Review
ISSN 2413-0516

Application of platelet rich fibrin in the regeneration of intra oral defects: a systematic review

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(Submitted: 12 May 2019 – Revised version received: 28 May 2019 – Accepted: 10 June 2019 – Published online: 26 August 2019)

Objective To systematically review the randomized clinical trials (RCTs) on the effect of Platelet Rich Fibrin (PRF) concentrate on the tissue regeneration of intra-oral defects.
Methods An electronic search was performed in PubMed/Medline and Cochrane Library using relevant keywords until June 2018. RCTs which used PRF concentrate for treatment of intrabony defects, sinus augmentation, furcation involvement, endo-periodontal lesions, gingival recession, and ridge preservation were included in the present review.
Results In total, 79 studies that were used PRF either solely or mixed in human trials were included and divided based on the defect type. Most of the studies used PRF to treat intra-bony defects showed that it would improve treatment outcomes. In case of furcation involvement, the application of leukocyte-PRF in addition to open flap debridement improved the bone regeneration in grade II mandibular furcation involvement. In case of ridge preservation and sinus floor augmentation, the results were controversial.
Conclusion The result of the current systematic review implied that the treatment outcome of PRF application for periodontal and soft tissue repair depends on the treatment strategies and type of the defect. It was shown that PRF application is a practical approach to accelerate and enhance new bone formation in human studies in intrabony defects and furcation involvements. However, further clinical trials for evaluation of other types of intra-oral defects are required.
Keywords platelet rich fibrin, bone regeneration, periodontal defects, sinus floor augmentation

Introduction

The second generation of platelet concentrate, platelet-rich fibrin (PRF) was introduced by Choukroun et al.[1] to accelerate the healing procedures. PRF can be easily prepared following the centrifugation of non-coagulated blood without requiring additional anticoagulants such as bovine thrombin.[2,3] The obtained product would be an autologous matrix of dense fibrin which is rich in platelets, growth factors and platelet cytokines.[4,5]

Various growth factors and cytokines were detected in PRF including platelet-derived growth factor (PDGF), vascular endothelial growth factor, insulin-like growth factors, transforming growth factor-beta 1 (TGF-β), interleukin-1β (IL-1β), interleukin-4 (IL-4), and interleukin-6 (IL-6).[6,7] The PRF concentrate is highly biocompatible. As no anticoagulants are used in this system, PRF forms a fibrin matrix in the later stages of the coagulation. This formed fibrin matrix contains platelets which are gradually releasing mentioned cytokines and growth factors, following the fibrin fabrication.[6] As a result of these features, the fibrin network of PRF can be used as the source of autologous growth factors especially in damaged tissues.[8] The biological characteristics of PRF was shown to positively influence the differentiation and proliferation of osteoblasts, fibroblasts, endothelial cells, and chondrocytes[9–11] and facilitate the osteointegration process.[12] All these procedures may initiate and accelerate the healing and regeneration process.[13]

Over the course of many years, platelets were identified to promote bone repair and the bone healing.[14,15] It has also been shown by various studies that growth factors may stimulate the bone regeneration in the intra-oral bone defects.[16] PRF provide an autologous concentrate of fibrin, platelets, leukocytes and their growth factors. Based on the previous data, it can be expected that the application of the platelet concentrates in the intraoral defects may lead to clinical success in less duration of time in addition to reduced postoperative symptoms.[17,18]

Platelet-rich fibrin, as a type of platelet concentrate, has been used widely in the various studies solely or in combination with other approaches in case of maxillofacial defects, such as facial plastic surgery,[19] maxillary sinus augmentation in combination with bone substitute materials,[20] root coverage with assistant of coronally displaced flap,[21] and the treatment of furcation defects.[22] These studies suggested that PRF can be used as the treatment or supplement in the bone defects of oral region. However, the additional benefit of PRF in clinical trials did not present as clinically significant in every situation.

The aim of the present systematic review is to investigate the effect of PRF on bone regeneration and healing in the intra-oral region including ridge preservation, sinus augmentation, endodontal and periodontal defects.

Materials and Methods

Study Design

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The search protocol was considered based on the patient, intervention, comparison, outcome (PICO) question of the study (Table 1).

Clinical studies regarding PRF application for accelerating tissue regeneration of the selected periodontal defects (intrabony defects, sinus augmentation, furcation involvement, endo-periodontal lesions, root coverage, gingival recession, and ridge preservation) were included. In this review only randomized clinical trials (RCTs) with parallel or split-mouth design were included. Inclusion criteria was English papers, more than 10 patients, and comparison of the effect of treatment with the control group (conventional treatment). Case reports and series, animal studies and review articles were excluded.

Search Strategy

A comprehensive electronic search was conducted in PubMed/Medline and Cochrane Library from January 2009 to June 2018 using the following terms: "platelet rich fibrin", "bone regeneration", "bone augmentation", "periodontal defect", "apical lesion", "maxillofacial surgery", and "gingival recession". Related published papers were found using the various combinations of the related search terms based on the PICO question (Table 1).

Study Selection and Data Extraction

Study selection was performed by two independent reviews. Disagreements were resolved by discussion. The initial paper selection was done by assessing the titles and abstracts. The full texts of the potentially suitable articles were obtained for final assessment according to the inclusion and exclusion criteria.

To perform the study, the following data were extracted: study design, study groups, the number of patients and samples, variables, data evaluation methods, the follow-up periods, and the treatment outcomes. Extracted data from selected articles were summarized in the tables for each defect type and compared in a qualitative manner. Due to the variety of defect types and various protocols for using PRF meta-analysis could not be performed.

Table 1 **Study question and related keywords based on patient, intervention, comparison, outcome format**

	Question of the review	Search keywords
Population (P)	Patients need bone or tissue regeneration for their defects (intrabony defects, sinus augmentation, furcation involvement, endo-periodontal lesions, gingival recession, and ridge preservation)	Periodontal defects, intrabony defects, sinus augmentation, furcation involvement, endo-periodontal lesions, root coverage, gingival recession, ridge preservation
Intervention (I)	Application of platelet concentrates including platelet-rich fibrin (PRF), leukocyte-PRF (L-PRF), and advanced PRF (A-PRF) alone or beside other conventional approaches as a supplement	PRF, L-PRF, A-PRF
Comparison (C)	Various kind of intra oral regenerative treatment approaches	-
Outcome (O)	Regeneration of bone and the periodontal tissue	Tissue regeneration, bone regeneration, new bone formation, healing

Results

Study Selection

After removing duplicate topics, a total of 370 articles were found in the electronic search. Following the initial screening of titles and abstracts, 106 studies were chosen for further evaluations as relevant for the aim of the study. Finally, 79 records completely fulfilled the inclusion criteria of the present study. Figure 1 demonstrated the details of the search strategy and study selection. Selected studies were categorized based on their defect type: intrabony defect, ridge preservation, sinus augmentation, endo-periodontal defect, furcation defect, and gingival recession. Because of the various approaches for the PRF application and different type of defects, conducting the meta-analysis was not possible.

PRF Application on the Treatment of Intrabony Defects

Totally, 29 clinical trials used PRF concentrates in the treatment of intrabony defects (Table 2). PRF concentrates were used solely[24–37] or in combination with other treatment approaches including demineralized freeze-dried bone allograft (DFDBA),[38] nanocrystalline hydroxyapatite (NcHA),[39] metformin,[40] bovine porous bone mineral (BPBM),[41] demineralized bone matrix (DBM),[42] rosuvastatin,[43] alendronate,[44] etc. (Table 2). The follow-up period was varied from 3 to 12

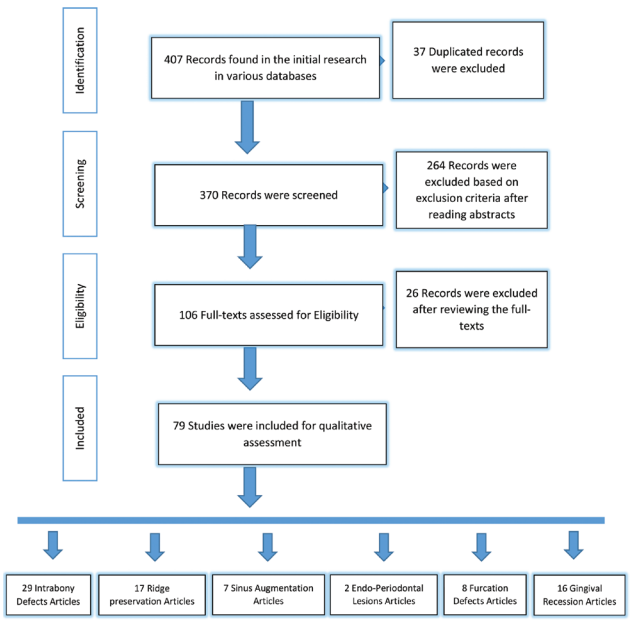

Fig. 1 **Flow diagram of study selection strategy.**

Table 2. **Review of published clinical trials evaluated the application of PRF concentrate on intrabony defects**

Authors (year)	Study design	Study size, defect type	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Pradeep et al.[45]	RCT	90, PID	3000 rpm (about 400 g) for 10 min	PRF + HA + OFD	OFD and OFD + PRF	Clinical and radiographic evaluation	9 Months	Significant differences were observed in mean PD reduction, mean CAL gain and percentage of mean bone fill with the advantage of OFD + PRF (3.90 ± 1.09, 3.03 ± 1.16 mm, and 56.46 ± 9.26%, respectively) and PRF + HA + OFD groups (4.27 ± 0.98, 3.67 ± 1.03 mm, and 63.39 ± 16.52%, respectively) in comparison to OFD group (2.97 ± 0.93, 2.67 ± 1.09 mm, and 15.96 ± 13.91%, respectively).
Naqvi et al.[46]	Split-mouth RCT	10 Patients with paired PID	3000 rpm (400 g) for 10 min	PRF + bioactive glass putty + OFD	Bioactive glass putty + OFD	Clinical and radiographic evaluation	9 Months	Significant differences were observed only in mean IBD reduction with the advantage of test group (7.1 ± 1.37 mm) groups in comparison to control group (5.7 ± 1.64 mm).
Thorat et al.[35]	Split-mouth RCT	10 Patients with paired PID and LAP	3000 rpm (400 g) for 12 min	PRF + MFO	MFO (Kirkland flap)	Clinical and radiographic evaluation	12 Months	Significant differences were observed in mean PD reduction, mean CAL gain and RBF with the advantage of test groups (with mean CAL gain and bone fill of 4.0 ± 0.63 and 3.09 mm) in comparison to control group. About 80% of the PRF-treated sites showed ≥50% bone fill.
Yajamanya et al.[37]	CT	38 Patients with 90 PIDs	3000 rpm for 10 min	PRF + OFD	OFD and Perio-Glass + OFD	Clinical and radiographic evaluation	9 Months	Significant differences were observed in mean PD reduction, mean CAL gain and percentage of mean bone fill with the advantage of OFD + PRF (6.11 ± 0.92, 6.74 ± 1.55 mm, and 75.01 ± %7.85) and PerioGlass + OFD (5.57 ± 1.10, 6.57 ± 1.45 mm, and 74.44 ± 8.57%) groups in comparison to OFD group (3.68 ± 0.72, 4.14 ± 0.76 mm, and 69.29 ± 7.73%).
Yasaswini et al.[47]	Split-mouth RCT	14 Patients with paired PID	3000 rpm (400 g) for 12 min	PRF + Perio-Glass	MPPG + Perio-Glass	Clinical & Radiographic Evaluation	6 and 9 Months	Significant differences were observed only in case of bone fill with the advantage of PRF groups in comparison to MPPG group (70.55 ± 15.99 vs. 55.30 ± 11.87 at month 6 and 84.55 ± 11.74 vs. 72.2 ± 9.91 at month 9).
Patel et al.[30]	Split-mouth RCT	13 Patients with paired PID	3000 rpm for 10 min	PRF + OFD	OFD	Clinical and radiographic evaluation	6, 9 and 12 Months	Significant differences were observed only in mean PD reduction, mean CAL gain and percentage of mean bone fill with the advantage of PRF group (4.1 ± 0.31, 3.4 ± 0.69 mm, and 45.18 ± 7.57%) in comparison to OFD group (5.5 ± 0.52, 4.7 ± 0.67 mm and 21.6 ± 9.3%)
Bajaj et al.[25]	RCT	17 Patients with 44 PIDs	3000 rpm (about 400 g) for 10 min	PRF + OFD	OFD	Clinical and radiographic evaluation	9 Months	Significant differences were observed only in mean PD reduction, mean CAL gain, mean IBD reduction and percentage of mean bone fill with the advantage of PRF group (3.14 ± 1.26, 2.66 ± 1.07, 2.24 ± 0.66 mm, and 46.14 ± 11.39%) in comparison to OFD group (2.14 ± 1.26, 1.59 ± 1.01, 0.84 ± 0.99 mm, 15.76 ± 18.77%).

(*Continued*)

Table 2. **Review of published clinical trials evaluated the application of PRF concentrate on intrabony defects—Continued**

Authors (year)	Study design	Study size, defect type	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Galav et al.[27]	RCT	20, PID	3000 rpm (about 400 g) for 10 min	PRF + OFD	ABG + OFD	Clinical and radiographic evaluation	3, 6, and 9 Months	Significant differences were observed only in case of RBF with the advantage of ABG group (30.34% compared with PRF 20.22%).
Chadwick et al.[26]	RCT	36, PID	3000 rpm for 10 min	OFD + PRF	OFD + DFDBA	Clinical and radiographic evaluation	6 Months	There were no significant differences between the groups (DFDBA: mean CAL gain = 1.16 ± 1.33 mm, mean bone fill = 1.53 ± 1.64 mm, and mean radiographic bone fill = 1.14 ± 0.88 mm; PRF: mean CAL gain = 1.03 ± 0.86 mm, mean clinical bone fill = 1.35 ± 1.60 mm, and mean radiographic bone fill = 1.10 ± 1.01 mm).
Chandradas et al.[42]	RCT	36, PID	3000 rpm for 12 min	OFD + PRF + DBM	OFD, OFD + PRF	Clinical and radiographic evaluation	9 Months	Mean PD reduction and RAL gain of PRF (4.25 ± 1.48 and 3.92 ± 0.90 mm) and PRF + DBM (4.25 ± 1.48 and 3.92 ± 0.90 mm) groups was significantly better than the control group (3.00 ± 1.21 and 2.25 ± 0.62 mm). LBG and percentage of mean bone fill PRF + DBM group (3.47 ± 0.53 mm, and 61.53 ± 4.54%) was significantly better than other groups (2.55 ± 0.61 mm, and 49.60 ± 14.08% in PRF group and 1.21 ± 0.80 mm, 24.69 ± 15.59% in control group).
Pradeep et al.[43]	RCT	90, PID	3000 rpm (400 g) for 10 min	OFD + PRF + 1.2% RSV	OFD and OFD + PRF	Clinical and evaluation	9 Months	Significant differences were observed in mean PD reduction, mean CAL gain and mean defect depth reduction with the advantage of OFD + PRF + 1.2% RSV group (4.90 ± 0.31, 3.93 ± 0.78, and 3.63 ± 0.67 mm compared with PRF group 4.03 ± 0.18, 3.30 ± 0.65, and 3.17 ± 0.65 mm and control group 3.10 ± 0.30, 2.47 ± 0.77, and 1.43 ± 0.50 mm).
Kanoriya et al.[44]	RCT	90, PID	3000 rpm (about 400 g) for 10 min	Access therapy + PRF + 1% ALN	Access therapy, access therapy + PRF	Clinical and radiographic evaluation	9 Months	Significant differences were observed in mean PD reduction, mean CAL gain and mean defect depth reduction with the advantage of access therapy + PRF + 1% ALN group (4.53 ± 0.81, 5.16 ± 0.46, and 2.84 ± 0.26 mm compared with PRF group 3.7 ± 0.91, 4.2 ± 0.66, and 2.42 ± 0.21 mm and control group 2.86 ± 0.68, 3.03 ± 0.18, and 0.38±0.26 mm).
Martande et al.[49]	RCT	96, PID	3000 rpm for 12–14 min	OFD + PRF + 1.2% ATV	OFD and OFD + PRF	Clinical and radiographic evaluation	9 Months	Significant differences were observed in mean PD reduction, mean CAL gain and percentage of mean defect depth reduction with the advantage of OFD + PRF + 1.2% ATV group (4.06 ± 1.22, 3.66 ± 1.42 mm, and 50.96 ± 4.88%) in comparison to OFD group (2.76 ± 1.43, 2.50 ± 1.33 mm, 5.54 ± 1.71%).
Aydemir Turkal et al.[50]	Split-mouth RCT	28 Patients with paired PID	3000 rpm for 10 min	EMD + PRF + OFD	EMD + OFD	Clinical and radiographic evaluation	6 Months	There were no significant differences between the groups.

Table 2. **Review of published clinical trials evaluated the application of PRF concentrate on intrabony defects—Continued**

Authors (year)	Study design	Study size, defect type	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Agrawal et al.[38]	Split-mouth RCT	30 Patients with paired PID	400 g for 12 min	L-PRF + DFDBA	DFDBA	Clinical and radiographic evaluation	12 Months	Clinical and radiographic outcomes of L-PRF treated groups was significantly better than the control group (PD: 4.15 ± 0.84 vs. 3.60 ± 0.51 mm; CAL: 3.73 ± 0.74 vs. 2.61 ± 0.68 mm; REC: 0.47 ± 0.56 vs. 1.00 ± 0.61 mm; bone fill: 3.50 ± 0.67 vs. 2.49 ± 0.64 mm; and defect resolution: 3.73 ± 0.63 vs. 2.75 ± 0.57 mm).
Ajwani et al.[24]	Split-mouth RCT	30 Patients with paired PID	3000 rpm (about 400 g) for 10 min	L-PRF + OFD	OFD	Clinical and radiographic evaluation	9 Months	Only radiographic outcomes of L-PRF treated groups was significantly better than the control group (Cement enamel junction to base of the defect: 2.60 ± 1.10 vs. 1.30 ± 0.2 mm; and alveolar crest to base of the defect: 1.45 ± 0.49 vs. 0.80 ± 0.35 mm).
Elgendy et al.[39]	Split-mouth RCT	20 Patients with paired PID	3000 rpm (about 400 g) for 10 min	L-PRF+ NcHA + OFD	NcHA + OFD	Clinical and radiographic evaluation	6 Months	Both clinical and radiographic outcomes (PPD, CAL, bone density) of L-PRF treated group (3.42 ± 0.49, 3.55 ± 0.51, and 107.59 ± 9.45 mm) were significantly better than the control group (3.82 ± 0.54, 3.90 ± 0.44, and 93.20 ± 5.78 mm).
Pradeep et al.[40]	RCT	120, PID	3000 rpm (about 400 g) for 10 min	1% Metformin + L-PRF + OFD	1% Metformin + OFD, L-PRF + OFD, OFD	Clinical and radiographic evaluation	9 Months	PD reduction, RAL gain outcomes, and percentage of defect depth reduction of study group (4.90 ± 0.30, 4.90 ± 0.30 mm, 52.65 ± 0.031%) were significantly better than the control groups (MF: 3.93 ± 0.25, 3.93 ± 0.25 mm, 48.69 ± 0.026%, PRF: 4.00 ± 0.18, 4.03 ± 0.18 mm, 48 ± 0.029%, and OFD alone: 3.00 ± 0.18, 2.96 ± 0.18 mm, 9.14 ± 0.04%).
Mathur et al.[29]	CT	38, PID	3000 rpm for 10 min	OFD + L-PRF	OFD + ABG	Clinical evaluation	6 Months	There were no significant differences between the groups. (PPD change: PRF group: −2.67 ± 1.29, ABG group: −2.40 ± 1.06, CAL gain: PRF group: −2.53 ± −1.06, ABG group: −2.53 ± −1.63).
Shah et al.[33]	Split-mouth RCT	20 Patients with paired PID	3000 rpm for 10 min	OFD + L-PRF	OFD + DFDBA	Clinical evaluation	6 Months	There were no significant differences between the groups (The mean reduction in PD: PRF group: 3.67 ± 1.48 mm, DFDBA group: 3.70 ± 1.78 mm. Gain in RAL: PRF group: 2.97 ± 1.42 mm, DFDBA group: 2.97 ± 1.54 mm, Gingival margin migrated apically: PRF group: 0.43 ± 1.31 mm, DFDBA group: 0.72 ± 2.3 mm).
Gupta et al.[28]	RCT	44, PID with CP	3000 rpm for 12 min	L-PRF + OFD	EMD + OFD	Clinical and CBCT	6 Months	Only defect resolution was significantly higher in EMD group. (43.07 ± 12.21% vs. 32.41 ± %14.61).
Bansal et al.[52]	Split-mouth RCT	10 Patients with paired PID	3000 rpm for 10 min	DFDBA + L-PRF + OFD	DFDBA + OFD	Clinical and radiographic evaluation	6 Months	PD reduction and CAL gain of the study group (4.0 ± 0.816 and 3.4 ± 0.606 mm) were significantly better than the control group (3.1 ± 0.738 and 2.3 ± 0.699 mm).

(*Continued*)

Table 2. **Review of published clinical trials evaluated the application of PRF concentrate on intrabony defects—Continued**

Authors (year)	Study design	Study size, defect type	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Pradeep et al.[31]	CT	90, PID	3000 rpm (about 400 g) for 10 min	L-PRF + OFD	PRP + OFD, OFD	Clinical and radiographic evaluation	9 Months	Clinical and radiographic outcomes of L-PRF and PRP treated groups was significantly better than the control group (Mean PD reduction and CAL gain: PRF: 3.77 ± 1.19 and 3.17 ± 1.29 mm, PRP: 3.77 ± 1.07 and 2.93 ± 1.08 mm, control group: 2.97 ± 0.93 and 2.83 ± 0.91 mm. Percentage of mean bone fill: PRF: 55.41 ± 11.39%, PRP: 56.85 ± 14.01%, control group: 1.56 ± 15.12%).
Lekovic et al.[41]	Split-mouth RCT	17 Patients with paired PID	1000 g for 10 min	L-PRF + BPBM + OFD	L-PRF + OFD (control)	Clinical and radiographic evaluation	6 Months	Clinical and radiographic outcomes of study groups were significantly better than the control group (Reduction in pocket depth: PRF-BPBM: 4.47 ± 0.78 mm on buccal and 4.29 ± 0.82 mm on lingual sites. PRF: 3.35 ± 0.68 mm on buccal and 3.24 ± 0.73 mm on lingual sites. CAL gain: PRF-BPBM: 3.82 ± 0.78 mm on buccal and 3.71 ± 0.75 mm on lingual sites. PRF: 2.24 ± 0.73 mm on buccal and 2.12 ± 0.68 mm on lingual sites. Defect fill: PRF-BPBM: 4.06 ± 0.87 mm on buccal and 3.94 ± 0.73 mm on lino gual sites, PRF: 0.21 ± 0.68 mm on buccal and 2.06 ± 0.64 mm on lingual sites).
Thorat et al.[36]	CT	32, PID	400 g for 12 min	L-PRF + OFD	OFD	Clinical and radiographic evaluation	9 Months	Mean PD reductions, CAL gain and bone fill of L-PRF groups (4.56 ± 0.37, 3.69 ± 0.44 mm, and 46.92%) was significantly better than the control group (3.56 ± 0.27, 2.13 ± 0.43 mm, and 28.66%).
Sharma et al.[34]	RCT	56, PID	3000 rpm (about 400 g) for 10 min	L-PRF + OFD	OFD	Clinical and radiographic evaluation	9 Months	Radiographic outcomes (bone fill) of L-PRF treated groups was significantly better than the control group (48.26 ± 5.72% vs. 1.80 ± 1.56%).

RCT: randomized clinical trial, CT: clinical trial, PID: periodontal intrabony defect, LAP: localized aggressive periodontitis, DFDBA: demineralized freeze-dried bone allograft, OFD: open flap debridement, NcHA: nanocrystaline hydroxyapatite, ABG: autogenous bone grafting, EMD: enamel matrix derivative, BPBM: bovine porous bone mineral, DBM: demineralized bone matrix, RSV: rosuvastatin, ALN: alendronate, ATV: atorvastatin, GTR: guided tissue regeneration, HA: hydroxyapatite, MFO: modified flap operation, MPPG: marginal periosteal pedicle graft.

months. All the studies evaluated the treatment outcomes through clinical improvement including periodontal pocket depth (PPD) reductions and clinical attachment loss (CAL) gains. Most of them also did the radiographic assessment for further evaluations (Table 2).

Most of the studies showed that the application of PRF improved treatment outcomes at least in one measured parameter (Table 2). Only, Ajwani et al.[24] reported that additional use of L-PRF did not lead to improving the treatment outcome in comparison with open flap debridement (OFD) alone. Moreover, Shah et al.[33] and Chadwick et al.[26] compared the effect of PRF in combination with OFD versus DFDBA in combination with OFD. In both studies, no advantages were observed by both treatment approaches. Also, Mathur et al.[29] and Galav et al.[27] showed that PRF has no advantage in comparison with autogenous bone graft (ABG). Only Thorat et al.[35] selected patients with aggressive periodontitis. They reported that the additional use of PRF in comparison to Kirkland flap alone improved both clinical and radiographic outcomes.

PRF Application in the Ridge Preservation

A total of 17 clinical trials used PRF approach for the ridge preservation (Table 3). PRF concentrates were used solely[53–65] or in combination with plaster of paris[66] and DFDBA.[67] Only one study used advanced platelet-rich fibrin (A-PRF) in addition to FDBA for ridge preservation.[68] The follow-up period was varied from 1 week to 6 months. Unlike intrabony defects, various methods including scintigraphic evaluation,[54,57] serial radio visio-graphic analysis,[56] and histomorphometric evaluation[65,68] were used to evaluate the treatment outcome other than clinical and radiographic assessment.

In all the studies with radiographic evaluation, improvement in the bone filling was observed in the ridge preserved by PRF concentrates. In case of the additional application of PRF concentrates in the socket when compared with not using any intervention, the results were controversial. In this case, approximately half of the clinical trials shows the advantage of using PRF.[53,59,62,63,65] Thakkar et al.[67] showed that using additional PRF besides DFDBA enhanced ridge preservation process in comparison to DFDBA alone. Furthermore, the effectiveness of PRF when compared with beta-tri-calcium phosphate with collagen was observed in Das et al.[55] study. In the case of A-PRF, Clark et al.[68] showed the supplemental use of A-PRF for the ridge preservation in combination with FDBA did not lead to better results.

Sinus Floor Augmentation

Similarly, PRF concentrates has been evaluated in seven clinical trials with the aim of the sinus floor augmentation (Table 4). Six studies utilized supplemental L-PRF besides Bio-Oss[20,70–73] or NanoBone[74] in a two-stage method for sinus augmentation. Only Kanayama et al.[75] used sole L-PRF in the crestal approach of sinus floor elevation. The measured outcomes and follow up periods were varied among the selected studies.

Most of the measured outcomes in the included clinical trials showed the additional application of L-PRF has no additional benefit compared with the bone graft alone. Tatullo et al.[73] reported that supplemental L-PRF can reduce the healing time. Furthermore, in the Bolukbasi et al.'s study,[70] less change in the bone length/the implant length ratio was observed in the L-PRF treated patients. Kanayama et al.[75] reported that L-PRF only approach led to from 4.00 ± 1.63% to 4.38 ± 1.67% bone gain in the sandblasted acid-etched implants and the hydroxyapatite implants respectively.

Endo-periodontal Defects

In the case of endo-periodontal lesions, only two clinical trials included in the present systematic review (Table 5). Dhiman et al.[76] found that the application of L-PRF in apicomarginal lesions can improve the clinical outcomes. Moreover, the complete bone filling was observed in the L-PRF treated patients in the Singh et al.'s study.[77]

Management of Furcation Defects

Eight clinical trials were aimed at evaluating the bone regeneration in grade II mandibular furcation involvement (Table 6). Three studies evaluated the treatment outcomes of L-PRF besides OFD compared with OFD alone.[22,78,79] In four studies, L-PRF was applied mixed with other materials including metformin gel,[80] bioactive ceramic composite granules (BCCG),[81] rosuvastatin,[82] hydroxyapatite (HA),[82] and alendronate.[83] Asimuddin et al.[84] compared the effect of PRF alone with allograft and healiguide collagen membrane. All the studies did clinical and radiographic assessments to evaluate the treatment outcomes. The follow-up period was from 6 to 9 months (Table 5).

Bajaj et al.[78] and Sharma et al.[22] reported that the application of L-PRF in addition to OFD improved the bone regeneration defects in grade II mandibular furcation involvement. Siddiqui et al.[79] suggested that using β-tricalcium phosphate (β-TCP) lead to better treatment outcomes when compared with PRF. It was shown that when PRF applied mixed with rosuvastatin and HA,[82] alendronate,[83] and metformin,[80] the treatment outcome improved when compared with PRF alone. Furthermore, Lohi et al.[81] reported that supplemental use of PRF besides BCCG led to significant improvements in all measured parameters.

Coverage of Gingival Recessions

In case of gingival recessions, 16 articles using PRF concentrates were met the requirements for inclusion in the present systematic review. The included clinical trials used PRF for root coverage of patients with class I or II Miller gingival recession (Table 7). Six studies evaluated the clinical outcomes of additional PRF to coronally advanced flap (CAF),[85–88] modified CAF (MCAF),[21] and lateral sliding bridge flap[89] compared with flap sole approach. Culhaoglu et al.[90] compared the effect of two- and four-layers PRF in root coverage procedure. Other studies compared the outcomes of using supplemental PRF in gingival recession with other supplemental approaches including connective tissue graft (CTG),[90–94] subepithelial CTG (SCTG),[95,96] enamel matrix derivative,[97] amniotic membrane,[98] and resin-modified glass ionomer cement.[99] All studies assessed clinical parameters in their follow-up periods. The follow-up period was varied from 1[21,87,90] to 24 months.[89]

Except for Padma et al.[87] when the application of PRF was compared with flap alone, no additional benefit by PRF was observed in the treatment outcomes.[21,85,86,88,89] In two studies conducted by Eren et al.,[95] and Öncü[96] the use of PRF did not lead to a significant improvement in clinical parameters when compared with SCTG. Agarwal et al.[98] reported a significant advantage of PRF compared with the amniotic membrane in case of root coverage percentage. In studies comparing PRF to CTG, the outcomes were controversial. Only Mufti et al.[93]

Table 3 **Review of published clinical trials evaluated the application of PRF concentrate on ridge preservation**

Authors (year)	Study design	Site (patient)	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				Test	CTR			
Clark et al.[68]	RCT	40 Non-molar teeth	1300 rpm (200 g) for 8 min	A-PRF + FDBA	A-PRF, FDBA, blood clot (control)	micro-CT and histomorphometric analysis	15 Weeks	More bone density (551 ± 58 mg/cm^3 vs. 487 ± 64 mg/cm^3), more vital bone (46 ± 18% vs. 29 ± 14% and less loss of ridge height (1.8 ± 2.1 mm vs. 1.0 ± 2.3 mm) was present in the A-PRF group compared with the FDBA group and more bone mineral density was observed in the FDBA group compared with control significantly.
Zhang et al.[65]	CT	28 Molar	400 g for 10 min	PRF	No intervention	Radiographic and histomorphometric evaluation	7 Days, 1 and 3 months	The histomorphometric evaluation (the osteoid area/tissue area) shows significant bone formation (9.7624 ± 4.0121%) in PRF group in comparison to control (2.8056 ± 1.2094%).
Girish Kumar et al.[66]	RCT	90 Sockets in 48 patients	3000 rpm for 10 min	PRF + Plaster of paris	No intervention and PRF	Clinical and radiographic evaluation	6 Months	There were no significant differences between groups (Alveolar height loss: POP–PRF: 2.8 ± 0.46, PRF: 3 ± 0.8, Control: 3.3 ± 0.61; Alveolar width loss: POP–PRF: 2.9 ± 0.8, PRF: 3 ± 0.64, Control: 3 ± 0.83; Bone fill: POP–PRF: 10.1 ± 2.9, PRF: 9.83 ± 2.24, Control: 7.9 ± 1.5).
Alzahrani et al.[53]	RCT	24 Sockets	3000 rpm (about 400 g) for 10 min	PRF	No intervention	Clinical and radiographic evaluation	1, 4 and 8 Weeks	Significant improvement was observed the test group compared with the control group in case of ridge width proportions (11.33 ± 2.30 mm vs. 12.04 ± 2.50 at week 4 and 10.97 ± 2.33 mm vs. 11.54 ± 2.42 at week 8) and radiographic bone fill percentage (74.05 ± 1.66% vs. 68.82 ± 1.07% at week 1, 81.54 ± 3.33% vs. 74.03 ± 2.61 at week 4 and 88.81 ± 1.53% vs. 80.34 ± 2.61% at week 8).
Thakkar et al.[67]	RCT	36 Sites, single-rooted teeth	3000 rpm for 10 min	PRF + DFDBA	DFDBA	Clinical and radiographic evaluation	3 and 6 Months	There were no significant differences between groups [Ridge width difference (from baseline to 180 days): DFDBA: 1.3611 ± 0.70305 mm, DFDBA-PRF: 0.75 ± 0.493 mm. Ridge height difference (from baseline to 180 days): DFDBA: −1.3889 ± 0.50163 mm, DFDBA–PRF: −1.0833 ± 0.42875 mm].
Temmerman et al.[63]	Split-mouth RCT	22 Sockets	2700 rpm for 10 min	L-PRF	No intervention	Clinical and radiographic (CBCT) evaluation	3 Months	Significant differences were observed in case of all evaluated parameters with the advantage of L-PRF group (Mean vertical height changes at the buccal were −1.5 ± 1.3 mm for control sites vs. 0.5 ± 2.3 mm for test sites ($P < 0.005$). At the buccal side, control sites values were −2.1 ± 2.5, −0.3 ± 0.3 ($P < 0.005$) and −0.1 ± 0.0 mm, and test sites values were −0.6 ± 2.2 ($P < 0.005$), −0.1 ± 0.3, and 0.0 ± 0.1 mm. Significant differences were found for total width reduction between test (−22.84%) and control sites (−51.92%) at 1 mm below crest level.).

Table 3 **Review of published clinical trials evaluated the application of PRF concentrate on ridge preservation—Continued**

Authors (year)	Study design	Site (patient)	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				Test	CTR			
Kumar et al.[58]	RCT	31 Mandibular molars	3000 rpm for 10 min	L-PRF	No intervention	Clinical and radiographic evaluation	1 and 3 Months	Significantly mean pocket depth reduction was observed in both groups. There were no significant differences between groups.
Baslarli et al.[54]	Split-mouth CT	40 Mandibular molars	3000 rpm for 10 min	L-PRF	No intervention	Scintigraphic evaluation	1 and 3 Months	There were no significant differences between groups in case of technetium-99m methylene diphosphonate uptake (L-PRF 4.1 ± 1.0 vs. control 3.9 ± 1.1).
Yelamali et al.[64]	Split mouth RCT	20 Patients with bilateral impacted third molar	3000 rpm for 10 min	L-PRF	PRP	Clinical evaluation	4 Months	Significant differences were observed in case of soft tissue healing with the advantage of L-PRF group.
Marenzi et al.[59]	Split mouth RCT	26 Patients with extracted	2700 rpm for 12 min	L-PRF	No intervention	Clinical evaluation	7 Days	Significant differences were observed in case of healing and post-operative pain with the advantage of L-PRF group.
Girish Rao et al.[56]	CT	44 Third mandibular molars	360–400 rpm for 20 min	L-PRF	No intervention	Serial radio visio-graphic analysis	1 Day and 1, 3 and 6 months	The mean pixels recorded was not significantly different between groups.
Suttapreya-sri et al.[62]	Split-mouth CT	20 Premolars	3000 rpm for 10 min	L-PRF	No intervention	Clinical evaluation	1 Week	Horizontal resorption buccal aspect was significantly lower in PRF treated group (L-PRF group: 1.9 ± 1.1 mm vs. 2.6 ± 0.7 mm). PRF had faster bone healing than control (Not significant).
Hauser et al.[69]	RCT	23 Premolars	2700 rpm for 12 min	L-PRF, L-PRF + mucosal flap	No intervention	Micro-CT and histologic evaluation	8 Weeks	A significant difference in case of intrinsic bone quality seen preservation of the alveolar width was seen using PRF and. L-PRF + flap in comparison to control group (Bone volume/total volume for PRF: 0.281 ± 0.037, PRF + flap: 0.197 ± 0.027, and control: 0.249 ± 0.037).
Singh et al.[61]	CT	40 Third mandibular molars	3000 rpm for 10 min	L-PRF	No intervention	Clinical and radiographic evaluation	12 Weeks	The trabecular bone formation was seen in all of both groups, there were no significant differences between groups. (gray scale value for L-PRF: 146.9 and for control: 123).
Simon et al.[50]	CT	Six Molars and 15 premolars	1450 g for 15 min	L-PRF	No intervention	Clinical and radiographic evaluation	4 Months	There were no significant differences between groups [Mean width resorption for L-PRF: 0.32 mm (4.71%) and control: 0.57 mm (7.38%)].
Gurbuzer et al.[57]	RCT	14 Patients with bilaterally soft tissue impacted 3rd mandibular molars	2030 rpm (400 g) for 10 min	PRF	No intervention	Scintigraphic evaluation	4 Weeks	There were no significant differences between groups in case of technetium-99m methylene diphosphonate uptake (L-PRF 4.5 ± 1.0 vs. control 4.6 ± 1.0).

RCT: randomized clinical trial, CT: clinical trial, DFDBA: demineralized freeze-dried bone allograft, β-TCP-CI: beta-tri-calcium phosphate with collagen, FDBA: freeze-dried bone allograft.

Table 4 **Review of published clinical trials evaluated the application of PRF concentrate on sinus augmentation**

Authors (year)	Study design	Site (patient)	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Nizam et al.[72]	RCT split mouth	13, 26, 58	400 g for 12 min	T: Bio-Oss® + L-PRF two-stage (lateral)	C: Bio-Oss®	Radiographic and HA	6 Months	T: FBH 13.60 ± 1.09, C: FBH 13.53 ± 1.20. T: NBF 21.38 ± 8.78%; RGM 25.95 ± 9.54%; Bone-to-bone substitute contact 47.33 ± 12.33%; CT 52.67 ± 12.53%, C: NBF 21.25 ± 5.59%; RGM 32.79 ± 5.89%. Bone-to-bone substitute contact 54.04 ± 8.36%; CT 45.96 ± 8.36%, implant SR (18 months): 100%.
Bolukbasi et al.[70]	RCT parallel	25, 32, 66	400 g for 12 min	T: Bio-Oss® + L-PRF two-stage (lateral)	C: Bio-Oss® + RCM	Radiographic and HA	6 Months	T: NBF 35.0 ± 8.60%: RGM 33.05 ± 6.29%; CT 30.63 ± 7.53%. C: NBF 32.97 ± 9.71%; RGM 33.79 ± 8.57%; CT 33.94 ± 9.15%. The differences between groups were not statistically significant. T: 10 days after sinus lifting: GSH/OSH 4.26; 10 days after implant placement: BL/IL 1.43, GSH/OSH 4.78; 6 months after implant placement: BL/IL 1.38, GSH/OSH 4.78; 6 months after loading: BL/IL 1.37, GSH/OSH 4.39; 12 months after loading: BL/IL 1.32, GSH/OSH 4.39; 24 months after loading: BL/IL 1.30, GSH/OSH 4.36. C: 10 days after sinus lifting: GSH/OSH 4.2; 10 days after implant placement: BL/IL 1.46, GSH/OSH 4.55; 6 months after implant placement: BL/IL 1.43, GSH/OSH 4.52; 6 months after loading: BL/IL 1.37, GSH/OSH 4.09; 12 months after loading: BL/IL 1.29, GSH/OSH 3.81; 24 months after loading: BL/IL 1.23, GSH/OSH 3.67. T showed statistically less change in the BL/IL ratio. The difference of GSH/OSH ratio was insignificant between groups. Implant SR (30 months): 100%.
Kanayama et al.[75]	CT	27, -, 39	400 g for 10 min	Only L-PRF one-stage (osteotome)	None	Bone gain (Radiographic)	12 Months	The mean bone gains: in the sandblasted acid-etched implants 4.38 ± 1.67 and in the hydroxyapatite implants 4.00 ± 1.63 mm.
Bosshardt et al.[74]	RCT parallel	12, 16, 16	Not mentioned	T: NanoBone + L-PRF (two-stage)	C: NanoBone + RCM	Radiographic and HA	7–11 Months	T: NBF 28.6 ± 6.90%; RGM 25.7 ± 8.8%. C: NBF 28.7 ± 5.4; RGM 25.5 ± 7.6. Implant SR (12 weeks): 100%.
Gassling et al.[71]	RCT Split-mouth	6, 12, 32	400 g for 12 min	T: Bio-Oss® + ABG + L-PRF membrane two-stage (lateral)	C: Bio-Oss® + ABG + RCM (Bio-Gide®)	Radiographic and HA	5 Months	T: NBF 17%; RGM 15.9%. C: NBF 17.2%; RGM 17.3%. The differences between groups were not statistically significant. Implant SR (12 months): 100%.
Zhang et al.[20]	RCT parallel	10, 11, -	300 g for 10 min	T: Bio-Oss® + L-PRF two-stage (lateral)	C: Bio-Oss®	HA	6 Months	T: NBF 18.35 ± 5.62% (1.4 times of that in control); RGM 19.16% ± 6.89% (1.5 times lesser than that in control); Bone-to-bone substitute contact 21.45 ± 14.57%. C: NBF 12.95 ± 5.33%; RGM 28.54 ± 12.01%; Bone-to-bone substitute contact 18.57 ± 5.39%. The differences between groups were not statistically significant.

Table 4 **Review of published clinical trials evaluated the application of PRF concentrate on sinus augmentation**

Authors (year)	Study design	Site (patient)	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
Tatullo et al.[73]	RCT parallel	60, 72, 240	3000 rpm for 10 min	T: Bio-Oss® + L-PRF two-stage (lateral)	C: Bio-Oss®	Radiographic and HA	106, 120, 150 Days	T: after 106 days: trabecular bone 22.79%, osteoid tissue 7.01%, medullary spaces 70.2%; after 120 days: trabecular bone 26.15%, osteoid tissue 3.84%, medullary spaces 70.1%; after 150 days: trabecular bone 37.06%, osteoid tissue 3.53%, medullary spaces 61.41. C: after 106 days: trabecular bone 26.44%, osteoid tissue 5.12%, medullary spaces 68.44%; after 120 days: trabecular bone 28.7%, osteoid tissue 3.12%, medullary spaces 68.18%; after 150 days: trabecular bone 38.97%, osteoid tissue 2.88%, medullary spaces 58.15%. ISQ values: after 106 days: 37.2 ± 4.2; after 120 days: 36.8 ± 6.1; after 150 days: 39.1 ± 9.0. The differences between groups were not statistically significant. L-PRF reduced the healing time. Implant SR: 100%.

RCT: randomized clinical trial, CT: clinical trial, HA: histomorphometric analysis, ABG: autologous bone graft, CT scan: computed tomographic scan, RCM: resorbable collagen membrane, GSH/OSH: the grafted and the original sinus height ratio, NBF: new bone formation, RGM: residual graft material.

Table 5 **Review of published clinical trials evaluated the application of PRF concentrate on endo-periodontal lesion**

Authors (year)	Study design	Site (patient)	PRF preparation protocol	intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Dhiman et al.[76]	RCT	30, Apicomarginal lesions	3000 rpm for 10 min	L-PRF	-	Clinical and radiographic evaluation	12 Months	The statistically significant difference in L-PRF group with the control group was observed in case of PDR (8 ± 0.92 mm vs. 7.27 ± 0.96 mm). In case of CAL (7±0.92 mm vs. 6.6 ± 1.18 mm) and SPLR (93.41 ± 7.00 vs. 94.57 ± 5.87) no significant differences were observed.
Singh et al.[77]	CT	15, Peri-apical lesions	3000 rpm for 10 min	L-PRF	-	Clinical and radiographic evaluation	6 Months	Complete bone regeneration was observed in the L-PRF treated patients.

RCT: randomized clinical trial, CT: clinical trial, CAL: clinical attachment loss.

Table 6 **Review of published clinical trials evaluated the application of PRF concentrate on furcation defects**

Authors (year)	Study design	Sample size, site	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Sharma et al.[80]	RCT	30, Furcation involvement (degree II) of mandibular molars	3000 rpm for 10 min	OFD + PRF + 1% metformin gel	OFD + PRF	Clinical and radiographic evaluation	6 Months	Clinical parameters (PD reduction, RVAL and RHAL gain) showed statistically significant improvement at OFD + PRF + 1% metformin groups when compared with control group.
Asimuddin et al.[84]	RCT	22, Furcation involvement (degree II) of mandibular molars	3000 rpm for 10 min	PRF	Allograft + Healiguide collagen membrane	Clinical and radiographic evaluation	9 Months	There were no significant differences in most of the evaluated parameters. The RVCAL at baseline was 12.03 ± 1.04 and at nine months after surgery was 8.42 ± 0.97 in group A, the radiographic linear bone fill (RVGBF) at baseline was 13.0 ± 0.89 in group A and at 9 months after surgery was 9.91 ± 0.54. Intergroup comparison showed statistically significant difference of RVCAL and RVGBF in relation to PRF group (Group A) when compared with allograft + GTR group (Group B), 9 months post-surgery.
Lohi et al.[81]	RCT	20, Furcation involvement (degree II) of mandibular molars	3000 rpm (about 400 g) for 10 min	PRF + Bioactive ceramic composite granules	Bioactive ceramic composite granules	Clinical and radiographic evaluation	6 Months	Significant improvement was observed in the test group compared with the control group in all the measured parameters (The mean PPD reduction of 3.38 ± 1.06 mm and mean clinical attachment gain of 3.00 ± 0.93 mm, mean reduction in VDF 1.38 ± 0.52 mm and in BP-H 2.00 ± 0.76 mm in compares with a mean reduction in VDF of 0.60 ± 0.70 mm and BP-H of 1.10 ± 0.88 mm in control group, Mean percent horizontal and vertical defect fill in the test group was 47.06% and 40.68% when compared with 24.44% and 20% in control group, mean increase in radiographic bone density after 6 months follow-up was 20.08 ± 19.53 gray levels in test group and in the control group 5.26 ± 5.94 gray levels).
Kanoriya et al.[83]	RCT	32, Furcation involvement (degree II) of mandibular molars	3000 rpm (about 400 g) for 10 min	Access therapy with PRF and 1% ALN (1)	Access therapy alone (2), access therapy with PRF (3)	Clinical and radiographic evaluation	9 Months	Group 3 sites showed a significantly greater percentage of radiographic defect fill (56.01 ± 2.64%) when compared with group 2 (49.43 ± 3.70%) and group 1 (10.25 ± 3.66%) at 9 months.
Pradeep et al.[82]	RCT	105, Furcation involvement (degree II) of mandibular molars	3000 rpm (about 400 g) for 10 min	1.2 mg RSV gel + PRF + HA with OFD (1)	OFD + placebo gel (2), PRF + HA with OFD (3)	Clinical and radiographic evaluation	9 Months	Mean PD reduction was greater in group 2 (3.68 ± 1.07 mm) and group 3 (4.62 ± 1.03 mm) than group 1 (2.11 ± 1.25 mm), and mean rvCAL and rhCAL gain were greater in group 2 (3.31 ± 0.52 and 2.97 ± 0.56 mm, respectively) and group 3 (4.17 ± 0.70 and 4.05 ± 0.76 mm) compared with group 1 (1.82 ± 0.78 and 1.62 ± 0.64 mm). A significantly greater percentage of mean bone fill was found in group 2 (54.69 ± 1.93%) and group 3 (61.94 ± 3.54%) compared with group 1 (10.09% ± 4.28%).

Table 6 **Review of published clinical trials evaluated the application of PRF concentrate on furcation defects—Continued**

Authors (year)	Study design	Sample size, site	PRF preparation protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Bajaj et al.[78]	RCT	72, Buccal furcation (degree II) of mandibular molars	About 400 g for 10 min	L-PRF + OFD	PRP + OFD, OFD	Clinical and radiographic evaluation	9 Months	Relative vertical clinical attachment level gain was also greater in PRF (2.87 ± 0.85 mm) and PRP (2.71 ± 1.04 mm) sites as compared with control site (1.37 ± 0.58 mm).
Sharma et al.[22]	RCT	36, Buccal Furcation (degree II) of mandibular molars	3000 rpm (about 400 g) for 10 min	L-PRF + OFD	OFD	Clinical and radiographic evaluation	9 Months	Relative vertical clinical attachment level gain was greater in PRF (2.87 ± 0.85 mm) and PRP (2.71 ± 1.04 mm) sites as compared with control site (1.37 ± 0.58 mm).

RCT: randomized clinical trial, DFDBA: demineralized freeze-dried bone allograft, OFD: open flap debridement, RSV: rosuvastatin, ALN: alendronate, HA: hydroxyapatite, β-TCP: beta-tri-calcium phosphate, PD: probing depth, RVAL: relative vertical attachment level, RHAL: relative horizontal attachment level.

Table 7. **Review of published clinical trials evaluated the application of PRF concentrate on gingival recession**

Authors (year)	Study design	Site (patient)	PRF Preparation Protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Ramireddy et al.[99]	RCT	20 Patients with Miller Class I or II (78 defects)	2700 rpm for 12 min	PRF + CAF	CAF + RmGIC	Clinical evaluation	3 and 6 Months	Both the groups showed optimal root coverage. In case of KTT, PRF group shows significant advantages (2.95 ± 0.18 mm vs. 2.19 ± 0.12 mm), in case of Dentin Sensitivity, RmGIC was significantly lower (83% of sites without sensitivity vs. 46%).
Culhaoglu et al.[90]	RCT	63 Patients with Miller Class I	2700 rpm for 12 min	Two layers PRF + CAF (I) and four layers PRF + CAF (II)	Connective tissue graft (CTG) + CAF	Clinical evaluation	1, 3, and 6 Months	In case of KTT, control group shows significant advantages (2.35 ± 1.02 mm vs. 1.86 ± 0.49 mm for test I and 1.78 ± 0.42 mm for test II). In case of root coverage scores, test I group score was significantly lower (56.34 ± 14.51 vs. 80.13 ± 18.93 for control and 69.65 ± 15.28 for test II).

(*Continued*)

Table 7. **Review of published clinical trials evaluated the application of PRF concentrate on gingival recession**

Authors (year)	Study design	Site (patient)	PRF Preparation Protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Mufti et al.[93]	RCT	32 Patients with Miller class I	3000 rpm for 10 min	CAF + PRF	CAF + CTG	Clinical evaluation	6 Months	In the test group, significant improvement was seen in all parameters from baseline to 6 months (unlike control). Moreover, in some parameters (KTT, CAL), PRF group shows significant advantages. (KTT mean rank: CAF + PRF: 13.34, CAF + CTG: 19.66, CAL mean rank: CAF + PRF: 10.28, CAF + CTG: 22.72).
Agarwal et al.[98]	Split-mouth RCT	30 Patients with Miller class I or II	Not mentioned	CAF + PRF	CAF, CAF + amniotic membrane	Clinical evaluation	3 and 6 Months	The percentage of root coverage was 56% for the CAF + PRF group, 36% for the CAF + amniotic membrane group and 33% for the CAF group ($P < 0.05$).
Keceli et al.[92]	Split-mouth RCT	40 Patients with Miller class I or II	Not mentioned	CAF+ connective tissue graft + PRF	CAF + CTG	Clinical evaluation	3 and 6 Months	The percentage of root coverage was 79.9% for the control group and 89.6% for the test group ($P < 0.05$).
Tunaliota et al.[94]	Split-mouth RCT	22 Patients with Miller class I or II	2700 rpm for 12 min	CAF + PRF	CAF + CTG	Clinical evaluation	12 Months	The percentage of root coverage was 77.4% for the control group and 76.6% for the test group (no significant differences).
Thamaraiselvan et al.[88]	Split-mouth RCT	20 Patients with Miller class I or II	3000 rpm for 10 min	CAF + PRF	CAF	Clinical evaluation	3 and 6 Months	The percentage of root coverage was 65% for the control group and 74.2% for the test group (no significant differences).
Gupta et al.[86]	Split-mouth RCT	26 Patients with Miller class I or II	2700 rpm for 12 min	CAF + PRF	CAF	Clinical evaluation	3 and 6 Months	The percentage of root coverage was 86.6% for the control group and 91% for the test group (no significant differences).
Bozkurt Doğan et al.[85]	Split-mouth RCT	20 Patients with Miller class I or II	Acceleration for 30 s, 2700 rpm for 2 min, 2400 rpm for 4 min, 2700 rpm for 4 min, 3000 rpm for 7 min, and deceleration for 36 s	CAF + PRF	CAF	Clinical evaluation	6 Months	The percentage of root coverage was 82.1% for the control group and 86.7% for the test group (no significant differences).
Rajaram et al.[89]	Split-mouth RCT	20 Patients with Miller class II	2700 rpm for 12 min	PRF + lateral sliding bridge flap	Lateral sliding bridge flap	Clinical evaluation	12 and 24 Months	The percentage of root coverage was 80% for the control group and 78.8% for the test group (no significant differences).
Eren et al.[95]	Split-mouth RCT	22 Patients with Miller class I or II	400 g for 12 min	PRF + CAF	CAF + SCTG	Clinical evaluation	6 Months	The percentage of root coverage was 94.2% for the control group and 92.7% for the test group (no significant differences).
Padma et al.[87]	Split-mouth RCT	15 Patients with Miller class I or II	3000 rpm for 10 min	CAF + PRF	CAF	Clinical evaluation	1, 3, and 6 Months	Full root coverage obtained in study groups (100%). The root coverage percentage in the study group was significantly higher than the control group (68/4%) ($P < 0.0001$).

Table 7. **Review of published clinical trials evaluated the application of PRF concentrate on gingival recession—Continued**

Authors (year)	Study design	Site (patient)	PRF Preparation Protocol	Intervention		Variable outcome	Follow-up period	Result
				PRF groups	Control			
Jankovic et al.[97]	Split-mouth RCT	20 Patients with Miller class I or II	3000 rpm (about 400 g) for 10 min	CAF + PRF	CAF + EMD	Clinical evaluation	12 Months	The percentage of root coverage was 70.5% for the control group and 72.1% for the test group (no significant differences).
Aroca et al.[21]	Split-mouth RCT	20 Patients with Miller class I or II	3000 rpm for 10 min	PRF + MCAF	MCAF	Clinical evaluation	1, 3, and 6 months	The percentage of root coverage was 91.5% for the control group and 80.7% for the test group ($P < 0.004$).

RCT: randomized clinical trial, CAF: coronally advanced flap, MCAF: modified coronally advanced flap, SCTG: subepithelial connective tissue graft, CTG: connective tissue graft, RmGIC: resin modified glass inomer cement, EMD: enamel matrix derivative, KTW: keratinized tissue width, KTT: keratinized tissue thickness, CAL: clinical attachment loss.

reported advantages of PRF in some measured parameters (root coverage percentage and CAL, respectively).

Discussion

Choukroun's[6] PRF is a second-generation platelet concentrate that contains a vast amount of cytokines and growth factors within an autologous dense fibrin matrix rich in platelets. PRF is used as a surgical additive to accelerate healing and regeneration processes.[100] Due to its advantages, PRF have recently gained much attention among researchers as a safe approach in various procedures solely or in combination with other treatment approaches including the regeneration of soft and hard tissue defects of periodontium,[21,38,101] maxillary sinus-lift procedures,[102,103] wound healing[104,105] and facial reconstruction plastic surgery.[19] The present systematic review aimed to assess the current evidenced in regards to the clinical benefit of PRF concentrates in the regenerative procedures of soft and hard tissue intra-oral defects. Application of PRF was performed either solely or in combination with other regenerative materials in intra-oral defects. The evaluated clinical trials were categorized according to the types of defects including intrabony defects, sockets preservation, sinus floor augmentation, endo-periodontal defects, furcation defects, gingival recessions. In each included study, the type of used concentrate, study groups, defect location, sample size, follow-up periods, evaluation method, and treatment outcome were reported. As mentioned before, due to the application of various types of PRF concentrates on different kinds of defects, conducting the meta-analyze was not possible in the current systematic review.

Biochemical analysis of the PRF concentrate structure showed that it consists of platelets, leukocyte, and cytokines; and circulating hematopoietic precursor cells within a fibrin 3D network polymerized in a tetra molecular structure.[106] There are various components and growth factors in PRF including fibrin, fibronectin, PDGF, and TGF-β that all are important in the tissue healing and regeneration process.[106,107] It is also found that using PRF can lead to an increase in leukocyte degranulation and cytokine release of pro-inflammatory mediators including IL-1β and IL-6 as well as anti-inflammatory cytokines, such as IL-4. Furthermore, the dense fibrin scaffold of PRF leads to a slow release of cytokines and glycoproteins (such as thrombospondin-1) in the first 7 days in the site.[5,9] With all these features, it has been shown in the literature that PRF can play an important role through its growth factors in modulating the healing and regeneration procedures by inducing the proliferation and recruitment of endothelial cells, gingival fibroblast, chondrocytes, and osteoblasts.[108,109] However, recent studies addressed a new aspect in evaluating the effect of PRF on different regenerative approaches. In this case, the influence of the applied relative centrifugal force (RCF) during the centrifugation of PRF on its composition and bioactivity was investigated. Interestingly, different *in vitro* and *in vivo* preclinical studies proved that the value of the applied RCF has an enormous influence on PRF bioactivity.[110–113] Therefore, a high RCF was shown to produce a PRF matrix with significantly lower number of platelets and leukocytes and a significantly lower concentrations of different growth factors. Not only the composition and bioactivity were influenced by the applied RCF, but also its function. Recent preclinical studies have shown that PRF that was prepared

with low RCF induced significantly higher rate of vascularization *in vitro* and *in vivo* compared with a PRF matrix that was prepared using a high RCF.[114,115] Based on these studies, the low speed centrifugation concept (LSCC) was introduced to standardize the centrifugation protocols in the preparation of blood concentrates.[110]

Application of autologous PRF is safe and low-cost methods when compared with using growth factors concentrations in the recombinant form.[7]

In respect to the intrabony defects in consequence of chronic periodontitis, studies showed that using PRF lead to favourable outcomes in case of PPD reductions and CAL gains when compared with the flap only approach.[24,25,30,32,34,36] However, when PRF concentrates compared the other novel treatment approaches additional benefits were observed. Furthermore, application of PRF in combination with DFDBA lead to more PPD reductions and CAL gains. Also, in the case of aggressive periodontitis, only one study was found suggesting that using PRF cause better clinical outcomes.[35] The present study confirmed the outcomes of Miron et al.'s[7] systematic review and Ghanaati et al.[116] that reported the beneficial effect of PRF in the treatment of intrabony defects. In case of using PRF concentrates on accelerating the ridge preservation and dimensional changes following tooth extraction, the results of clinical trials were controversial. Although, it was shown that using PRF besides a bone graft material can result in a better clinical outcome in regards to the reduction of ridge width.[67] The only included clinical trial that applied A-PRF in the present systematic review was Clark et al.'s[68] study that showed using A-PRF besides FDBA has no significant advantages when compared with A-PRF or FDBA alone.

Despite the limited number of clinical trials concerning sinus floor augmentation, when supplemental L-PRF used in addition to bone graft materials, no additional benefits were observed. However, it has been reported that using L-PRF may reduce the healing time[70] and can cause less change in the bone length/the implant length ratio.[75] Regarding endo-periodontal defects, both included studies showed that the use of L-PRF acts as an ideal material by accelerating the bone filling.[76,77] However, since only two studies evaluated the outcomes of PRF concentrates on endo-periodontal lesions, further research is required to support the advantage of PRF application.

Platelet-rich fibrin concentrates showed a significant effect on the improvement of clinical and radiographic parameters when used as an adjunctive treatment or sole treatment for furcation involvement of mandibular molars.[22,78–84] However, when PRF was used as alternative material compared with β-TCP, it showed a significant advantage in PPD reductions, CAL gains and bone filling.[79] In case of the root coverage of Miller class I and II defects, significant enhancement of root coverage procedures was not observed when PRF concentrates were applied. Similar to our study, in a systematic review has been reported that platelet concentrates do not lead to improvement in soft tissue root coverage of gingival recessions.[13] However, it was found that PRF had similar advantages in the treatment of gingival recessions when compared with CTG. In one study, it has been reported that using PRF instead of CTG can lead to significant improvement in higher keratinized tissue and CAL gain.[93] Application of CTG approach showed high patient morbidity and the reaching a desirable treatment outcome is depends on the technical ability of the clinician.[92,93,96] For these reasons, PRF concentrates may be applied for similar indication as the application of CTG, when autologous transplantation is undesired or too complex to be performed.

Other than evaluated defects, PRF concentrates have been utilized with the aim of bone regeneration in various oral and maxillofacial defects including reconstruction of unilateral alveolar cleft,[117] ridge augmentation,[118] cystic bone defect.[119,120] In addition to the regenerative use of PRF, Hoaglin et al.[121] reported that PRF might help wound healing process of extraction sites by the prevention of localized osteitis. Antibacterial effect of PRF is mostly because of the recruitment of white blood cells and macrophages to the site.[7]

All together the present systematic review evaluated the recent advances in the clinical application of PRF in different defects morphologies. At this point, it is noteworthy to outline that many different centrifugation protocols were used throughout the studies showing different results, that were sometimes controversial. Additionally, some studies did not report the specific centrifugation setting they used in their studies, which makes the evaluation of such studies even more difficult. However, this aspect is currently a topic of discussion in the literature. Some researchers and clinicians are keen to provide guidelines on the report of clinical studies when using blood concentrate.[122] The authors strongly encourage to use these guidelines to at least define the type of PRF used in the studies. Additionally, attempt to standardize the preparation protocols according to the previously introduced LSCC are ongoing. This concept was thoroughly investigated and proved in preclinical studies.[113–115] However, randomized controlled clinical studies following this standardization concept are still needed to eventually prove its benefit for the clinical application.

Conclusion

In conclusion, the final treatment outcome utilizing PRF concentrates depends on the treatment strategies and the type of the defect. In case of intrabony defects and furcation involvement, the studies clearly showed that the use of PRF concentrates alone or as a supplement could be helpful. In case of ridge preservation, sinus floor augmentation, and endo-periodontal lesions due to a limited number of evidence or controversial results, further clinical trials are required. Future clinical studies with histological evaluation are needed. Additionally, the clinical applciation of PRF requires more standardization in the preparation protocols of blood concentrated to provide reproducable clinical sucsess.

Conflicts of interest

The authors report no other conflicts of interest related to this study. ■

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