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Efficacy of platelet-rich fibrin on bone formation, part 1: Alveolar ridge preservation

KEY WORDS

advanced platelet-rich fibrin, alveolar ridge preservation, biomaterials, extraction site management, growth factors, leucocyte- and platelet-rich fibrin, platelet concentrates, platelet-rich fibrin, systematic review

ABSTRACT

Purpose: To investigate the use of platelet-rich fibrin for alveolar ridge preservation compared to natural healing, bone graft material and platelet-rich fibrin in combination with bone graft material.

Materials and methods: The present systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. The review examined randomised controlled trials comparing the clinical outcomes of platelet-rich fibrin with those of other modalities for alveolar ridge preservation. Studies of third molar extraction site healing were excluded. The studies were classified into three categories: natural wound healing vs platelet-rich fibrin; bone graft material vs platelet-rich fibrin; and bone graft material vs bone graft material and platelet-rich fibrin.

Results: From 179 articles identified, 16 randomised controlled trials were included. Owing to the heterogeneity of the investigated parameters, it was not possible to perform a meta-analysis. In total, 10 randomised controlled trials compared platelet-rich fibrin to natural wound healing, with seven of these demonstrating favourable outcomes to either limit postextraction dimensional changes or improve new bone formation in the platelet-rich fibrin group. Three of four studies comparing healing with bone graft material to platelet-rich fibrin found that the latter led to significantly greater horizontal or vertical bone resorption, and the bone graft material was more able to maintain the ridge dimensions. Two out of three randomised controlled trials investigating healing with both bone graft material and platelet-rich fibrin reported better outcomes using this combined approach than with bone graft material alone. All studies investigating soft tissue healing with platelet-rich fibrin demonstrated better outcomes in the platelet-rich fibrin group.

Conclusions: The majority of studies comparing healing with platelet-rich fibrin to natural healing concluded that the former more successfully limits postextraction dimensional changes than the latter. However, 75% of studies investigating platelet-rich fibrin vs bone graft material reported better results in the bone graft group with respect to its ability to maintain postextraction dimensional changes. The addition of platelet-rich fibrin to bone graft material may improve clinical outcomes, although data are limited.

Conflict-of-interest statement: *Richard J Miron holds intellectual property on platelet-rich fibrin. All other authors declare no conflicts of interest related to this study.*

Introduction

In the United States alone, over 36 million people are completely edentulous, and 120 million people are missing at least one tooth[1]. It is now widely understood that following tooth loss, marked alterations in the dimensions of the alveolar bone structure also occur[2,3]. Although numerous advances have been made and various research articles have examined how ridge dimensions can be preserved following tooth loss, as yet, no single therapy has been shown to preserve the ridge effectively or entirely post-extraction, with the majority of studies demonstrating a 2.0- to 2.5-mm reduction in a horizontal direction and/or a 0.5- to 1.5-mm reduction in a vertical direction following a 2- to 6-month healing period[4-11]. A great deal of research has been conducted into bone graft (BG) material, different types of barrier membranes, biological agents and growth factors to minimise postextraction dimensional changes[4-11].

The biomaterial most commonly used to limit postextraction dimensional changes is BG material[4-11]. To date, however, many other strategies have been employed for the same purpose, either as an alternative to or in combination with BGs. One such strategy that has gained popularity in recent years is the use of platelet concentrates[12-14]. Platelet-rich plasma (PRP) was first utilised in regenerative medicine and dentistry due to its supraphysiological doses of platelets and accompanying growth factors, but its incorporation of anticoagulants has more recently been shown to interfere with the angiogenic and regenerative responses mediated by platelets[15]. For these reasons, a second-generation platelet concentrate termed platelet-rich fibrin (PRF) has been proposed with anti-coagulant removal[16]. A number of randomised clinical studies in various avenues of dentistry have demonstrated its ability to promote regeneration of either hard or soft tissues[12-14].

The present systematic review (SR) aimed to investigate the use of PRF for alveolar ridge preservation after tooth extraction. The primary outcome was the ability of PRF to limit postextraction dimensional changes compared to natural wound healing and BG material, and when utilised in combination with BG material. The effects of PRF on soft tissue healing and patient-reported pain scores were assessed as secondary outcomes.

Materials and methods

Protocol

The present SR followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[17]. The study protocol was based on the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[18]. A protocol comprising all aspects of an SR methodology was developed prior to initiation of the SR. This involved defining the focused question, patient, intervention, comparison, outcome (PICO) question, search strategy, study inclusion criteria, outcome measures, and the methods for screening, data extraction, analysis and synthesis. There were no deviations from the initial protocol. The focused question was as follows: ‘What is the effectiveness of PRF in limiting postextraction dimensional changes compared to natural wound healing or BG material?’

Eligibility criteria and study selection process

The eligibility criteria were based on a population, intervention, comparison, outcomes and study design (PICOS) strategy[19]. The search and screening process was conducted by two independent reviewers (MFK and RJM). First, titles and abstracts were analysed, then full texts were selected for close reading and matched with the eligibility criteria for future data extraction. Any disagreements between the reviewers were resolved through careful discussion. The eligibility criteria were as follows:

- Population: Systemically healthy people in need of tooth extraction;
- Intervention: Surgical management of bone defects through the use of PRF alone or in combination with other biomaterials;

- Comparison: PRF vs natural wound healing or in combination with other biomaterials;
- Outcomes: Change in horizontal and vertical bone dimensions post-extraction, new bone formation and soft tissue healing;
- Study design: Randomised clinical trials (RCTs).

Search strategy

MEDLINE (via PubMed), Central (Cochrane Library), Scopus, Embase and LILACS were used to search for articles published before June 2020. A search of the grey literature using the Grey Literature Report and OpenGrey databases was also conducted. Finally, the reference lists of potential articles were examined (cross-referenced) to identify other potential studies for inclusion. The search strategy was as follows: (platelet rich fibrin OR PRF OR platelet-rich fibrin OR leukocyte platelet rich fibrin OR leukocyte platelet-rich fibrin OR LPRF OR L-PRF OR advanced platelet rich fibrin OR advanced PRF OR A-PRF OR APRF) AND (socket preservation OR ridge preservation OR extraction).

Reference lists of all articles identified were screened. Finally, hand searching of the Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontal Research, Journal of Periodontology, Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, Clinical Oral Investigations and the International Journal of Periodontics and Restorative Dentistry was performed to identify articles published from January 2000 until June 2020.

Criteria for study selection and inclusion

Only articles published in English and describing the human clinical evaluation of PRF for the aforementioned procedures were considered. Studies of third molar extraction socket healing were excluded. Original human studies evaluating the effects of PRF compared to those of an appropriate control or another regenerative modality were included, whereas human studies evaluating PRF in a case report or case series that did not include a control were excluded. All animal and in vitro studies were also excluded.

Risk of bias assessment

Two reviewers (VM and RJM) analysed the risk of bias in RCTs using the Cochrane risk-of-bias tool for randomised trials (RoB-2)[20]. For each study, the randomisation method, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported research were classified as low risk, some concerns or high risk of bias. Studies that were classified as low risk in all five areas were judged as low risk; as some concerns when they raised some concerns in at least one area; and high risk when they were judged as high risk in at least one domain or when they were judged to raise some concerns in multiple domains in such a way as to substantially lower confidence in the result (Table 1).

Data synthesis

The following study data were extracted, where available, from the included studies by MFK and RJM: author, study design, follow-up, number of treated cases, type of extraction socket, number of subjects, age range, sex, number of smokers, surgical technique, mean horizontal/vertical bone loss, bone density, visual analogue scale (VAS) score, soft tissue healing response, centrifugation system, volume of blood drawn, and centrifugation parameters. Due to the heterogeneity of the parameters investigated in the studies, meta-analysis could not be performed. Instead, the data were reported in a systematic fashion, with an overview of all studies fitting the search descriptions. Thereafter, data were extracted from the articles and discussed accordingly.

Results

Literature search

The search process, including the selection and reasons for excluding studies, is illustrated in Fig 1. A total of 16 RCTs[21-36] were included, including 12 investigating the use of PRF vs natural wound healing, four examining the use of PRF vs BG, and

Table 1 Assessment of the risk of bias of RCTs

Study	Domain					
	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias judgement
Hauser et al[25]	Low	Low	Low	Low	Low	Low
Suttapreyasri and Leepong[28]	High	Some concerns	Low	Low	Low	Some concerns
Temmerman et al[29]	Low	Low	Low	Low	Low	Low
Du Toit et al[31]	Low	Low	Low	Low	Low	Low
Alzahrani et al[21]	High	Some concerns	Low	Low	Low	Some concerns
Clark et al[32]	Low	Low	Low	Low	Low	Low
Srinivas et al[27]	High	Some concerns	Low	Low	Low	Some concerns
Zhang et al[30]	High	Some concerns	Low	Low	Low	Some concerns
Areewong et al[22]	Low	Low	Low	Low	Low	Low
Canellas et al[23]	Low	Low	Low	Low	Low	Low
Marenzi et al[26]	High	Some concerns	Low	Low	Low	Some concerns
de Almeida Barros Mourão et al[24]	Low	Low	Low	Low	Low	Low
Das et al[33]	High	Some concerns	Low	Low	Low	Some concerns
Mendoza-Azpur et al[35]	Low	Low	Low	Low	Low	Low
Thakkar et al[36]	Low	Low	Low	Low	Low	Low
De Angelis et al[34]	Low	Low	Low	Low	Low	Low

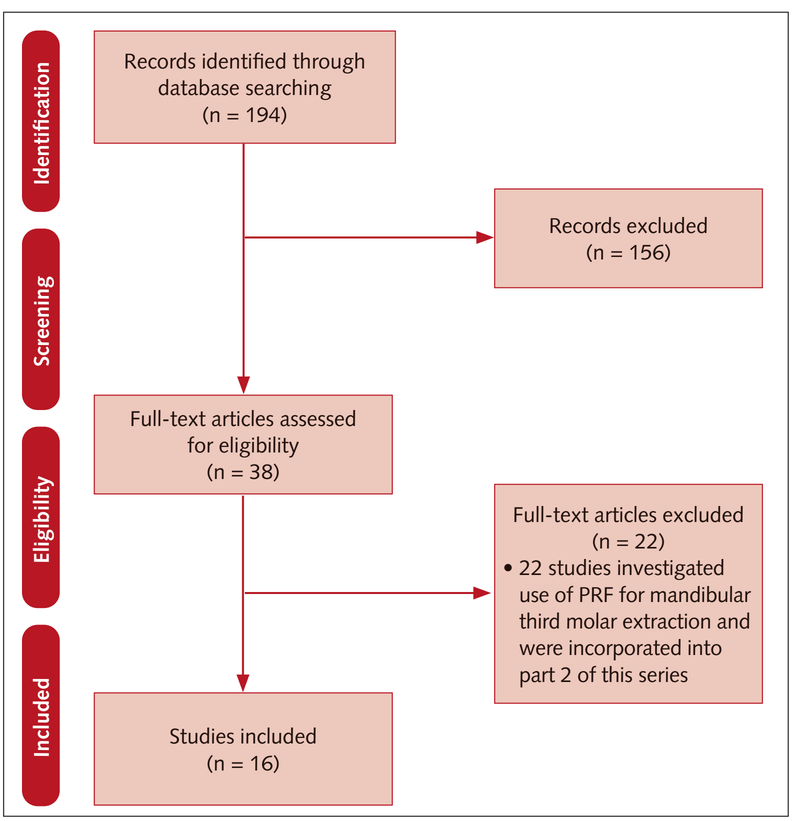

Fig 1 Flow diagram illustrating the screening and selection process.

three overlapping studies investigating BG vs BG and PRF. Nine of the 16 RCTs utilised the IntraSpin (Intra-Lock, Boca Raton, FL, USA) or Heittich EBA 20 system (Hettich, Tuttlingen, Germany), and seven followed the manufacturer's recommended protocol of 2700 revolutions per minute (rpm) for 12 minutes.

PRF versus natural wound healing

Tables 2 and 3 present the currently available studies evaluating postextraction dimensional changes with PRF compared to natural wound healing[21-32].

Hauser et al[25] were the first to show that PRF was more capable of inducing new bone formation in extraction sockets compared to controls. Microcomputed tomography (microCT) analysis showed better bone healing, with improvements in the microarchitecture in the group treated with PRF. PRF was also shown to have a significant effect on intrinsic bone tissue quality and preservation of alveolar width. Interestingly, an invasive surgical procedure with a mucosal flap appeared to completely neutralise the advantages of PRF[25]. For this reason, it is advisable not to raise a flap during routine tooth extraction.

Suttapreyasri and Leepong[28] demonstrated that PRF showed better early healing of soft tissue covering socket orifices in the first 4 weeks; however, neither better alveolar ridge preservation nor enhanced bone formation was observed in the PRF group.

Temmerman et al[29] found that use of PRF as a socket filling material is beneficial to preserve horizontal and vertical ridge dimensions 3 months after tooth extraction. The ridge width at 1 mm below the crest was better maintained when PRF was utilised (23% loss) compared to the control (52% loss)[29].

Du Toit et al[31] conducted a histological study in split-mouth human bone biopsy specimens from extraction sockets treated with PRF versus natural healing at 3 months. At the time of implant placement, a trephined bone core was retrieved and processed for histological evaluation. The findings resulted in a 9.9 ± 5.9% gain in newly formed osteoids in the PRF group versus 4.0 ± 2.1% for specimens derived from the control sites; however, due to the low sample size, this was not deemed significant ($P = 0.089$)[31].

Alzahrani et al[21] investigated the ridge width assessed using cast analysis with an acrylic stent and calipers. Radiographic analysis of the socket surface area was performed using graphics software at 1, 4 and 8 weeks, and it was concluded that the mean residual bone fill was significantly higher in the PRF group than in the control group at all time intervals[21].

Clark et al[32] found that the ridge height was significantly lower in the blood clot group (3.8 ± 2.0 mm) than in the PRF group (1.8 ± 2.1 mm) ($P < 0.05$), and significantly more vital bone was present in the latter.

Zhang et al[30] performed CBCT and investigated alveolar ridge height and width, bone mineral density and histomorphometry at 3 months. Histological analysis of new bone formation confirmed that PRF enhanced the quality and rate of bone formation, although the effect of PRF was not significant in reducing alveolar bone resorption in the extraction socket alone[30].

Srinivas et al[27] investigated bone height and density in a split-mouth study using PRF vs natural wound healing and found that patients in the PRF group had a better Healing Index than those without PRF and showed comparable improvements in bone density.

Areewong et al[22] compared new bone formation using PRF versus normal healing via histomorphometric analysis. They concluded that the use of PRF did not significantly enhance new bone formation after tooth extraction compared to normal wound healing[22].

Canellas et al[23] performed CBCT immediately after tooth extraction and at 3 months after tooth extraction prior to implant surgery, and compared bone density at both stages. A higher percentage of new bone formation was observed in the PRF group than in the control group[23].

Three studies investigated the effects of PRF on soft tissue healing when compared to natural wound healing, and all found that PRF improved postoperative pain, promoted soft tissue healing and reduced the early adverse effects of inflammation[24,26,29].

In summary, seven of these ten studies showed that using PRF to either limit postextraction dimensional changes or improve new bone formation offers significant advantages, whereas the remaining three found it offered no advantage. All ten studies showed that soft tissue wound healing presented some form of benefit.

PRF versus BG

Table 4 presents four RCTs that compared BG to PRF[32-35]. Das et al[33] investigated the use of PRF in comparison to beta-tricalcium phosphate with collagen (β-TCP-Cl) to preserve extraction sockets at 6 months and found that the use of either autogenous PRF or β-TCP-Cl was effective in socket preservation. The results obtained for PRF were similar to those for β-TCP-Cl, although there was significantly greater vertical bone loss in the coronal third in the PRF group; it was therefore concluded that this synthetic BG was slightly superior to PRF[33].

Clark et al[32] performed one of the largest studies on the topic in which four groups (natural

Table 2 Main characteristics of the included studies comparing PRF to natural wound healing for extraction socket healing (bone)

Study	Study design and participants	Outcomes evaluated	Follow-up	Groups	Horizontal bone loss
Hauser et al[25]	RCT. 23 patients (23 sites; 9 men and 19 women; mean age 47.4 y). Patients' smoking habits were not reported	Microarchitecture and intrinsic bone tissue quality of the alveolar bone after premolar extraction therapy	8 wk	C: 8, clot T1: 9, PRF T2: 6, mucosal flap + PRF	C: 0.43 ± 0.18 mm T1: 0.06 ± 0.05 mm T2: 0.42 ± 0.20 mm
Suttapreyasri and Leepong[28]	RCT. 8 patients (20 sites; 3 men and 5 women; mean age 22.6 y). Patients' smoking habits were not reported	Alveolar ridge contour changes and crestal bone resorption in dental casts and periapical radiographs post-premolar extraction	Up to 8 wk	C: 10, clot T: 10, PRF	C: B, 1.61 ± 0.43 mm; L, 1.78 ± 0.47 mm T: B, 1.79 ± 0.90 mm; L, 0.42 ± 0.39 mm
Temmerman et al[29]	Split-mouth RCT. 22 patients (44 sites; 15 men and 7 women; mean age 54 y); non-smokers	Single bilateral and closely symmetrical tooth extractions (incisor-premolar region). Mean ridge width differences between timepoints at three levels below the crest on both the buccal and lingual sides (crest 1, 3 and 5 mm)	3 mo	C: 22, clot T: 22, PRF	C: 51.92 ± 40.31% T: 22.84 ± 24.28%
Du Toit et al[31]	RCT. 4 patients (8 sites; 3 men and 1 woman; mean age 39.5 y); non-smokers	Split-mouth, human bone biopsy specimens from extraction sockets treated with PRF versus natural healing	3 mo	C: 4, clot T: 4, PRF	NR
Alzahrani et al[21]	RCT. 24 (24 sites; 9 men and 15 women; mean age 37.8 y); non-smokers	Ridge width using cast analysis with an acrylic stent and calipers, and radiographic analysis of socket surface area	1, 4 and 8 wk	C: 12, clot T: 12, PRF	C: 13.54 ± 6.57% T: 8.58 ± 1.73%
Clark et al[32]	RCT. 40 patients (40 sites; sex and mean age not reported); non-smokers	Efficacy of PRF alone or with freeze-dried allogeneic bone vs natural clot in improving vital bone formation and alveolar dimensional stability during ridge preservation	15 wk	C: 10, clot T: 10, PRF	C: 2.9 ± 1.7 mm T: 2.8 ± 1.2 mm
Srinivas et al[27]	Split-mouth RCT. 30 patients (60 sites; sex not reported, age range 20–50 y). Patients' smoking habits were not reported	Bone height and density by CBCT	3 mo	C: 30, clot T: 30, PRF	NR
Zhang et al[30]	RCT. 28 patients (28 sites; 14 men and 14 women; mean age 33.9 y); non-smokers	Alveolar ridge height and width, bone mineral density by CBCT and histomorphometry	3 mo	C: 14, clot T: 14, PRF	C: 2.08 ± 1.67 mm T: 1.05 ± 1.78 mm
Areewong et al[22]	RCT. 33 patients (36 sites; 15 men and 21 women; mean age 50.7 y); smokers	New bone formation between using PRF versus normal healing via histomorphometric analysis	2 mo	C: 18, clot T: 18, PRF	NR
Canellas et al[23]	RCT. 48 patients (48 sites; 21 men and 27 women; mean age 44.8 y); non-smokers	Bone resorption by CBCT and new bone formation by histomorphometry	3 mo	C: 24, clot T: 24, PRF	C: 2.27 ± 1.20 mm T: 0.93 ± 0.90 mm

B, buccal; C, control group; D, distal; L, lingual; M, mesial; NR, not reported; T, test group.

	Vertical bone loss	Bone density/bone fill	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters	Conclusions
	C: M, 0.77 ± 0.17 mm; D, 2.07 ± 0.81 mm T1: M, 1.21 ± 0.40 mm; D, 0.76 ± 0.25 mm T2: M, 0.86 ± 0.34 mm; D, 2.15 ± 1.05 mm	C: 780 ± 10 mmHA/ccm T1: 820 ± 23 mmHA/ccm T2: 832 ± 18 mmHA/ccm	NR	8-ml tubes (total 32 ml)	2700 rpm for 12 min	Microcomputed tomography analysis showed better bone healing with improvement of the microarchitecture ($P < 0.05$) in the PRF group without a flap. An invasive surgical procedure with a mucosal flap appeared to completely neutralise the advantages of PRF
	C: M, 1.33 mm; D, 1.14 mm T: M, 0.70 mm; D, 1.23 mm	NR	EBA 20	10-ml glass tubes	3000 rpm for 10 min	Clinically, PRF showed early healing of soft tissue covering socket orifices in the first 4 wk. Neither better alveolar ridge preservation nor enhanced bone formation were observed with PRF in the extraction socket
	C: B, 1.5 ± 1.3 mm; L, 0.7 ± 0.8 mm T: B, 0.5 ± 2.3 mm; L, 0.4 ± 1.1 mm	C: 63.3 ± 31.9% T: 94.7 ± 26.9%	IntraSpin	10-ml tubes (total 20–50 ml)	2700 rpm for 12 min	Use of PRF as a socket filling material to preserve horizontal and vertical ridge dimension 3 mo after tooth extraction is beneficial
	NR	C: 47.9 ± 18.1% T: 50.7 ± 13.3%	EBA 20	10-ml tubes (total 20 ml)	3000 rpm for 10 min	Bone histologically derived from PRF did not differ from bone that healed without intervention
	NR	C: 80.3 ± 2.6% T: 88.8 ± 1.5%	Hermle Labortechnik (Wehingen, Germany) (exact product not stated)	10-ml tubes (total 20 ml)	2700 rpm for 12 min	Ridge width proportions were significantly higher in the test group as compared to the control group between baseline and 4 and 8 wk, respectively. Bone formation was significantly higher in the test group than the control group at all time intervals
	C: 3.8 ± 2.0 mm T: 1.8 ± 2.1 mm	CBCT values: C: 487 ± 64 mg/cm^3 T: 493 ± 70 mg/cm^3	Duo Quattro, Process for PRF (Nice, France)	10-ml glass tubes	1300 rpm (200 g) for 8 min	Significantly greater loss of ridge height was noted in the control group (3.8 ± 2.0 mm) compared to the test group (1.8 ± 2.1 mm) ($P < 0.05$). Significantly more vital bone was present in the test group
	C: 1.90 ± 0.50 mm T: 1.65 ± 0.28 mm	CBCT values: C: 295.87 ± 87.21 mg/cm^3 T: 564.76 ± 94.86 mg/cm^3	NR	10-ml tubes	3000 rpm for 10 min	Patients in the test group had a better Healing Index when compared to the control group. Use of PRF showed a comparable increase in bone density
	C: B, 2.80 ± 1.81 mm; L, 2.05 ± 1.29 mm T: B, 1.60 ± 1.46 mm; L, 1.00 ± 0.71 mm	Osteoid area: C: 2.81 ± 1.21% T: 9.76 ± 4.01%	Universal 320 (Hettich)	9-ml tubes (total 18 ml)	400 g for 10 min	Histological analysis confirmed that PRF increased the quality of new bone and enhanced the rate of bone formation; however, the effect of PRF was not significant enough to reduce alveolar bone resorption in the extraction socket alone
	NR	C: 26.33 ± 19.63% T: 31.33 ± 18.00%	IntraSpin	NR	2700 rpm for 12 min	Use of PRF in alveolar socket preservation does not statistically significant enhance new bone formation after tooth extraction compared to normal wound healing
	C: 1.39 ± 1.20 mm T: 0.70 ± 0.70 mm	C: 39.69 ± 11.13% T: 55.96 ± 11.97%	IntraSpin	9-ml tubes (total up to 54 ml)	2700 rpm for 12 min	PRF provided significant benefits in terms of alveolar preservation, decreasing horizontal and vertical resorption, and improved total bone volume after 3 mo

Table 3 Main characteristics of the included studies comparing PRF to natural wound healing for extraction socket healing

Study	Study design and participants	Outcomes evaluated	Groups	VAS score (0–10)	Healing Index (4–12)
Marenzi et al[26]	Split-mouth RCT. 26 patients (108 sites; 9 men and 17 women; mean age 53 y); non-smokers and smokers including light smokers (< 5 cigarettes/day)	Pain (VAS) score at 1, 2, 3 and 4 d; soft tissue Healing Index (4 to 12) at 3, 7, 14 and 21 d	C: 54, clot T: 54, PRF	3 d: C: 4.5 ± 0.7 T: 3.2 ± 0.3	7 d: C: 4.9 ± 0.3 T: 4.5 ± 0.5
Temmerman et al[29]	Split-mouth RCT. 22 patients (44 sites; 15 men and 7 women; mean age 54 y); non-smokers	Up to 7 d	C: 22, clot T: 22, PRF	3 d: C: 2.45 (0.09–4.64) T: 1.65 (0.09–3.12)	NR
de Almeida Barros Mourão et al[24]	RCT. 32 patients (32 sites; 13 men and 19 women; mean age 37.3 y); non-smokers	1 and 2 wk	C: 16, clot T: 16, PRF	1 wk: C: 4.00 ± 1.15 T: 5.12 ± 1.08	1 wk: C: 3.18 ± 0.54 T: 3.81 ± 0.65

Table 4 Main characteristics of the included studies comparing BG to PRF

Study	Study design and participants	Outcomes evaluated	Follow-up	Groups	Horizontal bone loss (mm)
Das et al[33]	RCT. 26 patients (30 sites; 13 men and 13 women; mean age 31.2 y); non-smokers	Clinicoradiographic efficacy of PRF and β-TCP-Cl in preserving extraction sockets	6 mo	C: 15, β-TCP-Cl T: 15, PRF	C: 0.86 ± 1.76 T: 1.52 ± 1.22
Clark et al[32] (additional group with freeze-dried allogeneic bone reported in Table 5)	RCT. 40 patients (40 sites; sex and mean age not reported); non-smokers	Efficacy of PRF alone or with freeze-dried allogeneic bone in improving vital bone formation and alveolar dimensional stability	15 wk	C: 10, FDBA T: 10, PRF	C: 2.5 ± 1.1 T: 2.8 ± 1.2
De Angelis et al[34] (additional group with xenogeneic bone + PRF reported in Table 5)	RCT. 45 patients (45 sites; 19 men and 26 women; mean age 51.2 y); non-smokers	Clinical and radiographic outcomes of different ridge preservation procedures based on use of PRF vs xenogeneic bone	6 mo	C: 15, xenogeneic bone T: 15, PRF	C: 1.12 ± 0.28 T: 2.80 ± 0.31
Mendoza-Azpur et al[35]	RCT 51 participants (51 sites; 21 men and 30 women; mean age 47.7 y); non-smokers	Clinical and histological differences when using a combination of β-TCP and a cross-linked collagen membrane versus PRF in ridge preservation after dental extraction and healing	4 mo	C: 25, β-TCP T: 26, PRF	C: 1.16 ± 0.55 T: 2.19 ± 0.80

β-TCP, beta-tricalcium phosphate; β-TCP-Cl, β-tricalcium phosphate with collagen; HU, Hounsfield units.

wound healing, PRF, freeze-dried allogeneic bone and freeze-dried allogeneic bone and PRF) were evaluated for vital bone formation and alveolar dimensional stability during ridge preservation at 15 weeks. Significantly greater loss of ridge height was noted in the blood clot group (3.8 ± 2.0 mm) compared to the PRF group (1.8 ± 2.1 mm), and significantly more vital bone was present in the PRF group (46 ± 18%) than in the freeze-dried allogeneic bone group (29 ± 14%) ($P < 0.05$)[32]. Similar outcomes were reported between the PRF and freeze-dried allogeneic bone groups in terms of their ability to limit postextraction horizontal and vertical bone dimensions[32].

In a study by de Angelis et al[34], three groups were compared at 6 months: PRF, xenogeneic bone, and xenogeneic bone and PRF. It was concluded that the PRF group experienced significantly greater

	Analgesic intake	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters	Conclusions
	NR	IntraSpin	9-ml tubes (total 18–54 ml)	2700 rpm for 12 min	PRF improved postoperative pain, promoted soft tissue healing and reduced early adverse effects of inflammation
	NR	IntraSpin	10-ml tubes (total 20–50 ml)	2700 rpm for 12 min	A significantly lower amount of postoperative pain was observed at sites treated with PRF during the early healing phases
	1 wk: C: 1.75 ± 0.85 T: 1.00 ± 1.15	IntraSpin	10-ml tubes	2700 rpm for 12 min	Whenever improved healing of the extraction socket is needed, use of PRF should be considered. Use of PRF decreased postoperative pain and discomfort

	Vertical bone loss (mm)	Bone density	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters	Conclusions
	C: 0.35 ± 6.52 T: 1.17 ± 5.96	C: 695.45 ± 157.31 HU T: 842.43 ± 52.64 HU	Remi Laboratories (Mumbai, India)	10-ml glass tubes	NR	Use of either autogenous PRF or β-TCP-Cl was effective in socket preservation. Results obtained from the test group were similar to the control group, though there was significantly greater vertical bone loss in the coronal third in the test group
	C: 2.2 ± 1.8 T: 1.8 ± 2.1	C: 551 ± 58 mg/cm^3 T: 493 ± 70 mg/cm^3	Process for PRF	10-ml glass tubes	1300 rpm (200 g) for 8 min	Significantly more vital bone was present in the test group (46 ± 18%) compared to the control group (29 ± 14%) ($P < 0.05$), with comparable maintenance of ridge dimensions
	C: 0.75 ± 0.26 T: 2.24 ± 0.66	NR	IntraSpin	9-ml glass-coated plastic tubes	2700 rpm for 12 min	The test group experienced significantly greater horizontal and vertical bone resorption. Statistically significant differences in postoperative pain and wound healing were observed, with the control group in particular having higher values for pain and experiencing delayed wound healing
	NR	Mineralised tissue: C: 26.14 ± 7.49% T: 77.33 ± 9.80%	NR	10-ml tubes	3000 rpm for 10 min	PRF concentrate accelerates wound healing in post-extraction sockets in terms of the new component of mineralised tissue. However, use of β-TCP biomaterial appears to be superior to maintain buccolingual volume and the final position of the mucogingival junction

horizontal and vertical bone resorption than the xenogeneic bone, which demonstrated less vertical and horizontal bone resorption, and reduced postoperative pain and better wound healing were observed in the same group[34].

Mendoza-Azpur et al[35] investigated β-TCP compared to PRF after 4 months of healing. It was concluded once again that PRF accelerated wound healing in postextraction sockets in terms of new mineralised tissue components; however, β-TCP biomaterial was superior at maintaining the buccolingual volume and the final position of the mucogingival junction[35].

Three of these four studies found that BG showed a better ability to maintain ridge dimension than PRF alone[33-35], whereas PRF alone was better able to accelerate wound healing and mineralisation towards bone (BG is typically not fully

Table 5 Main characteristics of the included studies comparing BG to BG + PRF

Study	Study design and participants	Outcomes evaluated	Follow-up	Groups	Horizontal bone loss (mm)
Thakkar et al[36]	RCT. 36 patients (36 sites; 21 men and 15 women; age range 20 to 55 y); non-smokers	Clinical and radiographic bone fill in extraction sockets	3 and 6 mo	C: 18, demineralised freeze-dried allogeneic bone T: 18, demineralised freeze-dried allogeneic bone + PRF	C: 1.36 ± 0.70 T: 0.75 ± 0.49
Clark et al[32]	RCT. 40 patients (40 sites; sex and mean age not reported); non-smokers	Efficacy of PRF alone or with freeze-dried allogeneic bone in improving vital bone formation and alveolar dimensional stability	15 wk	C: 10, freeze-dried allogeneic bone T: 10, freeze-dried allogeneic bone + PRF	C: 2.5 ± 1.1 T: 1.9 ± 1.1
De Angelis et al[34]	RCT. 45 patients (45 sites; 19 men and 26 women; mean age 51.2 y); non-smokers	Clinical and radiographic outcomes of different ridge preservation procedures based on use of PRF vs xenogeneic bone	6 mo	C: 15, xenogeneic bone T: 15, xenogeneic bone + PRF	C: 1.12 ± 0.28 T: 1.05 ± 0.23

resorbed and remains within the site at the time of analysis).

BG versus BG and PRF

Only three RCTs investigated the use of BG versus BG and PRF [32,34,36]. Thakkar et al[36] investigated demineralised freeze-dried allogeneic bone with and without PRF for extraction site management at 3 and 6 months and observed that the addition of PRF to demineralised freeze-dried allogeneic bone favoured the maintenance of ridge width, although the improvements were not statistically significant between the groups.

In a study by Clark et al[32], the ridge height and width were better maintained with PRF and freeze-dried allogeneic bone (1.0 ± 2.3 mm) than with freeze-dried allogeneic bone alone (1.8 ± 2.1 mm). The addition of PRF also favoured significantly greater new vital bone[32]. In the previously mentioned study by de Angelis et al[34], although the PRF group experienced significantly greater horizontal and vertical bone resorption than the xenogeneic bone group, the combination of BG and PRF demonstrated significantly less vertical and horizontal bone resorption than xenogeneic bone alone. PRF also reduced patient-reported postoperative pain[34].

Two of these three studies therefore demonstrated that the combination of BG and PRF offers significant advantages, including its ability to further limit dimensional changes and/or improve new vital bone post-extraction compared to BG alone[32,34].

Discussion

To date, several excellent SRs have addressed the topic of postextraction dimensional changes when comparing PRF to natural wound healing alone[12,14,37-43], but there are currently no studies comparing the effects of PRF to those of a BG material. The present comparative investigation was conducted to improve clinical recommendations specifically on this topic.

Over the past two decades, much research has focused on minimising postextraction dimensional changes by utilising a variety of bone biomaterials. Most frequently, BG materials have been favoured by clinicians owing to their ability to better maintain ridge dimensions. Furthermore, various barrier membranes including collagen, polytetrafluoroethylene (PTFE) and, more recently, PRF, have also been utilised to either prevent soft tissue infiltration or promote faster soft tissue healing.

It is now well known from various SRs that postextraction dimensional changes tend to be in the range of 0.5 to 1.0 mm when BG materials are used[4-11]. Most RCTs investigating the use of

	Vertical bone loss (mm)	Bone density (mg/cm³)	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters	Conclusions
	C: 1.39 ± 0.50 T: 1.08 ± 0.43	NR	NR	10-ml glass tubes	3000 rpm for 10 min	The addition of PRF to demineralised freeze-dried allogeneic bone favoured the prevention of reduction of ridge width, though there were no statistical differences
	C: 2.2 ± 1.8 T: 1.0 ± 2.3	C: 551 ± 58 T: 521 ± 58	Process for PRF	10-ml glass tubes	1300 rpm (200 g) for 8 min	The test group demonstrated the best ability to limit postextraction dimensional changes
	C: 0.75 ± 0.26 T: 0.58 ± 0.25	NR	IntraSpin	9-ml glass-coated plastic tubes	2700 rpm for 12 min	The test group experienced significantly less vertical and horizontal bone resorption than the control group. The test group also reported less patient-reported postoperative pain

PRF report changes ranging from 1.0 to 2.5 mm, with some studies even demonstrating no advantage over simple natural healing with a blood clot (Tables 2 and 3). Additionally, a recent SR showed that PRF played a positive role in reducing postoperative pain and ridge dimension changes after tooth extraction, and the meta-analysis also recorded smaller mesial bone height changes and a greater percentage of bone fill in the PRF group[42]. Thus, even in well-conducted studies on the topic, PRF was shown to lead to a greater loss of ridge dimensions than BG, both in previous SRs and comparative RCTs (Table 4). This highlights the need to consider the use of BG material for all extraction sockets, especially when the buccal and/or lingual plate is compromised.

Over the past 15 years, research has also convincingly demonstrated the negative impact of flap raising during tooth extraction. Since the periodontal ligament, the main source of the blood supply, is removed following tooth loss, it has been the focus of much research to evaluate the effect of flap elevation during routine extractions[44]. As demonstrated by Hauser et al[25] investigating PRF, a more invasive surgical procedure with mucosal flap elevation during routine extractions completely neutralises the advantages of PRF. It is therefore necessary that tooth extraction be performed as atraumatically as possible without flap elevation, especially if PRF is used alone.

Furthermore, the reported clinical outcomes when utilising PRF alone for alveolar ridge preservation demonstrated more pronounced and significant variability (Tables 2 and 3), with some studies showing no advantage at all. In addition, a risk of bias analysis revealed that six of the 15 studies raised some concerns (Table 1). In light of these findings and in parallel with the considerable variations in humans (genetics, medication taken, etc.), clinicians should consider that not all sockets resorb equally, that not all patients are genetically predisposed to resorb equally, and that PRF may contribute to greater differences in ridge preservation/loss between sites and patients. For instance, a study by Chappuis et al[11] demonstrated convincingly that facial bone thickness in the aesthetic zone was a critical factor affecting postextraction dimensional changes. These differences may be more pronounced when sites are grafted with PRF compared to BG owing to the faster degradation rate of the former; one of the limitations of PRF is that it typically resorbs within 2 weeks. In parallel to these findings, a recent SR found that plasma rich in growth factors may offer advantages in some relevant clinical and radiographic outcomes, such as bone density and soft tissue healing, after tooth extraction, and reduce postoperative adverse events, complications and patient discomfort[38].

A notable benefit of socket grafting with PRF was the improvement in soft tissue healing reported in all studies (Tables 2 and 3). Together with previous findings from SRs investigating the use of PRF during gingival recession coverage and periodontal regeneration[12-14], it becomes increasingly clear that PRF promotes soft tissue healing. Studies have now demonstrated that when utilised either in combination with BG or as an outer PRF membrane to promote soft tissue healing, it leads to faster soft tissue healing and reduced postoperative pain and analgesic intake (Tables 2 and 3).

Further good quality research investigating comparative studies in additional well-conducted clinical trials is required. To date, only a few studies have compared the use of PRF to BG; use of the latter post-extraction is routine practice in many countries. As such, an increased ability to document the differences between findings for PRF and BG and to provide clinical recommendations for when to use PRF alone, BG alone or a combined approach may lead to improved clinical recommendations in the future.

Conclusion

In conclusion, the present SR found that the use of PRF alone was shown to limit postextraction dimensional changes compared to natural healing in seven out of ten studies comparing the two. The study also demonstrated that three out of four of the studies comparing PRF to BG found that BG was more able to maintain postextraction dimensional changes. BG should therefore be considered as the preferred option for extraction site management to limit postextraction dimensional changes. Interestingly, the approach combining use of BG and PRF demonstrated some additional clinical benefits: it showed a better ability to limit dimensional changes in two out of three studies, it promoted greater new bone formation and faster bone mineralisation, and favoured improved soft tissue healing in all studies compared with use of BG alone. Further research that seeks to better address and characterise the advantages of combining BG with PRF is needed.

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