Efficacy of Platelet-Rich Fibrin After Mandibular Third Molar Extraction: A Systematic Review and Meta-Analysis

Faez Saleh Al-Hamed, BDS, MSc, [*] *Mohamed Abdel-Monem Tawfik, BDS, MSc, PhD,* [†] *Ehab Abdelfadil, BDS, MSc, PhD,* [‡] *and Mohammed A. Q. Al-Saleh, BDS, MSc, PhD* [§]

Purpose: To assess the effect of platelet-rich fibrin (PRF) on the healing process of the alveolar socket after surgical extraction of the mandibular third molars.

Materials and Methods: PubMed, the Cochrane Central Register of Controlled Trials, Scopus, and relevant journals were searched using a combination of specific keywords ("platelet-rich fibrin," "oral surgery," and "third molar"). The final search was conducted on November 2, 2015. Randomized controlled clinical trials, as well as controlled clinical trials, aimed at comparing the effect of PRF versus natural healing after extraction of mandibular third molars were included.

Results: Five randomized controlled trials and one controlled clinical trial were included. There were 335 extractions (168 with PRF and 167 controls) in 183 participants. Considerable heterogeneity in study characteristics, outcome variables, and estimated scales was observed. Positive results were generally recorded for pain, trismus, swelling, periodontal pocket depth, soft tissue healing, and incidence of localized osteitis, but not in all studies. However, no meta-analysis could be conducted for such variables because of the different measurement scales used. The qualitative and meta-analysis results showed no significant improvement in bone healing with PRF-treated sockets compared with the naturally healing sockets.

Conclusions: Within the limitations of the available evidence, PRF seems to have no beneficial role in bone healing after extraction of the mandibular third molars. Future standardized randomized controlled clinical trials are required to estimate the effect of PRF on socket regeneration.

J Oral Maxillofac Surg 75:1124-1135, 2017

Extraction of mandibular third molars is the most common procedure performed by oral-maxillofacial surgeons.[1] The surgical procedure may be associated with considerable postoperative side effects and complications, which include pain, trismus, edema, infection, and dry sockets.[2-6]

Platelet-rich plasma (PRP) was found to reduce pain, swelling, and alveolar osteitis (AO), as well as improve soft and hard tissue healing, after mandibular third molar extractions.[7-9] However, placing PRP is a time-consuming technique, and it has poor mechanical properties that have discouraged many surgeons from routinely using it after extractions.[10]

Platelet-rich fibrin (PRF) is a second generation of the platelet concentrate. It is prepared with a simplified, inexpensive process and without biochemical blood handling.[11] It is an autologous soluble biologic material that does not introduce foreign material into

[*]Master Student at Oral and Maxillofacial Surgery, Faculty of Dentistry, Mansoura University, Mansoura, Egypt.

[†]Professor and Chairman of Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Mansoura University, Mansoura, Egypt.

[‡]Assistant Professor of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mansoura University, Mansoura, Egypt.

[§]Fellow at Orthodontics Department, Orthodontic Graduate Program, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada.

Conflict of Interest Disclosures: None of the authors have any relevant financial relationship(s) with a commercial interest.

Address correspondence and reprint requests to Dr Al-Hamed: Faculty of Dentistry, Mansoura University, Mansoura, Egypt; e-mail: f-alhamed@windowslive.com

Received January 21 2016

Accepted January 20 2017

0278-2391/17/30107-6

http://dx.doi.org/10.1016/j.joms.2017.01.022

the surgical site and prevents consequent foreign-body inflammatory responses.[12,13]

Similar to natural healing, slow polymerization during PRF preparation generates a fibrin network that enhances cell migration and proliferation. Being a reservoir of platelets, leukocytes, cytokines, and immune cells, PRF was reported to allow slow release of cytokines—transforming growth factor, platelet-derived growth factor, vascular endothelial growth factor, and epidermal growth factor—which play a critical role in angiogenesis, tissue healing, and cicatrization.[11,13-15]

Moreover, PRF has multiple applications in implant and dentoalveolar surgery. PRF may be used alone or combined with bone grafts as a socket preservation material and for treatment of periodontal bony defects.[16-21] PRF is used to enhance tissue healing and to minimize postoperative inflammatory complications after mandibular third molar extractions.[12,22-28]

To date, there is no evidence that summarizes the effect of PRF application on bone healing after mandibular third molar extractions. This study was conducted to systematically review and critically analyze the available evidence on the effect of PRF on tissue healing and potential complications after mandibular third molar extractions.

Materials and Methods

SEARCH STRATEGY

An electronic search was conducted in the following databases (from August 20 to November 2, 2015): PubMed, the Cochrane Central Register of Controlled Trials, and Scopus. The online databases of *Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery,* and *Journal of Cranio-Maxillo-Facial Surgery* were searched manually. "Platelet-rich fibrin," "oral surgery," and "third molar" were the keywords used for the electronic search. The reference lists of similar reviews were manually checked for studies that met the inclusion criteria.

The inclusion criteria included all English-language randomized clinical trials (RCTs) and controlled clinical trials that compared the effect of PRF application on fresh extraction sockets of mandibular third molars versus natural socket healing. Non–English-language studies, retrospective studies, case series, case reports, animal studies, and review studies were excluded. Studies that evaluated the role of PRF in extraction sockets of teeth other than the mandibular third molars, as well as studies that compared PRF as a socket filling with other biologic material, also were excluded.

DATA COLLECTION

The following data were collected for each study (when available): authors, publication year, country of origin, study design, mean age, age range, male-female ratio, medical status, participants, surgical sessions, closure technique, tooth angulation, bone removal, bone removal device, operation time, cointerventions, follow-up period, blood collection protocol, and outcome variables (Tables 1,2). Two researchers (E.A. and F.A.) independently reviewed the included articles and collected the data. Disagreements between the reviewers were resolved by consensus.

QUALITY ASSESSMENT

The quality assessment of the included studies was performed following the guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocols.[32,33] The Cochrane Collaboration's tool for assessing risk of bias in RCTs was used to assess the quality of the included articles.[34]

META-ANALYSIS

The meta-analysis standard scale was used to evaluate one common outcome (bone healing with bone scintigraphy) in 2 studies only.[30,31]

ASSESSMENT OF HETEROGENEITY

Heterogeneity among studies was estimated by the Cochrane test for heterogeneity and the I^2 statistic. The χ^2 test was used to determine the presence of statistical heterogeneity. Heterogeneity was considered statistically significant at $P < .10$. The interpretation of the I^2 statistic depended on the Cochrane Collaboration recommendations.[35]

Results

STUDY SELECTION

The electronic and manual searches identified 242 articles, of which 60 were duplicates and were excluded. The abstracts of the remaining 182 articles were screened, and the full text of the related studies was read by both researchers for potential inclusion. Of 13 full-text studies reviewed for potential inclusion, only 6 met the inclusion criteria and were assessed for reliability.[22,26,27,29-31] The other 7 articles were excluded for the following reasons: One study was a retrospective study[23]; one study compared PRP with PRF[12]; in one study, the prepared material was PRP gel, although the title mentioned it was PRF[24]; data analysis was not reported in one study[36]; and in three studies, multiple extractions were performed other

Table 1. CHARACTERISTICS AND PATIENT DEMOGRAPHIC DATA OF INCLUDED STUDIES

Authors, Year	Country	Design	Mean Age (Range), yr	M/F Ratio	Participants' Medical Status	Participants, n	Cases, n		Flap Design	Difficulty Level Between Groups
							PRF	Control		
Uyanık et al,[22]* 2015	Cyprus	RCT (sm)	22.5 (19-31)	10:10	Healthy	20	20	20	Triangular†	Similar
Kumar et al,[29] 2015	India	RCT (pa)	26.1 (19-35)	NR	Healthy	31	16	15	Triangular‡	NR
Baslarli et al,[30] 2015	Turkey	RCT (sm)	23.9 (19-34)	7:13	Healthy	20	20	20	Triangular	NR
Eshghpour et al,[26] 2014	Iran	RCT (sm)	25.1 (18-35)	33:45	ASA I or II	78	78	78	Envelope	Similar
Singh et al,[27] 2012	India	CCT (sm)	32 (18-50)	10:10	Healthy	20	20	20	NR	NR
Gürbüzer et al,[31] 2010	Turkey	RCT (sm)	24.9 (NR)	7:7	Healthy	14	14	14	Envelope	Similar

Abbreviations: ASA, American Society of Anesthesiologists class; CCT, controlled clinical trial; F, female; M, male; NR, not reported; pa, parallel design; PRF, platelet-rich fibrin; RCT, randomized clinical trial; sm, split-mouth design.

* This was a 4-arm study consisting of 4 groups: In groups 1 and 4, traditional surgery without PRF application was performed; in group 2, traditional surgery with PRF; and in group 3, piezosurgery with PRF.

† Archer flap.

‡ Modified Ward incision.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

than third molar extractions.[21,37,38] The included studies were quantitatively and qualitatively analyzed. Figure 1 presents the selection and review process of the studies.

CHARACTERISTICS OF INCLUDED STUDIES

Five articles were RCTs,[22,26,29-31] whereas one study was a controlled clinical trial.[27] Five articles used a split-mouth design,[22,26,27,30,31] and one used a

Table 2. ADDITIONAL CHARACTERISTICS OF INCLUDED STUDIES

Authors, Year	Surgical Sessions	Primary Closure	Tooth Angulation	Bone Removal	Bone Removal Device	Operation Time Between Groups	Cointerventions	Follow-Up, wk
Uyanık et al,[22] 2015	2	NR	Vertical	Yes	High-speed handpiece or piezosurgery device*	Nonsig	ATB-NSAID	1
Kumar et al,[29] 2015	2	Yes	Mesioangular or horizontal	Yes	Rotary	NR	ATB-NSAID	12
Baslarli et al,[30] 2015	1	Yes	Vertical or mesioangular	No	Not required	NR	ATB-NSAID	12
Eshghpour et al,[26] 2014	1	NR	Mixed†	Yes	Low-speed handpiece	NR	ATB-NSAID	1
Singh et al,[27‡] 2012	1	Yes	NR	NR	NR	NR	NR	12
Gürbüzer et al,[31] 2010	1	Yes	Vertical	No	Not required	Nonsig	ATB-NSAID	4

Abbreviations: ATB, antibiotics; Nonsig, not statistically significant; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs.

* A high-speed handpiece was used in groups 1, 2, and 4, whereas a piezosurgery device was used in group 3.

† *Mixed* refers to different angulations of impaction.

‡ We contacted the article's authors to provide us with the missing data, but they did not respond.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

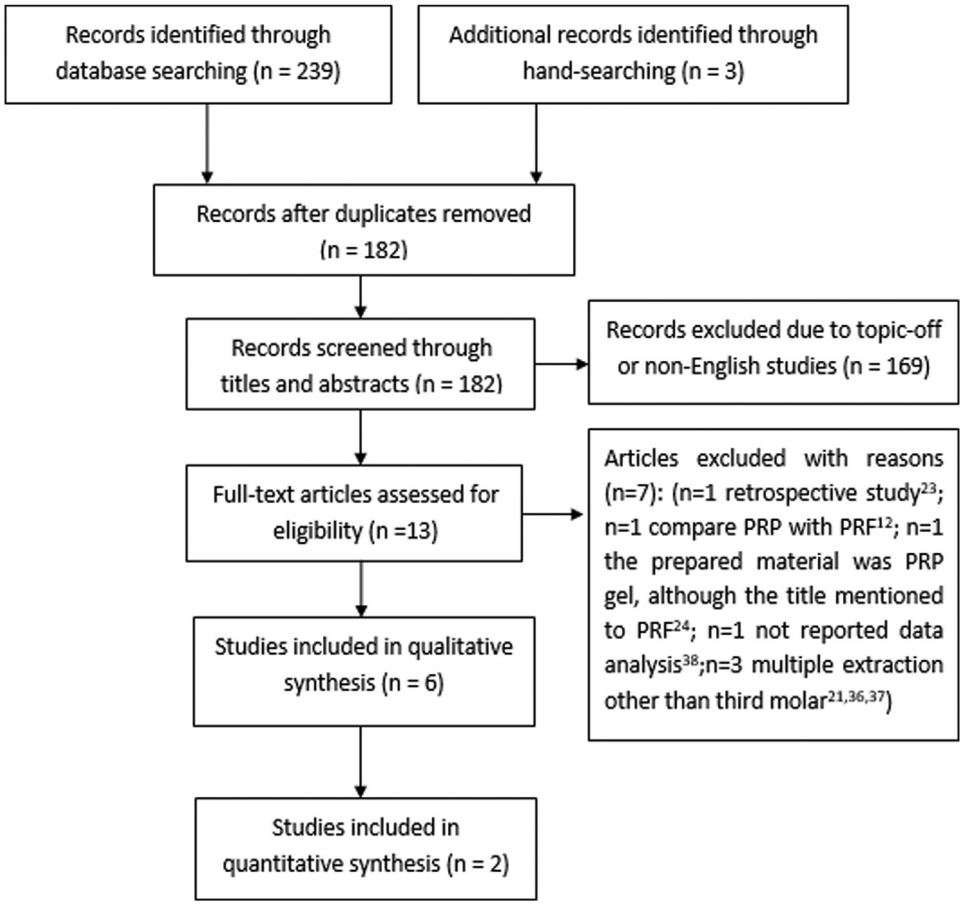

FIGURE 1. Flowchart of selection process. PRF, platelet-rich fibrin; PRP, platelet-rich plasma.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

parallel design.[29] The 6 included articles had a total of 183 participants with ages ranging from 19 to 50 years and 2 extraction patterns: *1)* PRF (168 cases) and *2)* naturally healing extraction (167 cases). Three articles used a triangle flap design,[22,29,30] and two articles used an envelope flap design.[26,31] Primary closure was used in 4 articles.[27,29-31] Antibiotics and analgesics were prescribed in 5 articles.[22,26,29-31] Bone removal was required in 3 studies.[22,26,29] The follow-up period ranged from 1 to 12 weeks (Tables 1,2).

QUALITY ASSESSMENT OF INCLUDED STUDIES

The Cochrane Collaboration's tool for assessing risk of bias in RCTs showed that 5 articles had a low risk of bias.[22,26,29-31] Only 1 study had a high risk of bias because of the non-randomization design, poor description of the surgical procedure, and inadequate reporting of the results.[27] No protocol in any of the studies was found to evaluate other potential biases. When additional information was required, the authors were contacted and the responses received were considered in the quality assessment (Figs 2, 3).

PAIN AND ANALGESIC CONSUMPTION

Only 3 trials evaluated postoperative pain.[22,27,29] However, different methods of pain measurement were used at different time intervals. Two studies showed statistically significant reductions in pain in the PRF group compared with the control group for the first postoperative day (P = .017),[29] and the sum of pain scores for the first, second, third, and seventh postoperative days.[22] One study showed no significant difference for pain encountered on the first, third, and seventh postoperative days.[27] Analgesic consumption was only evaluated in one study, and a significant difference was only reported for group 3 (PRF and piezosurgery, P = .015) over the other groups[22] (Table 3).

SWELLING

Two articles evaluated postoperative swelling.[22,29] They used different scales of measurement; a scale described by Pasqualini et al[39] was used in one article,[29] whereas a scale described by Gabka and Matsumura[40] was used in the other study.[22] One article evaluated swelling on the first

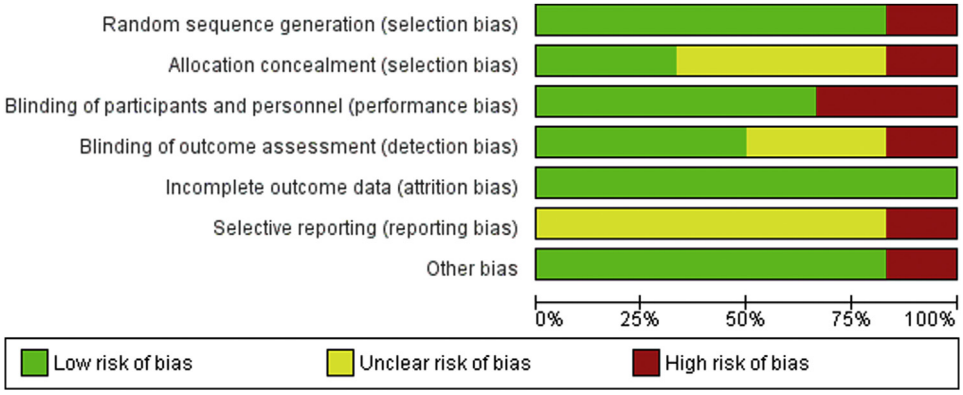

FIGURE 2. Risk-of-bias graph.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

postoperative day, whereas the other study evaluated swelling on the first, second, third, and seventh postoperative days. One article reported a significant reduction in postoperative swelling on the first postoperative day (P = .022),[29] whereas the other study showed a significant difference, favoring the use of PRF, only on the second postoperative day (P = .006)[22] (Table 4).

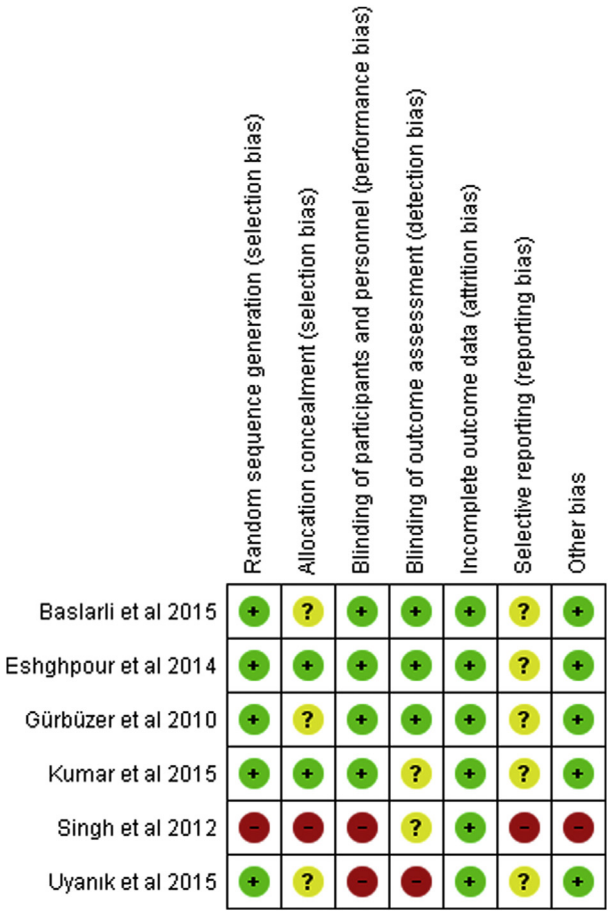

FIGURE 3. Risk-of-bias summary.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

TRISMUS

Two articles evaluated postoperative mouth opening.[22,29] One article used a divider and scale,[29] and the other article[22] depended on a scale described by Ustün et al.[41] The articles[22,29] showed a significant improvement in mouth opening on the first postoperative day favoring PRF application (P = .011 and .022 respectively). However, one article showed insignificant differences in mouth opening on the second, third, and seventh postoperative days[22] (Table 5, Fig 4).

ALVEOLAR OSTEITIS

Only 1 study evaluated the incidence of AO encountered during the first postoperative week.[26] A significant difference was reported favoring the use of PRF as a preventive measure for AO (p <.05) (Table 6, Fig 5).

PERIODONTAL POCKET DEPTH

Two studies evaluated periodontal pocket depth distal to the second molar.[29,30] They used different scales of measurement and reported inconsistent results. One study showed a significant reduction in pocket depth, comparing preoperative versus 1st month, preoperative versus 3rd month and 1st versus 3rd month in PRF group (P <.001) where as a significant reduction was observed only comparing the preoperative versus 3rd month in the control group (P = .011),[29] whereas the other study reported a nonsignificant difference[30] (Table 7).

BONE HEALING

Four articles evaluated bone healing using different scales at different time intervals.[27,29-31] None of them reported a significant difference between the PRF

Table 3. PAIN AND ANALGESIC CONSUMPTION WITHIN INCLUDED STUDIES

Authors, Year	Outcome	Measurement Method	Postsurgical Times of Measurement	Effect of PRF	*P* Value
Kumar et al,[29] 2015	Pain	VAS according to Pasqualini et al[39]	First day	Sig	.017
Uyanık et al,[22]* 2015		VAS (0-10) in conjunction with graphic rating scale	Sum of pain scores across first, second, third, and seventh postoperative days	Sig (G2 vs G1)	.001
				Sig (G3 vs G4)	.017
				Sig (G3 vs G1)	.0001
Singh et al,[27] 2012		VAS (0-10)	First day	Nonsig	
			Third day	Nonsig	
			Seventh day	Nonsig	†
Uyanık et al,[22] 2015	Analgesic consumption	No. of analgesic tablets	Sum of analgesics across 7 days	Sig (G3 vs G1)	.015
				Sig (G3 vs G4)	.033
				Nonsig (other groups)	>.05

Abbreviations: G1, group 1; G2, group 2; G3, group 3; G4, group 4; Nonsig, not statistically significant; PRF, platelet-rich fibrin; Sig, statistically significant; VAS, visual analog scale.

* This was a 4-arm study consisting of 4 groups: In G1 and G4, traditional surgery without PRF application was performed; in G2, traditional surgery with PRF; and in G3, piezosurgery with PRF.

† The authors presented their results in graphs. They stated that there was no significant difference between the PRF and control groups regarding pain scores; however, the *P* value was significant. We contacted the article's authors to provide us with the study tables, but they did not respond.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

and control groups. Two articles used bone scintigraphy to evaluate early bone healing after the first and third postoperative months, respectively.[30,31] A meta-analysis was conducted using the data of these 2 studies[30,31] and showed no benefit of the application of PRF in bone regeneration 1 month postoperatively ($P = .98$; mean difference, −0.01%; 95% confidence interval, −0.50% to 0.49%) (Table 8, Fig 6).

SOFT TISSUE HEALING

One study evaluated soft tissue healing during the first, third, and seventh postoperative days[27] following the scale of Landry et al.[42] It showed considerable better healing in the PRF group on the third and seventh postoperative days (Table 8).

METHODS OF PRF PREPARATION

The included studies used different blood volumes for PRF preparation. However, the protocol for PRF preparation was the same in all of the included studies,[22,26,27,29,30] with the exception of one study[31] (Table 9).

Discussion

Platelet concentrates have been used extensively in oral and maxillofacial surgery.[28,43,44] The use of PRF in

Table 4. SWELLING WITHIN INCLUDED STUDIES

Authors, Year	Outcome	Measurement Method	Postsurgical Times of Measurement	Effect of PRF	*P* Value
Kumar et al,[29] 2015	Swelling	According to Pasqualini et al[39]	First day	Sig	.022
Uyanık et al,[22]* 2015		Using modification of tape measure method described by Gabka and Matsumura[40]	First, third, and seventh days	Nonsig	>.05
			Second postoperative day	Sig (G2 vs G4)	.006

Abbreviations: G2, group 2; G4, group 4; Nonsig, not statistically significant; PRF, platelet-rich fibrin; Sig, statistically significant.

* This was a 4-arm study consisting of 4 groups: In groups 1 and G4, traditional surgery without PRF application was performed; in group 2, traditional surgery with PRF; and in group 3, piezosurgery with PRF.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

Table 5. TRISMUS WITHIN INCLUDED STUDIES

Authors, Year	Outcome	Measurement Method	Postsurgical Times of Measurement	Effect Size (CI)	Effect of PRF	*P* Value
Kumar et al,[29] 2015	Trismus	Using divider and scale	First day	1.93 (0.13-3.73)	Sig	.022
Uyanık et al,[22] 2015		Measuring distance between mesial incisal corner of upper and lower right incisor as described Ustün et al[41]	First day	−16.58 (−29.48 to −3.68)	Sig (G2 vs G1)	.011
				−17.13 (−31.46 to −2.80)	Sig (G2 vs G4)	.019
				−16.31 (−28.85 to −3.77)	Sig (G3 vs G1)	.019
				−16.86 (−30.86 to −2.86)	Sig (G3 vs G4)	.043
			Second, third, and seventh days		Nonsig	> .05

Abbreviations: CI, confidence interval; G1, group 1; G2, group 2; G3, group 3; G4, group 4; Nonsig, not statistically significant; PRF, platelet-rich fibrin; Sig, statistically significant.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

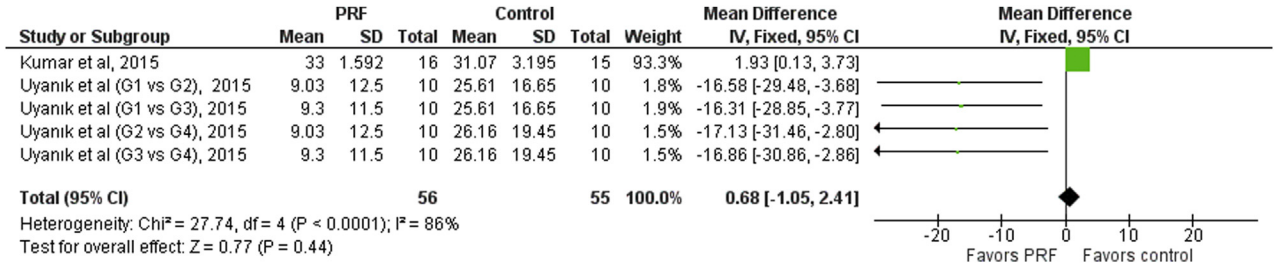

FIGURE 4. Forest plots for trismus on first postoperative day in platelet-rich fibrin (PRF) and control groups. CI, confidence interval; G1, group 1; G2, group 2; G3, group 3; G4, group 4; IV, inverse variance.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

Table 6. ALVEOLAR OSTEITIS WITHIN INCLUDED STUDIES

Authors, Year	Outcome	Measurement Method	Postsurgical Times of Measurement	Effect Size (CI)	Effect of PRF	*P* Value
Eshghpour et al,[26] 2014	Alveolar osteitis	Progressive and severe pain during first postoperative week, foul taste, halitosis, regional lymphadenitis, or loss of clot in extraction socket	Second and seventh postoperative days	0.38 (0.15-0.99)	Sig	<.05

Abbreviations: CI, confidence interval; PRF, platelet-rich fibrin; Sig, statistically significant.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

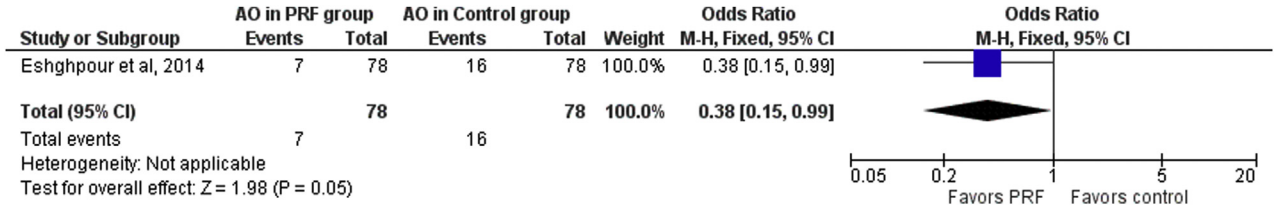

FIGURE 5. Forest plots for alveolar osteitis (AO) in platelet-rich fibrin (PRF) and control groups. CI, confidence interval; M-H, Mantel-Haenszel.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

the extraction sockets of mandibular third molars was introduced in an attempt to enhance the healing process and to reduce the potential postoperative complications.[22,23,25,26,30] This systematic review relied on prospective comparative studies that evaluated the efficacy of PRF in alveolar socket healing after mandibular third molar extractions.

Our review showed contradictory results concerning the effect of PRF on pain, swelling, trismus, and pocket depth after mandibular third molar extractions. This review highlighted the lack of effect of PRF on bone healing. Only 1 study reported the positive role of PRF in soft tissue healing.[27] However, the study was judged to have a high risk of bias.

Table 7. PERIODONTAL POCKET DEPTH WITHIN INCLUDED STUDIES

Authors, Year	Outcome	Measurement Method	Postsurgical Times of Measurement	Mean Difference, mm		Effect	*P* Value
				PRF	Control		
Kumar et al,[29] 2015	PD	Using UNC 15 periodontal probe taken along distal surface of second molar at 3 points (distobuccal, mid-distal, and distolingual)	Preoperative vs first month	1.063	0.844	Sig (PRF) Nonsig (control), *P* =.135	<.001
			Preoperative vs third month	2.542	1.311	Sig (PRF), *P* <.001 Sig (control), *P* = .011	.530
			First month vs third month	1.479	0.467 Sig (PRF), *P* <.001 Nonsig (control), *P* = .530		
			Preoperative PD, first and third month postoperatively		NR	Sig in both groups	
						PRF	<.001
						Control	.014
Baslarli et al,[30] 2015		Using Michigan periodontal probe, PD was measured in 6 points; mid, mesial, and distal parts of buccal and lingual aspect of second molar	First and third month		NR	Nonsig	NR

Abbreviations: Nonsig, not statistically significant; NR, not reported; PD, pocket depth; PRF, platelet-rich fibrin; Sig, statistically significant.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

Table 8. SOFT AND HARD TISSUE HEALING WITHIN INCLUDED STUDIES

				Results				
Authors, Year	Parameter	Measurement Method	Postsurgical Times of Measurement	Statistic	PRF	Control	Effect Size (CI)	Effect of PRF
Kumar et al,[29] 2015	Bone healing	Use of IOPARs and OPG images	Third month	Proportion*				Nonsig
				Mild to moderate increase	11 (68.8%)	14 (93.3%)	Not applicable	
				Severe increase	5 (31.3%)	14 (93.3%)		
Baslarli et al,[30] 2015		Bone scintigraphy	First month	Mean (SD)	4.71 (1.16)	4.6 (0.95)	0.11 (–0.55 to 0.77)	Nonsig
			Third month		4.1 (1.1)	3.96 (1.0)	0.14 (–0.51 to 0.79)	
Singh et al,[27] 2012		Measurement of bone density (gray line) on IOPA radiographs	First month	Proportion	8 (40%)	0 (0%)	Not applicable	NR
			Second month		18 (90%)	10 (50%)		Nonsig
			Third month		20 (100%)	20 (100%)		Nonsig
Gürbüzer et al,[31] 2010		Static phase scintigram: evaluation of early osteoblast activity as compared with activity of normal calvarial bone	First month	Mean (SD)	4.54 (1.03)	4.61 (1.02)	–0.16 (–0.92 to 0.60)	Nonsig
Singh et al,[27] 2012	Soft tissue healing	According to scale of Landry et al[42]	First day	Mean	3.4	2.9	Not applicable	NR
			Third day		4	3.2		Sig
			Seventh day		4.8	4.3		Sig

Abbreviations: CI, confidence interval; IOPAR, intra-oral periapical radiograph; IOPARs, intra-oral periapical radiographs; Nonsig, not statistically significant; NR, not reported; OPG, orthopantogram; PRF, platelet-rich fibrin; Sig, statistically significant difference favoring use of PRF.

* These proportions are presented for the overall density of newly formed bone.

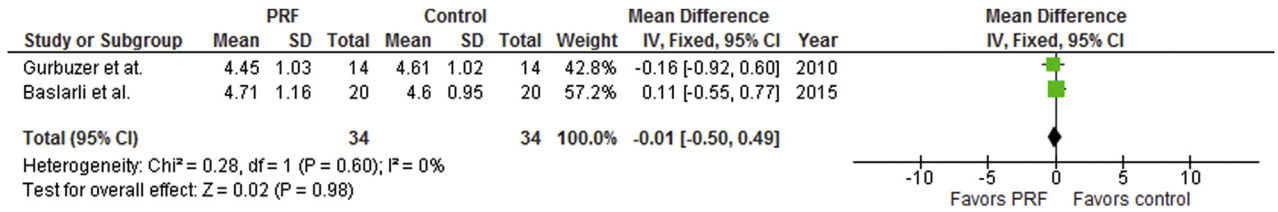

FIGURE 6. Forest plots for bone scintigraphy after 1 month in platelet-rich fibrin (PRF) and control groups. CI, confidence interval; IV, inverse variance.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

Despite the fact that most of the studies used different scales and time intervals to evaluate bone healing, none of them reported a clear benefit of the PRF application on bone regeneration compared with the control groups. This finding was confirmed by the qualitative synthesis and the meta-analysis of 2 studies.[30,31] However, the small sample sizes in these 2 studies are a limitation that requires accepting the conclusions with caution.

Although the healing of extraction sockets usually follows a specific scenario, the position of the tooth and the extraction technique affect the healing process. Bone removal appeared to be a confounding factor among the studies included in our review. Primary closure was obtained in most of the included studies, despite that it may be associated with more postoperative pain and swelling as reported in the literature.[45,46]

Only one study, which had the largest sample size and a low risk of bias, evaluated the incidence of AO after mandibular third molar extractions; it reported a significant reduction of AO favoring PRF.[26] This positive role was reported by Hoaglin and Lines[23] as well. This could be attributed to the positive effect of PRF on angiogenesis, immunity, and wound healing.[15] The slow polymerization during PRF preparation seems to generate a fibrin network that enhances cell migration and proliferation. As PRF is a reservoir of platelets, leukocytes, cytokines, and immune cells, it is reported to allow slow release of cytokines—transforming growth factor, platelet-derived growth factor, vascular endothelial growth factor, and epidermal growth factor—which play a critical role in angiogenesis, tissue healing, and cicatrization.[11,13,15] These properties could aid in the formation and stabilization of blood clots and hence decrease the incidence of AO.

A possible confounding factor is the quantity of PRF used. More PRF is obtained when a larger volume of blood is used for preparation, and hence an increased number of growth factors is consequently obtained. It is unclear to us whether the amount of blood volume could affect the healing process. However, most of the included studies reported the use of the same preparation protocol using 5 to 10 mL of venous blood, and hence the effect of PRF volume could not be evaluated.

The main limitations of the available evidence were the small sample sizes in the included studies, except for one study,[26] and the different study types, scales of measurement, and surgical protocols. In addition, this review did not include non–English-language studies, which may have contained useful information regarding the role of PRF after mandibular third molar surgery.

Table 9. METHODS FOR PRF PREPARATION IN INCLUDED STUDIES

Authors, Year	Centrifugation System (Manufacturer)	Volume of Blood Drawn, mL	Centrifugation Parameters: No.; Speed; Time
Uyanık et al,[22] 2015	Elektro-mag M415P (Istanbul, Turkey)	10	1; 3,000 rpm; 10 minutes
Kumar et al,[29] 2015	NR	5	1; 3,000 rpm; 10 minutes
Baslarli et al,[30] 2015	NR	9	1; 3,000 rpm; 10 minutes
Eshghpour et al,[26] 2014	Labofuge 400R centrifuge (Heraeus, Hanau, Germany)	10	1; 3,000 rpm; 10 minutes
Singh et al,[27] 2012	NR	5-10	1; 3,000 rpm; 10 minutes
Gürbüzer et al,[31] 2010	Bench-top centrifuge (universal 320; Hettich, Tuttlingen, Germany)	10	1; 2,030 rpm; 10 minutes

Abbreviation: NR, not reported.

Al-Hamed et al. Efficacy of Platelet-Rich Fibrin. J Oral Maxillofac Surg 2017.

In conclusion, the analysis of studies included in this systematic review showed controversial results regarding the effect of PRF on pain, swelling, trismus, and pocket depth after mandibular third molar removal. PRF has no positive effect on bone healing after the extraction of impacted mandibular third molars. However, because of heterogeneity and the small sample sizes of the included studies, further well-designed, split-mouth, prospective randomized controlled trials are recommended to further augment these results.

Acknowledgments

The authors thank Dr Abdel-Hady El-Gilany, Professor of Public Health, Faculty of Medicine, Mansoura University, Mansoura, Egypt, for his fruitful advice and help in quality assessment and the meta-analysis of this review.

References

1. Fuster Torres MA, Gargallo Albiol J, Berini Aytés L, Gay Escoda C: Evaluation of the indication for surgical extraction of third molars according to the oral surgeon and the primary care dentist. Experience in the Master of Oral Surgery and Implantology at Barcelona University Dental School. Med Oral Patol Oral Cir Bucal 13:E499, 2008
2. Bouloux GF, Steed MB, Perciaccante VJ: Complications of third molar surgery. Oral Maxillofac Surg Clin North Am 19:117, 2007
3. Sigron GR, Pourmand PP, Mache B, et al: The most common complications after wisdom-tooth removal: Part 1: A retrospective study of 1,199 cases in the mandible. Swiss Dent J 124:1042, 2014
4. Aravena P, Cartes-Velasquez R: Signs and symptoms of postoperative complications in third-molar surgery. Int J Oral Maxillofac Surg 40:1140, 2011
5. Susarla SM, Blaeser BF, Magalnick D: Third molar surgery and associated complications. Oral Maxillofac Surg Clin North Am 15:177, 2003
6. Kim J-C, Choi S-S, Wang S-J, Kim S-G: Minor complications after mandibular third molar surgery: Type, incidence, and possible prevention. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:e4, 2006
7. Antonello GdM, Torres do Couto R, Giongo CC, et al: Evaluation of the effects of the use of platelet-rich plasma (PRP) on alveolar bone repair following extraction of impacted third molars: Prospective study. J Craniomaxillofac Surg 41:e70, 2013
8. Ogundipe OK, Ugboko VI, Owotade FJ: Can autologous platelet-rich plasma gel enhance healing after surgical extraction of mandibular third molars? J Oral Maxillofac Surg 69:2305, 2011
9. Kaul RP, Godhi SS, Singh A: Autologous platelet rich plasma after third molar surgery: A comparative study. J Maxillofac Oral Surg 11:200, 2012
10. Del Corso M, Vervelle A, Simonpieri A, et al: Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part I: Periodontal and dentoalveolar surgery. Curr Pharm Biotechnol 13:1207, 2012
11. Dohan DM, Choukroun J, Diss A, et al: Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part II: Platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:e45, 2006
12. Yelamali T, Saikrishna D: Role of platelet rich fibrin and platelet rich plasma in wound healing of extracted third molar sockets: A comparative study. J Maxillofac Oral Surg 14:410, 2015
13. Dohan DM, Choukroun J, Diss A, et al: Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I: Technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:e37, 2006
14. Naik B, Karunakar P, Jayadev M, Marshal VR: Role of platelet rich fibrin in wound healing: A critical review. J Conserv Dent 16:284, 2013
15. Choukroun J, Diss A, Simonpieri A, et al: Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:e56, 2006
16. Montanari M, Callea M, Yavuz I, Maglione M: A new biological approach to guided bone and tissue regeneration. BMJ Case Rep 2013, 2013
17. Ranganathan AT, Chandran CR: Platelet-rich fibrin in the treatment of periodontal bone defects. J Contemp Dent Pract 15:372, 2014
18. Schwartz-Arad D, Levin L, Aba M: The use of platelet rich plasma (PRP) and platelet rich fibrin (PRP) extracts in dental implantology and oral surgery. Refuat Hapeh Vehashinayim (1993) 24:51, 2007 (in Hebrew)
19. Del Corso M, Mazor Z, Rutkowski JL, Dohan Ehrenfest DM: The use of leukocyte- and platelet-rich fibrin during immediate post-extractive implantation and loading for the esthetic replacement of a fractured maxillary central incisor. J Oral Implantol 38:181, 2012
20. Peck MT, Marnewick J, Stephen LXG, et al: The use of leukocyte- and platelet-rich fibrin (L-PRF) to facilitate implant placement in bone-deficient sites: A report of two cases. SADJ 67:54, 2012
21. Simon BI, Gupta P, Tajbakhsh S: Quantitative evaluation of extraction socket healing following the use of autologous platelet-rich fibrin matrix in humans. Int J Periodontics Restorative Dent 31:285, 2011
22. Uyanık LO, Bilginaylar K, Etikan İ: Effects of platelet-rich fibrin and piezosurgery on impacted mandibular third molar surgery outcomes. Head Face Med 11:25, 2015
23. Hoaglin DR, Lines GK: Prevention of localized osteitis in mandibular third-molar sites using platelet-rich fibrin. Int J Dent 2013:875380, 2013
24. Girish Rao S, Bhat P, Nagesh KS, et al: Bone regeneration in extraction sockets with autologous platelet rich fibrin gel. J Maxillofac Oral Surg 12:11, 2013
25. Kim JH, Lee DW, Ryu DM: Effect of platelet-rich fibrin on pain and swelling after surgical extraction of third molars. Tissue Eng Regen Med 8:80, 2011
26. Eshghpour M, Dastmalchi P, Nekooei AH, Nejat A: Effect of platelet-rich fibrin on frequency of alveolar osteitis following mandibular third molar surgery: A double-blinded randomized clinical trial. J Oral Maxillofac Surg 72:1463, 2014
27. Singh A, Kohli M, Gupta N: Platelet rich fibrin: A novel approach for osseous regeneration. J Maxillofac Oral Surg 11:430, 2012
28. Borie E, Oliví DG, Orsi IA, et al: Platelet-rich fibrin application in dentistry: A literature review. Int J Clin Exp Med 8:7922, 2015
29. Kumar N, Prasad K, Ramanujam L, et al: Evaluation of treatment outcome after impacted mandibular third molar surgery with the use of autologous platelet-rich fibrin: A randomized controlled clinical study. J Oral Maxillofac Surg 73:1042, 2015
30. Baslarli O, Tumer C, Ugur O, Vatankulu B: Evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. Med Oral Patol Oral Cir Bucal 20:e111, 2015
31. Gürbüzer B, Pikdöken L, Tunalı M, et al: Scintigraphic evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. J Oral Maxillofac Surg 68:980, 2010
32. Higgins JPT, Altman DG, Stern J: Assessing risk of bias in included studies, *in* Higgins JPT, Green S (eds): Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. London, Cochrane Collaboration, 2011
33. Moher D, Shamseer L, Clarke M, et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1, 2015
34. Higgins JP, Altman DG, Gotzsche PC, et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928, 2011
35. Deeks J, Higgins J, Altman D: Analysing data and undertaking meta-analyses, *in* Higgins J, Green S (eds): Cochrane Handbook for Systematic Reviews of Interventions. London, Cochrane Collaboration, 2009

36. Ruga E, Gallesio C, Boffano P: Platelet-rich fibrin and piezoelectric surgery: A safe technique for the prevention of periodontal complications in third molar surgery. J Craniofac Surg 22:1951, 2011
37. Hauser F, Gaydarov N, Badoud I, et al: Clinical and histological evaluation of postextraction platelet-rich fibrin socket filling: A prospective randomized controlled study. Implant Dent 22:295, 2013
38. Marenzi G, Riccitiello F, Tia M, et al: Influence of leukocyte- and platelet-rich fibrin (L-PRF) in the healing of simple postextraction sockets: A split-mouth study. Biomed Res Int 2015: 369273, 2015
39. Pasqualini D, Cocero N, Castella A, et al: Primary and secondary closure of the surgical wound after removal of impacted mandibular third molars: A comparative study. Int J Oral Maxillofac Surg 34:52, 2005
40. Gabka J, Matsumura T: Measuring techniques and clinical testing of an anti-inflammatory agent (tantum). Munch Med Wochenschr 113:198, 1971 (in German)
41. Ustün Y, Erdogan O, Esen E, Karsli ED: Comparison of the effects of 2 doses of methylprednisolone on pain, swelling, and trismus after third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96:535, 2003
42. Landry R, Turnbull R, Howley T: Effectiveness of benzydamine HCL in the treatment of peridontal post-surgical patients. Res Cin Forums 10:105, 1988
43. Del Corso M, Vervelle A, Simonpieri A, et al: Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part II: Periodontal and dentoalveolar surgery. Curr Pharm Biotechnol 13:1231, 2012
44. Simonpieri A, Del Corso M, Vervelle A, et al: Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: Bone graft, implant and reconstructive surgery. Curr Pharm Biotechnol 13:1231, 2012
45. Chaudhary M, Singh M, Singh S, et al: Primary and secondary closure technique following removal of impacted mandibular third molars: A comparative study. Natl J Maxillofac Surg 3:10, 2012
46. Danda AK, Krishna Tatiparthi M, Narayanan V, Siddareddi A: Influence of primary and secondary closure of surgical wound after impacted mandibular third molar removal on postoperative pain and swelling—A comparative and split mouth study. J Oral Maxillofac Surg 68:309, 2010