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Review

Clinical effect of platelet rich fibrin in the treatment of periodontal intrabony defects. Systematic review and meta-analysis.

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Abstract: Background: There is currently no gold standard biomaterial for the treatment of periodontal intrabony defects (PIDs). One of the current options is the use of platelet-rich fibrin (PRF). Objective: To determine the clinical effect of PRF in the treatment of PID through a systematic review and meta-analysis. Materials and Methods: A literature search was conducted up to February 2017 in the following biomedical databases: Pubmed, Embase, Scielo, Science Direct, SIGLE, LILACS and in the Cochrane Central Register of Clinical Trials. The selection criteria included: randomized clinical trials published in the last 5 years, reporting clinical effects (probing depth, clinical insertion level or gingival recession), with a follow-up time equal to or greater than 6 months, and sample size larger than or equal to 10 patients reporting the use of PRF as a treatment for PID. The methodological quality of the studies was analyzed using the Cochrane Handbook of Systematic Reviews of Interventions as a reference. Results: The search strategy yielded 20 articles. A reduction in probing depth and an increase in clinical insertion level or a reduction in gingival recession is reported, when using PRF alone or in combination with another biomaterial or substance that stimulates tissue regeneration. Conclusion: The literature suggests that the use of PRF in the treatment of PIDs has a beneficial clinical effect when compared to control treatments.

Keywords: Platelet-rich fibrin; periodontitis; review; meta-analysis.

INTRODUCTION.

Periodontal disease is characterized by clinical attachment loss with subsequent destruction of periodontal tissues.[1-3] If left untreated, the condition will lead to a premature loss of teeth.[2,4] Periodontal treatment aims to eliminate the inflammatory process, prevent the progression of periodontal disease, maintain natural dentition in optimal health and function, and regenerate lost periodontal tissues.[3,5,6] Therapeutic modalities for restoring the diseased periodontium have shown limited potential for good results because they fail to completely regenerate periodontal tissues.[4,5]

One of the consequences of periodontal disease is the appearance of periodontal intrabony defects (PIDs). Several biomaterials, such as autogenous and allogeneic bone grafts, have been used to treat PIDs. However, there is no single graft material to date considered as the gold standard for the treatment of DIP.[3,5,7] The key to regeneration is to stimulate a sequence of curative events that result in the formation of an integrated

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tissue. Such modulators include the use of growth factors (GFs), the application of extracellular matrix proteins and binding factors, and the use of bone morphogenetic proteins.[2,8,9] There is evidence demonstrating the effectiveness of GFs in periodontal regeneration.[2,4,10,11] GFs play a key role in the multiplication and development of vascular endothelial cells, smooth muscle cells and fibroblasts. GFs have multiple effects on cellular remodeling phenomena and modulate the inflammatory reaction in the healing and tissue regeneration processes.[2,3,5,9,12-15]

Platelet-rich fibrin (PRF) as described by Choukroun *et al.,*[16] is a second-generation platelet concentrate containing platelets and GFs in the form of fibrin membranes prepared from the patient's own blood, free of any anticoagulant or other artificial biochemical modifications.[3,6] PRF improves regeneration and wound healing and is superior to other platelet concentrates because of its ease of use and inexpensive preparation method, as no exogenous compounds such as bovine thrombin or calcium chloride are needed. PRF has emerged as one of the most promising regenerative materials in the field of periodontics.[3]

Although some studies have evaluated the effect of PRF in the treatment of PID, the diverse nature among them makes it difficult to obtain clear interpretations. The aim of this article was to evaluate the clinical effect of PRF in the treatment of periodontal intrabony defects

MATERIALS AND METHODS.

This review was carried out according to a previously designed research protocol following the guidelines established in the PRISMA standards.[17]

Search methodology

A broad search strategy was conducted in the biomedical databases Pubmed, Embase, Scielo, Science Direct, SIGLE (System of Information on Grey Literature in Europe), LILACS, IBECS, and in the Cochrane Central Register of Clinical Trials. A manual search was also conducted in higher impact journals of periodontology such as: *Periodontology 2000, Journal of Clinical Periodontology* and *Journal of Periodontology* from the 2nd of January, 2012 until the 28th of February, 2017; using a combination of topic or thematic headings with the following keywords: ("fibrina rica en plaquetas" OR "platelet-rich fibrin" OR "PRF" OR "plasma rich in growth factors") AND ("defecto intraóseo" OR "defecto periodontal" OR "infrabony defect" OR "periodontal defect").

Selection criteria

The following inclusion criteria were considered: articles reporting the use of PRF in the treatment of PID; reporting clinical effects (reduction in probing depth, increase in clinical insertion level and reduction in gingival recession) when using in the treatment of PID; articles published in the last 5 years, reporting a follow-up time equal to or greater than 6 months, with sample sizes equal to or greater than 10 patients.Articles reporting the use of PRF in the control group, and articles published in non-indexed journals were excluded from the study.

Process of selection and extraction of data

Titles and abstracts of all the articles complying with the aforementioned inclusion and exclusion criteria were reviewed. Full texts of the articles that seemed to meet the selection criteria were obtained in order to assess the bias risk. A checklist was made in duplicate to evaluate the studies and to extract the information of interest. Two reviewers (LG and EI) independently performed the evaluation of the articles regarding title, author, year of publication, type of study, number of patients, ages of patients, follow-up time, country where it was conducted, number of areas treated per group, number of patients per group, type of PID treated, reduction in probing depth, increase in clinical insertion level, reduction in gingival recession, number of centrifugations, primers used, post-surgical medication and risk of bias. For the resolution of any discrepancy between the reviewers, they met and discussed with a third reviewer (SR) in order to reach an agreement.

Assessment of the methodological quality and risk of bias of the studies

For the assessment of the methodological quality and risk of bias, each study was analyzed according to the Cochrane Handbook of Systematic Reviews of Interventions.[18] Each study was evaluated in seven domains: selection bias (random sequence generation and concealment of allocation), performance bias (blinding of participants and research staff), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting of results), and other biases. Each domain was assessed as high, low, or

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unclear risk.

Analysis of results

Data from each study were placed and analyzed with RevMan 5.3 (Cochrane Group, UK). For performing the meta-analysis, results of the studies were combined independent of the follow-up period length.

RESULTS.

The initial search in the biomedical databases yielded107 titles; Figure 1 shows the article selection flowchart. Table 1 also shows the characteristics and variables considered in the 20 selected articles. Figure 2 presents the analysis of the methodological quality and the risk of bias of the studies.

Figure 3 shows the forest plot for the reduction in probing

Figure 1. Article selection flowchart.

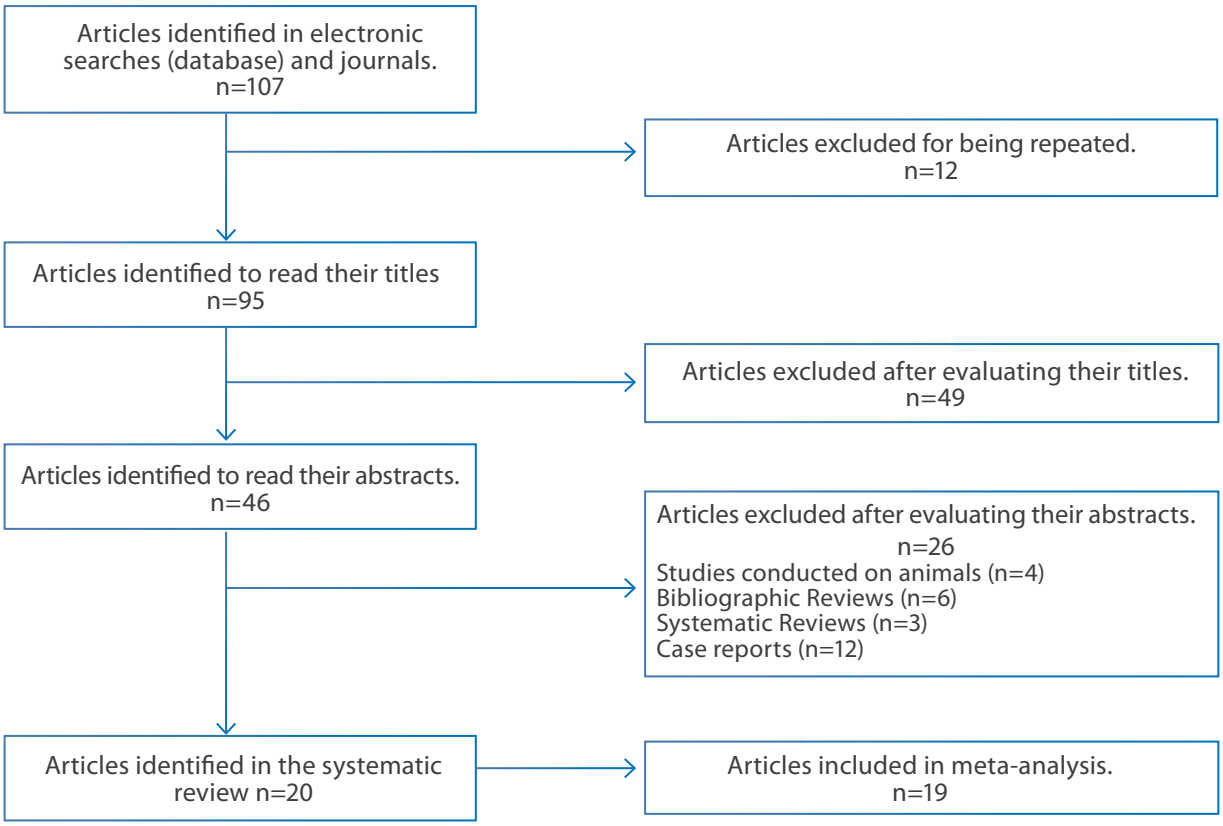


Figure 2. Risk of bias of the articles.

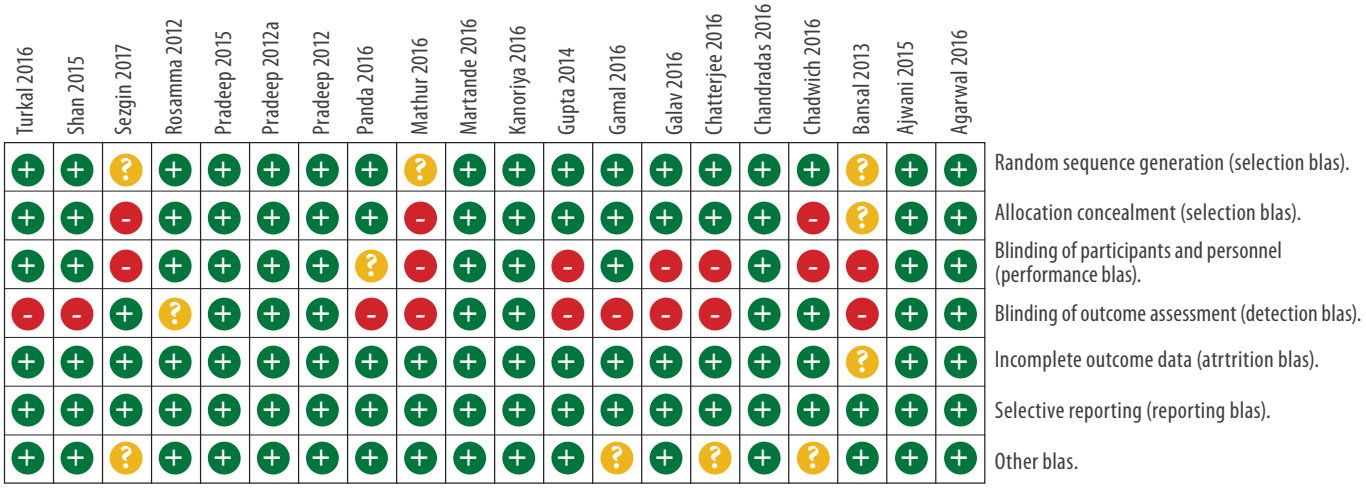


Table 1. Characteristics of included articles.

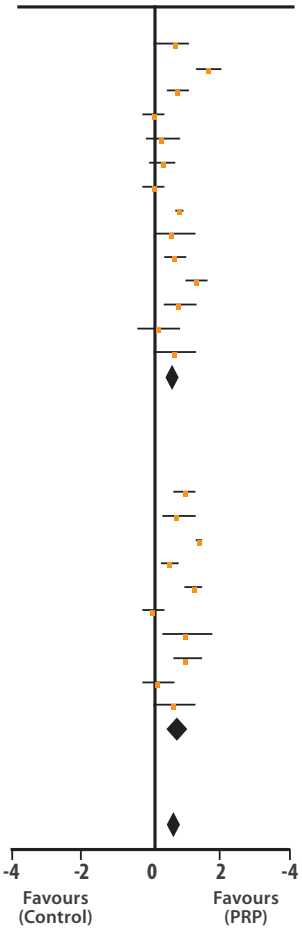
Author	Year	Type of study	N° Patients (males/ females)	Mean Age (range)	Follow-up time	Country	Groups of study	N° of patients per group	N° of treated areas	RPD (mm)	ICIL (mm)	RGR (mm)	Type of intrabony defect	N° of centrifugation cycles (rpm x m)	Post-surgical medication
Sezgin *et al.*[19]	2017	RCT	15 (8/7)	(38-61)	6 months	Turkey	Control (IBBM) Test (IBBM+PRF)	15 15	15 15	4.21±1.21 4.93±1.22	3.27±1.34 4.47±16	-0.94±0.7 -0.46±0.83	2 and 3 walls	2700rpm x 12m	Doxycycline 200mg and Paracetamol 100mg
Galay *et al.*[20]	2016	RCT	20	(30-55)	9 months	India	Control (ABG) Test (PRF)	NR NR	NR NR	4.8 ± 1.37 4.1 ± 1.53	4.5 ± 1.41 3.9 ± 1.29	NR NR	3 walls	3000rpm x 10m	Amoxicillin 500mg and Ibuprofen 800mg
Chadwic *et al.*[21]	2016	RCT	36(20/16)	54.9±12.1 (18–89)	6 months	United States	Control (DFDBA +Sterile saline serum) Test (PRF)	19 17	19 17	2.0±1.37 2.12±1.41	1.16±1.33 1.03±0.86	-0.84±0.88 -1.06±1.18	2 and 3 walls, combined 1,2,3 walls circumferential	3000rpm x 10m	Amoxicillin 500mg
Chandradas *et al.*[22]	2016	RCT	36(18/18)	44.4 (35–50)	9 months	India	Control (COFD) Test 1 (PRF+DBMG) Test 2 (PRF)	12 12 12	12 12 12	3.0±1.21 4.25±1.48 3.82±0.75	2.25±0.62 3.92 ± 0.9 3.27±0.65	-1.33±0.78 -0.17±0.39 -0.18±0.4	2 and 3 walls, combined	3000 rpmx 12m	Amoxicillin 500mg, Ibuprofen 400mg and Paracetamol 500mg
Kanoriya *et al.*[23]	2016	RCT	90 (43/47)	40.29 (30–50)	9 months	India	Control (COFD) Test 1 (COFD + PRF + 1% Alendronato) Test 2 (COFD+PRF)	30 30 30	30 30 30	2.86±0.68 4.53±0.81 3.7±0.91	3.03 ± 0.18 5.16±0.46 4.2 ± 0.66	-0.06±0.07 0.35±0.11 0.24±0.56	3 walls	300 rpm x 12m	Amoxicillin 500mg, Metronidazole 500 mg and Diclofenac sodium 500mg
Chatterjee *et al.*[24]	2016	RCT	28	(≥ 18)	9 months	India	Control (COFD) Test 1 (COFD+PRF)	32 32	32 32	3.68±0.72 5.46±1.04	4.14±0.76 6.57±1.45	NR NR	3 walls	3000 rpm x 10m	Amoxicillin 500mg and Diclofenac sodium 50mg
Aydemir Turkal *et al.*[25]	2016	RCT	28	(≥ 18)	6 months	Turkey	Control (EMD) Test 1 (PRF+EMD)	28 28	28 28	3.88±1.26 4.0 ±1.38	3.29 ± 1.3 3.42±1.28	0.58 ± 0.78 -0.71 ± 0.86	1,2,3 walls; combined 1,2,3 walls	3000rpm x 10m	NSAIDs
Martande *et al.*[26]	2016	RCT	96 (48/48)	37.6	9 months	India	Control (COFD) Test 1 (OFD+PRF + 1.2% Atorvastatin) Test 2 (COFD+PRF)	30 30 30	30 30 30	2.76±1.43 4.06±1.22 3.76±1.12	2.5 ± 1.33 3.66 ± 1.42 3.4±1.13	-0.06± 0.02 0.29± 0.18 0.22±0.1	3 walls	3000rpm x 12–14 m	Amoxicillin 500mg, Metronidazole 500 mg and Ibuprofen 800mg
Agarwal *et al.*[27]	2016	RCT	30 (17/13)	52 ± 7	1 year	India	Control (DFDBA + Saline serum) Test (PRF + DFDBA)	30 30	15 15	3.6±0.51 4.15±0.84	2.61±0.68 3.73±0.74	-1.0±0.61 -0.47±0.56	2 and 3 walls, combined 2, 3 walls	400g x 12m	Amoxicillin 500mg, and Ibuprofen 800mg
Gamal *et al.*[28]	2016	RCT	30 (21 / 9)	39.6 ± 3.9 (28 – 51)	9 months	Egypt	Control (Xenograft) Test (PRF +Xenograft)	10 10	10 10	3.8 ± 0.42 3.6 ± 0.45	1.8 ± 0.5 1.2 ± 0.36	NR NR	NR	NR	Amoxicillin 500mg, or Clindamycin 300 mg

Panda *et al.*[29]	2016	RCT	18 (10 / 8)	38.12±2.06 (30 – 50)	9 months	India	Control (RTG) Test (RTG+PRF)	16 16	18 18	3.19±1.33 3.88±1.15	3.38±1.45 4.44 ± 1.5	0.19 ± 0.4 0.56 ± 0.73	NR	3000rpm x 10m	Amoxicillin 500mg
Ajwani *et al.*[30]	2015	RCT	20 (10/10)	30.5	9 months	India	Control (OFD) Test (COFD+PRF)	20 20	20 20	1.6±0.84 1.9±0.74	1.3 ± 0.68 1.8 ± 0.63	-0.3 ± 0.68 -0.3 ± 0.48	2 and 3 walls	3000rpm x 10m	Novamox LB 500mg and Diclofenac 50mg
Shah *et al.*[31]	2015	RCT	20	(20-55)	6 months	India	Control (COFD+DFDBA) Test (COFD+PRF)	20 20	20 20	3.7 ± 0.68 3.67 ± 0.69	2.97 ± 1.68 2.97 ± 1.56	-0.32 ± 1.59 -0.42 ± 1.38	2 and 3 walls	3000rpm x 10m	Antibiotics
Pradeep *et al.*[32]	2015	RCT	120 (60/60)	41±6 (30-50)	9 months	India	Control (COFD) Test 1 (COFD+PRF) Test 2 (COFD + 1% Metformin) Test 3 (COFD + PRF + 1% Metformin)	30 30 30 30	30 30 30 30	3.0 ± 0.18 4.0 ± 0.18 3.93 ± 0.25 4.9 ± 0.3	2.96 ± 0.18 4.03 ± 0.18 3.93 ± 0.25 4.9 ± 0.3	-0.06 ± 0.04 0.27 ± 0.07 0.27 ± 0.05 0.33 ± 0.07	NR	3000rpm x 10m	Amoxicillin 500mg Metronidazole 500mg and Ibuprofen 800mg
Mathur *et al.*[33]	2015	ECA	25 (14/11)	39.66±5.72 (30 – 65)	6 months	India	Control (COFD+ABG) Test (COFD+PRF)	19 19	NR NR	2.4±1.06 2.67±1.29	2.67±1.63 2.53±1.06	-0.27±0.8 -0.07±0.46	3 walls	3000rpm x 10m	Amoxicillin 500mg and Paracetamol 500mg
Gupta *et al.*[34]	2014	RCT	30 (15/15)	(30 – 65)	6 months	India	Control (EMD) Test (PRF)	22 22	15 15	1.8 ± 0.56 1.8 ± 0.77	2.0±0.53 1.87±0.92	NR NR	3 walls	3000rpm x 12m	Amoxicillin 500mg and Paracetamol 500mg
Bansal *et al.*[35]	2015	RCT	10	NR	6 months	India	Control (COFD + DFDBA) Test (COFD+ DFDBA+PRF)	10 10	10 10	3.1±0.74 4.0±0.82	2.3±0.69 3.4±0.61	0.4±0.59 0.2±0.42	NR	3000rpm x 10m	Amoxicillin 500mg and Ibuprofen 400mg
Rosamma *et al.*[36]	2012	RCT	15 (6/9)	29.47±7.65 (17 – 44)	1 year	India	Control (COFD) Test (COFD+PRF)	15 15	15 15	2.4±0.63 4.67±0.9	1.4±1.06 4.73±0.88	-1.13±0.74 0.07±0.62	NR	3000rpm x 10m	Amoxicillin 500mg and Paracetamol 500mg
Pradeep *et al.*[37]	2012	RCT	54 (27/27)	36.8	9 months	India	Control (COFD) Test 2(COFD+PRF)	17 16	18 18	2.97 ± 0.93 3.77 ± 1.19	2.83 ± 0.91 3.17 ± 1.29	-0.27 ± 0.58 0.2 ± 0.71	3 walls	3000rpm x 10m	Amoxicillin 500mg and Ibuprofen 800mg
Pradeep *et al.*[38]	2012	RCT	63 (34/29)	39.7	9 months	India	Control (COFD) Test 1(COFD+PRF) Test 2(COFD+HA)	30 30 30	18 19 20	2.97 ± 0.93 3.9 ± 1.09 4.27 ± 0.98	2.67 ± 1.09 3.03 ± 1.16 3.67 ± 1.03	-0.17 ± 0.53 0.47 ± 0.73 0.67 ± 0.55	1, 2 and 3 walls	3000rpm x 10m	Amoxicillin 500mg and Ibuprofen 800mg

NR: Not reported, RCT: Randomized controlled trial; COFD: Conventional open-flap debridement; PRF: Platelet-rich fibrin; TPRF: Titanium-prepared platelet-rich fibrin; GTR: Guided tissue regeneration; ABBM: Inorganic bovine bone mineral; DFDBA: Demineralized Freeze Dried Bone Allograft; ABG: Autogenous bone graft; EMD: Enamel matrix derivative; HA: Hydroxyapatite; DBMG: Demineralized bone matrix graft; RPD: Reduction in probing depth; ICIL: Increase in clinical insertion level; RGR: Reduction in gingival recession; Mm: Millimeters; Rpm: Revolutions per minute; M: minutes; Mg: Milligrams; G: Relative centrifugal force

Figure 3. Forest plot of the event "Reduction of probing depth when using PRF in the treatment of periodontal intrabony defects".

Study or Subgroup	PRF Mean	PRF SD	PRF Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV Random, 95% CI	Year
Only PRP									
Pradeep 2012	3.77	1.19	16	2.97	0.93	17	3.8%	0.80 (0.07, 1.53)	2012
Agarwal 2016	4.67	0.9	15	2.4	0.63	15	4.3%	2.27 (1.71, 2.83)	2012
Pradeep 2012a	3.9	1.09	30	2.97	0.93	30	4.4%	0.93 (0.42, 1.44)	2012
Gupta 2014	1.8	0.77	22	1.8	0.56	22	4.6%	0.00 (-0.40, 0.40)	2014
Mathur 2015	2.67	1.29	19	2.4	1.06	19	3.8%	0.27 (-0.48, 1.02)	2015
Ajwani 2015	1.9	0.74	20	1.6	0.84	20	4.4%	0.30 (-0.19, 0.79)	2015
Shah 2015	3.67	0.69	20	3.7	0.68	20	4.5%	-0.03 (-0.45, 0.39)	2015
Pradeep 2015	4	0.18	30	3	0.28	30	5.0%	1.00 (0.88, 1.12)	2015
Panda 2016	3.88	1.15	16	3.19	1.33	16	3.5%	0.69 (-0.17, 1.55)	2016
Kanoriya 2016	3.7	0.91	30	2.86	0.68	30	4.6%	0.84 (0.43, 1.25)	2016
Chatterjee 2016	5.46	1.04	32	3.68	0.72	32	4.5%	1.78 (1.34, 2.22)	2016
Martande 2016	3.76	1.12	30	2.76	1.43	30	4.0%	1.00 (0.35, 1.65)	2016
Chadwick 2016	2.12	1.41	17	2	1.37	19	3.4%	0.12 (-0.79, 1.03)	2016
Chandradas 2016	3.82	0.75	12	3	1.21	12	3.6%	0.82 (0.01, 1.63)	2016
Subtotal (95% CI)			**309**			**312**	**58.4%**	**0.79(0.46, 1.11)**	
Heterogeneity: Tau²=0.29; Chi²=91.41, d_f =13 (p=0.00001); I²=86%									
Test for overall effect: Z=4.77 (p<0.00001)									
PRP combined with another biomaterial									
Pradeep 2012a	4.97	0.98	30	2.97	0.93	30	4.4%	1.30 (0.82, 1.78)	2012
Bansal 2013	4	0.82	10	3.1	0.74	10	3.9%	0.90 (0.22, 1.58)	2013
Pradeep 2015	4.9	0.3	30	3	0.28	30	5.0%	1.90 (1.75, 2.05)	2015
Agarwal 2016	4.15	0.84	30	3.6	0.51	30	4.7%	0.55 (0.20, 0.90)	2016
Kanoriya 2016	4.53	0.81	30	2.86	0.68	30	4.6%	1.67 (1.29, 2.05)	2016
Gamal 2016	3.6	0.45	10	3.8	0.42	10	4.6%	-0.20 (-0.58, 0.18)	2016
Chandradas 2016	4.25	1.48	12	3	1.21	12	3.0%	1.25 (0.17, 2.33)	2016
Martande 2016	4.06	1.22	30	2.76	1.43	30	4.0%	1.30 (0.63, 1.97)	2016
Turkal 2016	4	1.38	28	3.88	1.26	28	3.9%	0.12 (-0.57, 0.81)	2016
Sezgin 2017	4.93	1.22	15	4.21	1.21	15	3.5%	0.72 (-0.15, 1.59)	2017
Subtotal (95% CI)			**225**			**225**	**41.6%**	**0.96 (0.40, 1.52)**	
Heterogeneity: Tau²=0.72; Chi²=154.21, d_f =9 (p=0.00001); I²=94%									
Test for overall effect: Z=3.34 (p=0.0008)									
Total (95% CI)			**534**			**537**	**100.0%**	**0.86 (0.56, 1.15)**	
Heterogeneity: Tau²=0.45; Chi²=295.33, d_f =23 (p<0.00001); I²=92%									
Test for overall effect: Z=5.71 (p=0.007)									
Test for subgroup differences: Chi²=0.27, d_f =1 (p<0.61); I²=0%									



depth when using PRF in the treatment of periodontal intrabony defects. Figure 4 shows the forest plot for the increase in clinical insertion level when using PRF in the treatment of periodontal intrabony defects. Figure 5 presents the forest plot for the reduction in gingival recession when using PRF in the treatment of periodontal intrabony defects.

DISCUSSION.

Results revealed that the use of PRF in the treatment of PID produced an increase in the clinical insertion level, a reduction in probing depth, and a reduction in gingival recession significantly greater than the control treatment. Subgroup analysis showed that all these clinical effects were similarly beneficial if PRF was used alone, or if PRF was used in combination with another biomaterial or substance that stimulates tissue regeneration. In this study, a random effects model for the meta-analysis was used. In addition, it was found that there was no difference if the RCT had a parallel[21–23,26–28,32,34,37,38] *or* cross-over design.[19,24,25,29–31,33,35,36]

The studies showed positive clinical effects for the use of PRF in the treatment of PID. This is similar to the findings reported by Smail *et al.*,[39] who performed a study that did not provide sufficient evidence for the systematic differences in estimates of the effect of interventions between split-mouth and parallel-arm RCTs for continuous or binary

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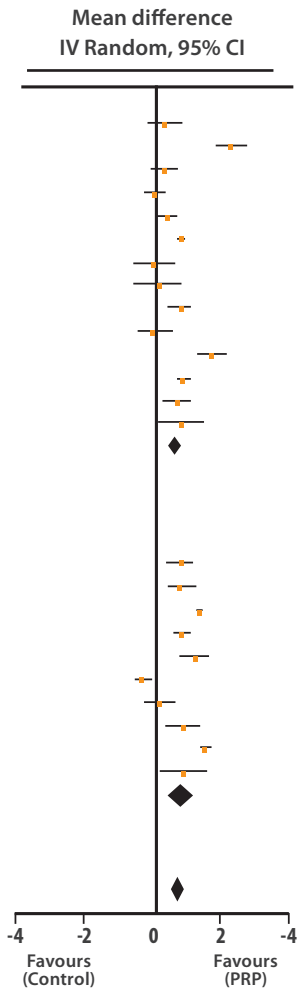
Figure 4. Forest plot of the event "Increase in clinical insertion level when using PRF in the treatment of periodontal intrabony defects".

Study or Subgroup	PRF Mean	PRF SD	PRF Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV Random, 95% CI	Year
Only PRP									
Pradeep 2012	3.17	1.29	16	2.83	0.91	17	3.8%	0.34(-0.43, 1.11)	2012
Rosamma 2012	4.73	0.88	15	1.4	1.06	15	4.0%	3.33 (2.63, 4.03)	2012
Pradeep 2012a	3.03	1.16	30	2.67	1.09	30	4.2%	0.36 (-0.21, 0.93)	2012
Gupta 2014	1.87	0.92	22	2	0.53	22	4.5%	-0.13 (-0.57, 0.31)	2014
Ajwani 2015	1.8	0.63	20	1.3	0.68	20	4.5%	0.50 (0.09, 0.91)	2015
Pradeep 2015	4.03	0.18	30	2.96	0.18	30	4.9%	1.07 (0.98, 1.16)	2015
Mathur2015	2.53	1.06	19	2.67	1.63	19	3.6%	-0.14(-1.01, 0.73)	2015
Shah 2015	2.97	1.56	20	2.97	1.68	20	3.3%	0.00 (-1.00, 1.00)	2015
Chandradas 2016	3.27	0.65	12	2.25	0.62	12	4.4%	1.02 (0.51, 1.53)	2016
Chadwick 2016	1.03	0.86	17	1.16	1.33	19	3.9%	-0.13 (-0.85, 0.59)	2016
Chatterjee 2016	6.57	1.45	32	4.14	0.76	32	4.2%	2.43 (1.86, 3.00)	2016
Kanoriya 2016	4.2	0.66	30	3.03	0.18	30	4.8%	1.17 (0.93, 1.41)	2016
Martande 2016	3.4	1.13	30	2.5	1.33	30	4.1%	0.90 (0.28, 1.52)	2016
Panda 2016	4.44	1.5	1.6	3.38	1.45	16	3.2%	1.06 (0.04, 2.08)	2016
Subtotal (95% CI)			**3.09**			**312**	**57.3%**	**0.87(0.51, 123)**	
Heterogeneity: Tau^2=0.37; Chi^2=129.34, d_f =13 (p=0.00001); I^2=90%									
Test for overall effect: Z=4.72 (p<0.00001)									
PRP combined with another biomaterial									
Pradeep 2012a	3.67	1.03	30	2.67	1.09	30	4.3%	1.00 (0.46, 1.54)	2012
Bansal 2013	3.4	0.61	10	2.3	0.69	10	4.2%	1.10 (0.53, 1.67)	2013
Pradeep 2015	4.9	0.3	30	2.96	0.18	30	4.9%	1.94 (1.81, 2.07)	2015
Agarwal 2016	3.73	0.74	30	2.61	0.68	30	4.6%	1.12 (0.76, 1.48)	2016
Chandradas 2016	3.92	0.9	12	2.25	0.62	12	4.1%	1.67 (1.05, 2.29)	2016
Gamal 2016	1.2	0.36	10	1.8	0.5	10	4.6%	-0.60 (1.05, 2.29)	2016
Turkal 2016	3.42	1.28	28	3.29	1.3	28	4.0%	0.13 (-0.55, 0.81)	2016
Martande 2016	3.66	1.42	30	2.5	1.33	30	4.0%	1.16 (0.46, 1.86)	2016
Kanoriya 2016	5.16	0.46	30	3.03	1.18	30	4.8%	2.13 (1.95, 2.31)	2016
Sezgin 2017	4.47	1.6	15	3.27	1.34	15	3.2%	1.20 (0.14, 2.26)	2017
Subtotal (95% CI)			**225**			**225**	**42.7%**	**1.10 (0.56, 1.63)**	
Heterogeneity: Tau^2=0.67; Chi^2=220.89, d_f =9 (p=0.00001); I^2=96%									
Test for overall effect: Z=4.01 (p<0.0001)									
Total (95% CI)			**534**			**537**	**100.0%**	**0.96 (0.65, 1.28)**	
Heterogeneity: Tau^2=0.52; Chi^2=475.30, d_f =23 (p<0.00001); I^2=95%									
Test for overall effect: Z=6.02 (p<0.00001)									
Test for subgroup differences: Chi^2=0.49, d_f =1 (p=0.48); I^2=0%									



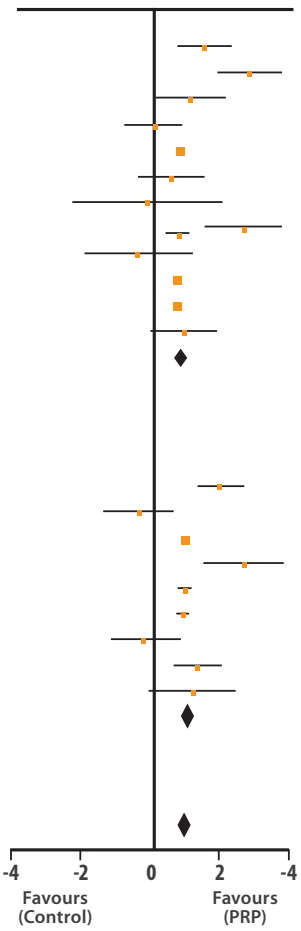
data. This review also demonstrates that PRF does not have a clear standard protocol because the type of centrifuge and configuration also differ from one study to another. Therefore more standardized protocols are needed to allow for a better comparison and homogenize the results.

One strength of this systematic review was the selection of the studies, because an exhaustive search was performed in the most important databases and strict inclusion criteria were followed. However, there are also limitations such as the presence of many RCTs that presented a high and unclear risk of bias. Another positive aspect is the comparison of these results with other systematic reviews on this subject.[40,41] These reviews confirm that using PRF produces a positive and beneficial clinical effect in the treatment of PIDs. It is important to consider that these reviews included RCTs published in years prior to those included in this study.

However, the promising effect of PRF for the treatment of PIDs cannot yet fully accepted. Most of the RCTs show a high heterogeneity and were conducted primarily in European and Asian countries, with only two from North America and one from Africa. As each continent and country has its own culture and diet, these factors can influence the clinical effects of PRF. It is advisable to carry out well-designed RCTs dealing with this issue in countries in other continents, especially in Latin America,

Figure 5. Forest plot of the event "Reduction in gingival recession when using PRF in the treatment of periodontal intrabony defects".

Study or Subgroup	PRF Mean	PRF SD	PRF Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV Random, 95% CI	Year
Only PRP									
Pradeep 2012a	0.47	0.73	30	-0.17	0.53	30	2.5%	0.64(0.32, 0.96)	2012
Rosamma 2012	0.07	0.26	15	-1.13	0.74	15	1.7%	3.33 (0.80, 1.60)	2012
Pradeep 2012	0.2	0.71	16	-0.27	0.58	17	1.4%	0.47(0.03, 0.91)	2012
Ajwani 2015	-0.3	0.48	20	-0.3	0.68	20	2.0%	0.00 (-0.36, 0.91)	2015
Pradeep 2015	0.27	0.07	30	-0.06	0.04	30	13.1%	0.33 (0.30, 0.36)	2015
Mathur2015	-0.07	0.46	19	-0.27	0.8	19	1.6%	0.20 (-0.21, 061)	2015
Shah 2015	-0.42	1.38	20	-0.32	1.59	20	0.4%	-0.10 (-1.02, 0.82)	2015
Chandradas 2016	-0.18	0.4	12	-1.33	0.78	12	1.2%	1.15 (0.62, 1.65)	2016
Chadwick 2016	-1.06	1.18	17	-0.84	0.88	19	0.6%	-0.22 (-0.91, 0.47)	2016
Kanoriya 2016	0.24	0.06	30	-0.06	0.07	30	12.9%	0.30 (0.27, 0.33)	2016
Martande 2016	0.22	0.1	30	-0.06	0.02	30	12.8%	0.28 (0.24, 0.32)	2016
Panda 2016	0.52	0.73	16	0.19	0.4	16	1.7%	0.37 (-0.04, 078)	2016
Subtotal (95% CI)			**2.55**			**258**	**51.9%**	**0.34(0.27, 0.41)**	
Heterogeneity: Tau^2=0.00; Chi^2=45.82, d_f =11 (p=0.00001); I^2=76%									
Test for overall effect: Z=9.55 (p<0.00001)									
PRP combined with another biomaterial									
Pradeep 2012a	0.67	0.55	30	-0.17	0.53	30	3.2%	0.84 (0.57, 1.11)	2012
Bansal 2013	0.2	0.42	10	0.4	0.59	10	1.4%	-0.20 (-0.65, 0.25)	2013
Pradeep 2015	0.33	0.07	30	-0.06	0.04	30	13.1%	0.39 (0.36, 0.42)	2015
Chandradas 2016	-0.17	0.39	12	-1.33	0.78	12	1.2%	1.16 (0.67, 1.65)	2016
Kanoriya 2016	0.35	0.11	30	-0.06	0.07	30	12.4%	0.41 (0.36, 0.45)	2016
Martande 2016	0.29	0.18	30	-0.06	0.02	30	11.5%	0.35 (0.29, 0.41)	2016
Turkal 2016	-0.71	0.86	28	-0.58	0.78	28	1.5%	-0.13 (-0.56, 0.30)	2016
Agarwal 2016	-0.47	0.56	30	-1	0.61	30	2.8%	0.53 (0.23, 0.83)	2016
Sezgin 2017	-0.46	0.83	15	-0.94	0.7	15	1.0%	0.48 (-0.07, 1.03)	2017
Subtotal (95% CI)			**215**			**215**	**48.1%**	**0.41 (0.33, 0.50)**	
Heterogeneity: Tau^2=0.01; Chi^2=35.10, d_f =8 (p=0.00001); I^2=77%									
Test for overall effect: Z=9.64 (p<0.0001)									
Total (95% CI)			**470**			**473**	**100.0%**	**0.38 (0.32, 0.44)**	
Heterogeneity: Tau^2=0.01; Chi^2=111.17, d_f =20 (p<0.00001); I^2=82%									
Test for overall effect: Z=13.27 (p<0.00001)									
Test for subgroup differences: Chi^2=1.49, d_f =1 (p=0.22); I^2=32.9%									



because Latin American countries have the greatest genetic diversification, culture, food and a wide range of climates.

CONCLUSION.

The clinical effect of PRF in the treatment of PID is positive either when used alone or in combination with another biomaterial. Its clinical effect was significant in reducing probing depth, reducing gingival recession, and increasing clinical insertion level, regardless of whether the RCT had a parallel or cross-over design

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