swelling after the extraction of an impacted mandibular third molar, comparing the application of an APC in the socket to unassisted healing, is: 4 out of 6 for PRP, 1 out of 1 for PRGF, and 15 out of 27 for L-PRF, all together 59%. This might be partially explained by their direct and indirect impact on wound healing and tissue repair, as mentioned in the previous paragraph. C-reactive protein (CRP), an acute phase protein, appears in the blood because of inflammation. Its concentration is a sensitive marker to monitor the tissue healing process. Nowak and co-workers[76] followed the fluctuation of CRP after the extraction of impacted mandibular third molars. Sockets filled with L-PRF showed significantly lower increase in CRP when compared to sockets with unassisted healing (0.17 vs. 1.79 mg/L), indicative of a better regenerative process; the latter was confirmed in their study by reduced swelling and lower pain intensity.

4.2 APCs and postextraction pain

The overall percentage of studies reporting a statistically significant reduction in pain intensity during the first week after the application of an APC in the extraction socket of an extracted mandibular third molar, compared to unassisted healing was: 5 out of 6 for PRP, 2 out of 3 for PRGF, and 23 out of 32 for L-PRF, all together 73%. Papers on PRP attribute their effect primarily to the ability of this concentrate to reduce the rate of prostaglandins, the primary mediator responsible for pain perception.[100, 101] The analgesic capacity of L-PRF is partially attributed to released growth factors and cytokines, but also to its stable fibrous network containing leukocytes, matrix proteins, and anti-inflammatory mediators released for a longer time, working throughout the inflammatory repair phase,[57, 69] as well as the slow dissolution of the L-PRF, preventing debris impaction, and protecting and stabilizing the underlying blood clot.[68, 102]

4.3 APCs and postoperative trismus

The overall percentage of studies supporting a statistically significant reduction in trismus after the application of an APC in the extraction socket of an extracted mandibular third molar compared to unassisted healing was: 2 out of 3 for PRP, and 7 out of 13 for L-PRF, all together 56%. PRP seems to be more successful than the L-PRF family. This might be explained by their higher release of cytokines and growth factors on the first day, compared to the slow and continuous release by second-generation concentrates.[103]

4.4 APCs and alveolitis

Alveolar osteitis, also termed dry socket or fibrinolytic osteitis, occurs in 2.3%–4.2% of patients after tooth extraction, especially when performed without post-op antibiotic intake.[104, 105] The incidence after third molar extraction is within the range of 1%–13%.[106] In some rare cases, these infections can affect the deep anatomical spaces, and affected patients may require hospitalization and surgical treatment.[107] Clinically, alveolar osteitis presents with pain and halitosis and happens (within the first 2 days) due to disruption of the blood clot because of fibrinolytic

activity.[108] Local factors like increased bone density, decreased blood flow, and decreased granulation tissue formation are thought to contribute to an elevated risk of alveolar osteitis at the mandibular third molar extraction site.[109, 110]

Eighteen studies applying L-PRF in the extraction socket of impacted mandibular third molars examined the incidence of alveolar osteitis and reported, in comparison to unassisted healing, an overall reduction from 13.1% to 3.7%, with 16 out of the 18 confirming this difference, one study with a similar incidence, and one study reporting no event (neither in the test nor in the control group).

Yüce and Kömerik[93] explored whether the application of A-PRF+ could improve the healing of alveolar osteitis following mandibular third molar extraction. They concluded that A-PRF+, compared to saline rinsing, reduced pain faster, and accelerated the soft tissue healing.

4.5 Postoperative bleeding

Two papers observed a statistically significant lower incidence of postextraction bleeding after L-PRF application.[75, 85] The L-PRF matrix indeed stabilizes the clotting, promotes platelet adhesion, and provides a physical barrier to prevent further bleeding. This hemostatic effect of L-PRF was even more obvious after extracting teeth in patients under anti-coagulant medication.[111-113]

4.6 APCs and soft healing

Several studies observed faster soft-tissue healing after the application of a PRP gel or L-PRF matrices in the extraction socket of mandibular third molars. This benefit was also reported during the alveolar ridge preservation procedure for nonthird molar extractions.[25] The soft-tissue healing capacity of APC is even more impressive when the wound closure of nonresponding extra-oral chronic wounds is analyzed.[32, 33]

4.7 Split-mouth versus parallel groups

For the analyses of the postoperative sequelae, we reported the data for split-mouth and parallel studies separately because of our impression that the study design could have an impact on the potential to observe differences. For postoperative pain intensity, the difference was negligible: 14/19 (74%) of the split-mouth studies reported lower pain levels after the use of L-PRF versus 9/13 (69%) for studies with parallel groups. For postoperative edema, the difference was larger, with 11/16 (69%) papers with split-mouth designs reporting less postoperative swelling after the use of L-PRF versus 4/11 (36%) for parallel studies. The corresponding data for trismus, which is even more susceptible to bias when estimated in a split-mouth trial, were 3/4 (75%) versus 4/9 (44% in parallel studies) reporting a lower incidence for L-PRF.

4.8 Growth factor and cytokine release at extraction sites

Several papers examined whether the application of an APC in an extraction socket really influences the concentration of growth factors and/or cytokines at the wound site, when compared to sites with unassisted healing. Mozzati and co-workers[49] observed, after the application of PRGF gel in

the sockets of extracted impacted mandibular third molars, an increase of the two tested proinflammatory cytokines (IL-1β and IL-6) accompanied by an increase of two anti-inflammatory cytokines (IL-10 and TGF-β). Da Silva and co-workers[114] compared the local concentration of growth factors and cytokines in the socket of extracted mandibular third molars after the application of L-PRF or unassisted healing. They reported that all growth factors (VEGF, FGF-2, PDGF-BB, TGF-β1) and the majority of the inflammatory cytokines (IL-1β, IL-4, TNF-α, IL-1RA, IL-10, and IFN-γ) were present at significantly higher levels in the L-PRF sites on day 1. However, by the end of 1 week, most of the differences had disappeared, except for VEGF, which attained a 2-fold increase, and the anti-inflammatory cytokines IL–10 and IL–1RA which were around 1.5 times increased at the L-PRF sites. Wang and co-workers[115] compared over time (6 h to 7 days) the local release profile of growth factors in wound fluid after the extraction of primarily upper premolars between sockets filled with either L-PRF or a blood clot. The L-PRF sites showed statistically higher concentrations of PDGF-AA, TGF-β1, and VEGF (up to day 7), PDGF-AB/BB and EGF (up to day 3), and FGF-2 (first 6 h), but not for ANG-2. In other words, all three papers concluded that the application of an APC in an extraction socket significantly influenced the release of growth factors and cytokines in the wound fluid.

4.9 Limitations

The large heterogeneity of studies included in this review (see above) made it impossible to perform a meta-analysis and hindered the proposal of airtight statements (superiority of one of the APC) and strong recommendations (optimal treatment strategy). Moreover, numerous factors affecting the reported outcomes, including prior toothache experience, medications use before and after surgery, general oral hygiene, surgeon experience, surgical duration, surgical complexity, etc., further complicate the interpretation of the results. Therefore, additional clinical studies with higher standardization, improved methodological quality, and a larger scale might help to better understand the actual effect of APC on pain perception, edema, and trismus.

The overall risk of bias was high, especially in the domains of blinding, both of participants/surgeons/personnel, as well as of the outcome assessors. The judgment might have been very strict, but when blinding was not reported “in detail” (e.g., was the socket management allocated after the extraction of “both” third molars in case of split-mouth studies; was blood collected from patients who did not receive an APC, could the assessor see whether a blood draw happened (e.g., wound plaster, local hematoma)), it was considered as high risk.

4.10 Agreement and disagreement with other recent systematic reviews

Zhu and co-workers[116] reported that L-PRF and its derivatives reduced postoperative pain and the incidence of alveolar osteitis after third molar surgery, and improved soft tissue healing.

Firoozi and co-workers[20] explored in their systematic review the impact of nonpharmacological complementary interventions on the management of pain after third molar surgery. They concluded that platelet-rich fibrin and its derivatives as well as ozone therapy outperform the other

nonpharmacological complementary interventions in reducing early and late postsurgical pain following third molar extraction, even though the results should be interpreted with caution due to an unclear risk of bias and lack of firm evidence in the included meta-analyses.

Ramos and co-workers[117] reported an improved control of postoperative complications (pain, consumption of analgesics, edema, not trismus) after the application of L- and/or A-PRF, as well as superior periodontal parameters distally of the neighboring second molar. Costa and co-workers[118] concluded that, based on low certainty of evidence, platelet concentrates were more efficient, compared to blood clots, in reducing pain and trismus after mandibular third molar surgeries.

4.11 Recommendations and future directions

The high risk of potential bias observed in the selected papers is a major concern hindering the creation of firm statements. New trials should give attention to the randomization protocol and especially to the blinding (surgeon, assessor, and patient).

The study design also seems to have some impact on the final outcome. In split-mouth trials, it may be difficult for the patient to evaluate each surgical site independently, as pain may irradiate to the opposite side. In such studies, it is highly recommended to wait for a minimum of 1 week before the second extraction. Moreover, a standardization of the pre- and/or postoperative medications (antibiotics, analgesics, inflammation inhibitors) is highly recommended. Also, the age of the enrolled patient should be taken into consideration since patients of ≥25 years have another healing and a different perception of pain intensity and reduction, compared to youngsters.[119]

Finally, to enhance the reproducibility and understanding of the applied APC, the authors should present more details on the APC preparation. Since the centrifugal force is partially influenced by the radius of the centrifuge, and not only the rotations per minute, it would be useful also to report the g-force.[120, 121] Since also the inner surface of the blood tubes has an impact on the formation of the APC matrix, a detailed description of the tubes is mandatory.

5 CONCLUSION

Within the limitations of this review, it can be concluded that APCs, especially the matrices within the L-PRF family, offer a beneficial effect in reducing postoperative pain, swelling, and trismus, as well as a lower incidence of alveolar osteitis. APCs seem to also have a positive effect on soft- and hard-tissue healing compared to unassisted healing.

CONFLICT OF INTEREST STATEMENT

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