

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

Heber Arbildo,^{1,2,3} Luis Gamarra,^{4,5} Sandra Rojas,⁵ Edward Infantes,^{2,4,6} César Lamas⁷ & Hernán Vásquez.⁸

Affiliations: ¹Escuela de Odontología, Universidad Particular de Chiclayo. Chiclayo, Perú. ²Escuela de Estomatología, Universidad Señor de Sipán. Chiclayo, Perú. ³Centro de Salud Odontológico San Mateo. Trujillo, Perú. ⁴Escuela de Estomatología, Universidad Privada Antonio Guillermo Urreru. Cajamarca, Perú. ⁵Facultad de Estomatología, Universidad Nacional de Trujillo. Trujillo, Perú. ⁶Escuela de Estomatología, Universidad César Vallejo. Piura, Perú. ⁷Escuela de Odontología, Universidad Católica los Ángeles de Chimbote. Chimbote, Perú. ⁸Facultad de Odontología, Universidad San Martín de Porres. Lima, Perú.

Corresponding author: Heber Arbildo. Av. Húsares de Junín 611. Trujillo, Perú. Phone: (044) 616644. E-mail: hiav_666@hotmail.com, hiav30@gmail.com

Receipt: 03/20/2017 **Revised:** 04/19/2017
Acceptance: 05/24/2017 **Online:** 05/24/2017

Conflict of interests: The authors declare no conflict of interest in relation to published results.

Ethics approval: None.

Funding: This study was self-financed.

Authors' contributions: Both authors contributed equality to the complete study.

Acknowledgements: None.

Cite as: Arbildo H, Gamarra L, Rojas S, Infantes E, Lamas C & Vásquez H. Clinical effect of platelet rich fibrin in the treatment of periodontal intrabony defects. Systematic review and meta-analysis. *J Oral Res* 2017; 6(5):127-135. doi:10.17126/joralres.2017.036

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 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 anti-coagulant 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 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 yielded 107 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 1. Article selection flowchart.

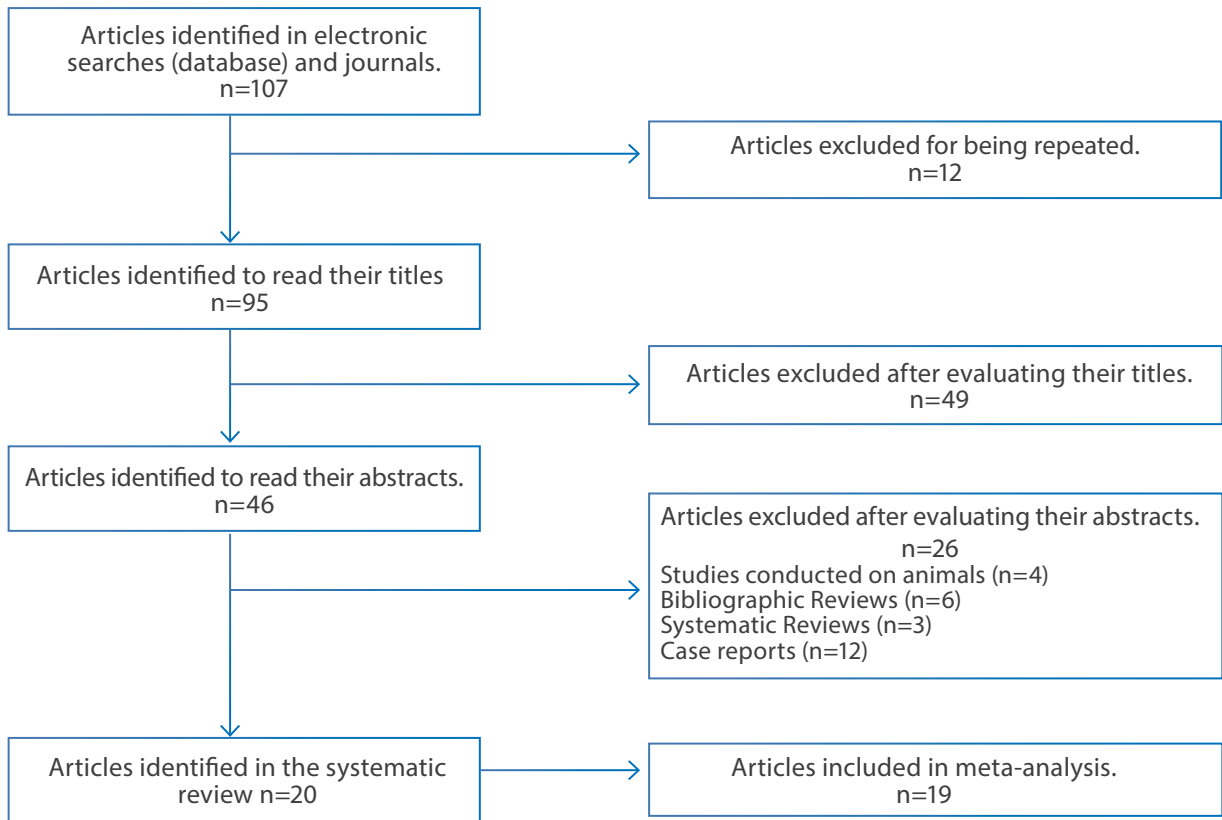


Figure 2. Risk of bias of the articles.

	Turkal 2016	Shan 2015	Sezgin 2017	Rosamma 2012	Pradeep 2015	Pradeep 2012a	Pradeep 2012	Panda 2016	Mathur 2016	Martande 2016	Kanoriya 2016	Gupta 2014	Gamal 2016	Galav 2016	Chatterjee 2016	Chandradas 2016	Chadwich 2016	Bansal 2013	Aiwani 2015	Agarwal 2016		
Random sequence generation (selection bias).	+	+	?	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	+	
Allocation concealment (selection bias).	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	?	+	+	+	
Blinding of participants and personnel (performance bias).	+	+	-	+	+	+	+	?	-	+	+	-	+	-	-	+	-	-	+	+	+	
Blinding of outcome assessment (detection bias).	-	-	+	?	+	+	+	-	-	+	+	-	-	-	-	+	+	-	+	+	+	
Incomplete outcome data (attrition bias).	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+	
Selective reporting (reporting bias).	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Other bias.	+	+	?	+	+	+	+	+	+	+	+	+	?	+	?	+	?	+	+	+	+	

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	Post-surgical medication cycles (rpm x m)
Sezgin <i>et al.</i> 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±1.16	-0.94±0.7 -0.46±0.83	2 and 3 walls	2700rpm x 12m	Doxycycline 200mg and Paracetamol 100mg
Galay <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ²²	2016	RCT	36(18/18)	44.4 (35-50)	9 months	India	Control (COFD) Test1 (PRF+DBMG) Test2 (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 rpm x 12m	Amoxicillin 500mg, Ibuprofen 400mg and Paracetamol 500mg
Kanoriya <i>et al.</i> ²³	2016	RCT	90 (43/47)	40.29 (30-50)	9 months	India	Control (COFD) Test1 (COFD + PRF +1% Alendronato) Test2 (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 <i>et al.</i> ²³	2016	RCT	28	(≥ 18)	9 months	India	Control (COFD) Test1 (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 <i>et al.</i> ²⁵	2016	RCT	28	(≥ 18)	6 months	Turkey	Control (EMD) Test1 (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 <i>et al.</i> ²⁶	2016	RCT	96 (48/48)	37.6	9 months	India	Control (COFD) Test1 (OFD+PRF + 1.2% Atorvastatin) Test2 (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 <i>et al.</i> ²⁷	2016	RCT	30 (17/13)	52 ± 7	1 year	India	Control (DFDBA + Saline serum) Test (PRF + DFDBA)	10 10	10 10	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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ³⁰	2015	RCT	20 (10/10)	30.5 (20-55)	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 <i>et al.</i> 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 NR	3000rpm x 10m	Antibiotics Amoxicillin 500mg
Pradeep <i>et al.</i> 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			Metronidazole 500mg and Ibuprofen 800mg
Mathur <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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; ICL: 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".

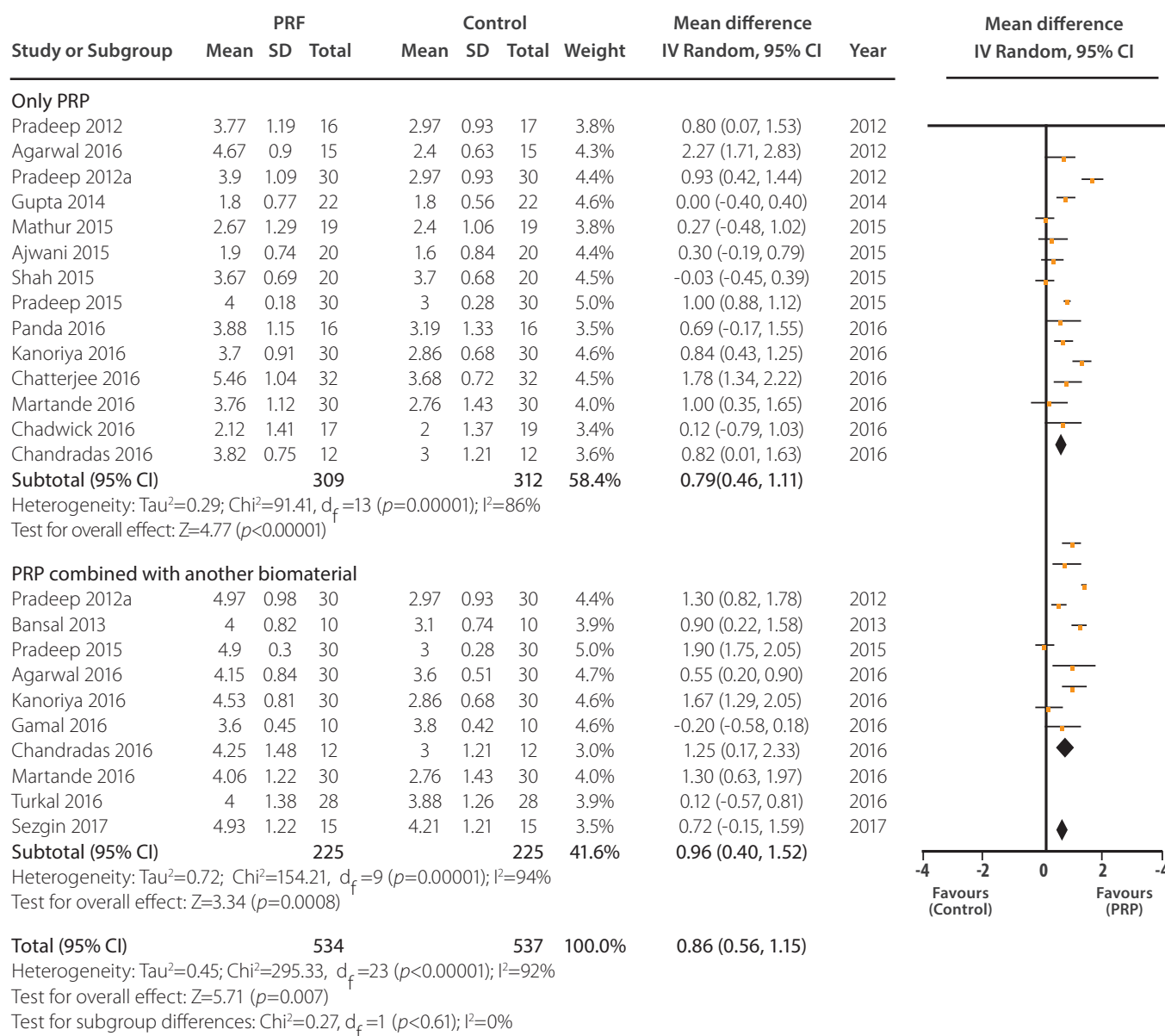


Figure 3 shows the forest plot for the reduction in probing depth when using PRF in the treatment of periodontal intrabony defects. Figure 4 shows the forest plot for the increase in clinical insertion level when using PRF in the treatment of periodontal intrabony defects. Figure 5 presents the forest plot for the reduction in gingival recession when using PRF in the treatment of periodontal intrabony defects.

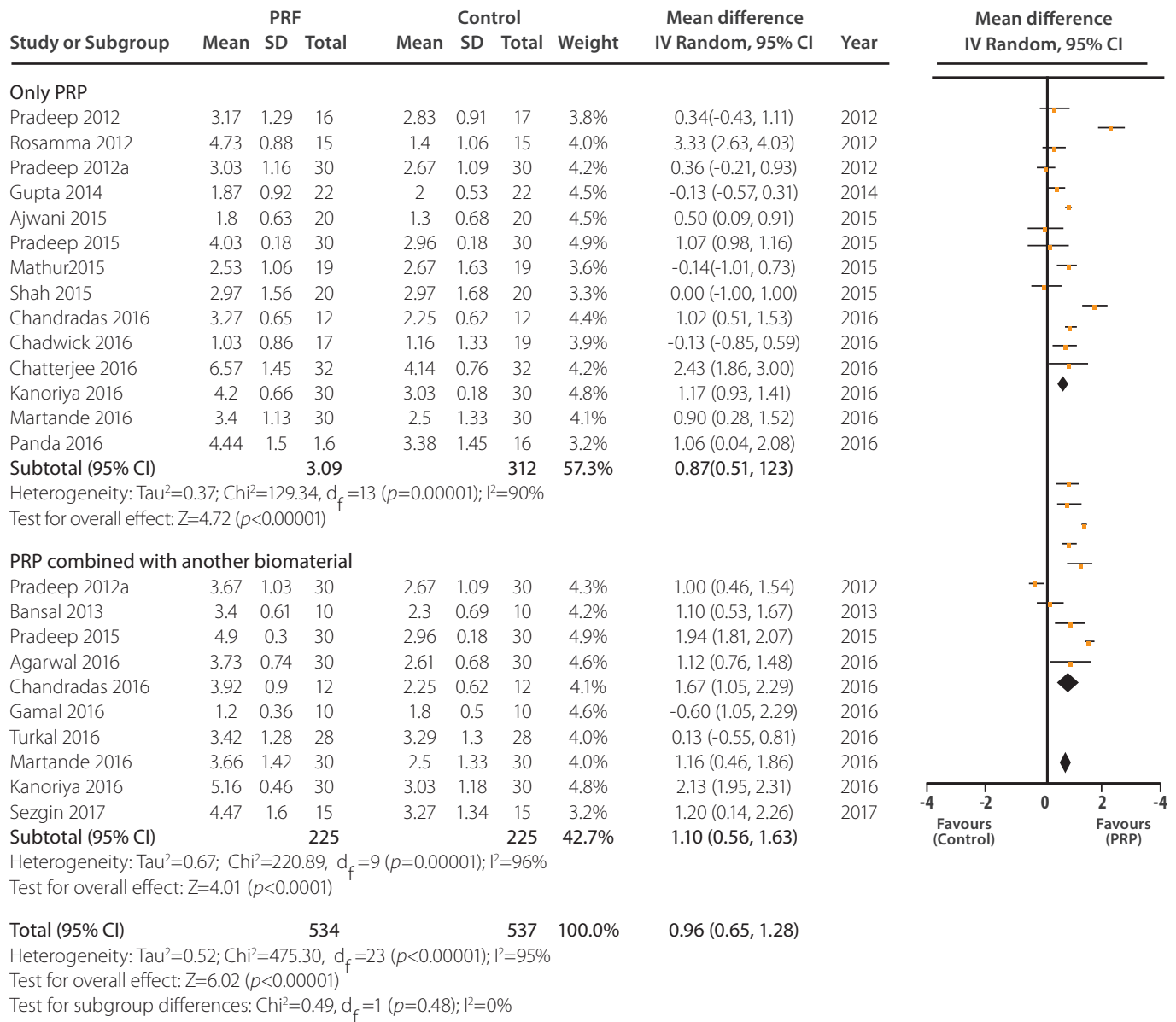
DISCUSSION.

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 paral-

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



lel-arm RCTs for continuous or binary data.

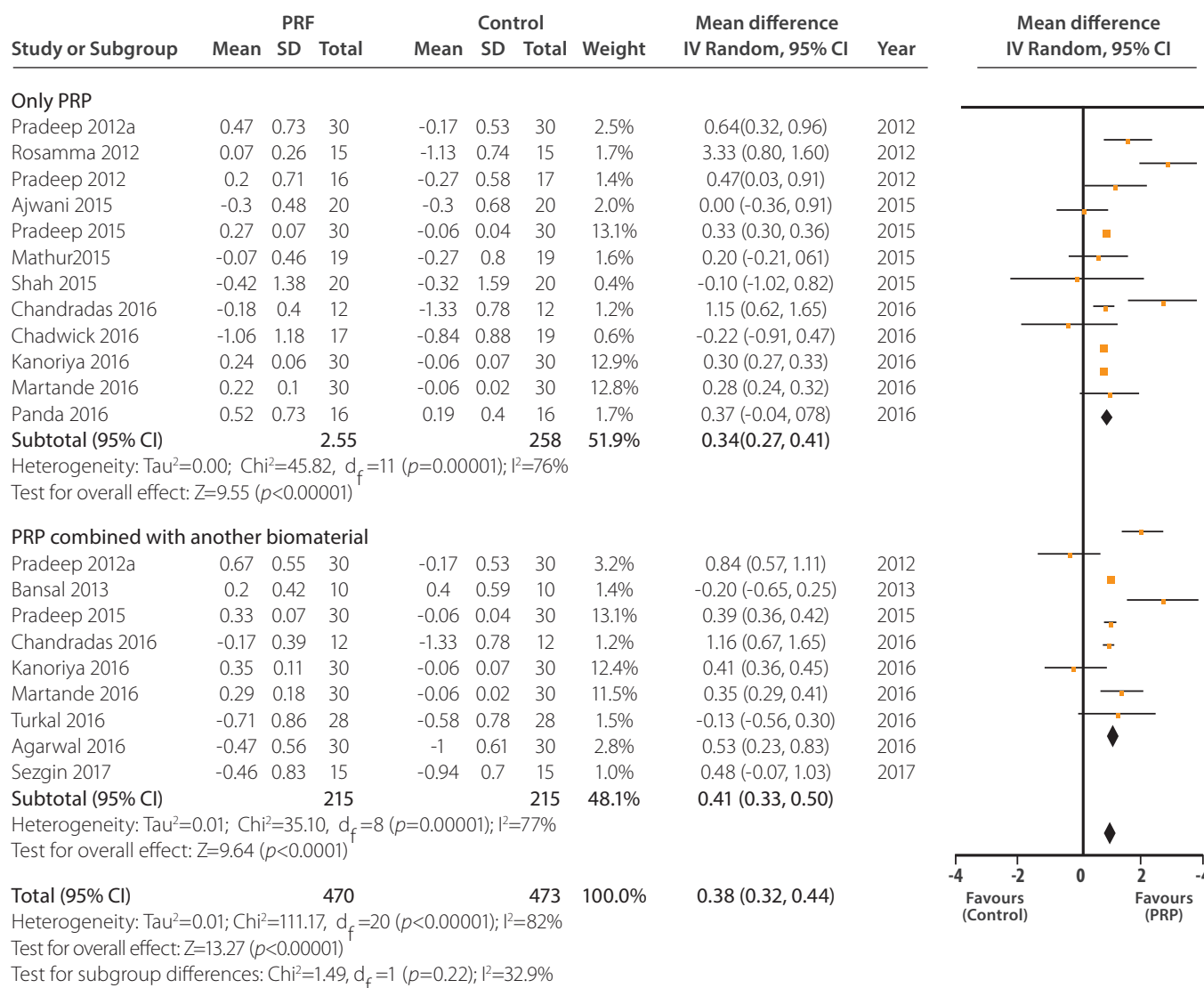
This review also demonstrates that PRF does not have a clear standard protocol because the type of centrifuge and configuration also differ from one study to another. Therefore more standardized protocols are needed to allow for a better comparison and homogenize the results.

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 sys-

tematic 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 oth-

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



er continents, especially in Latin America, 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

REFERENCES.

- Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet*. 2005;366(9499):1809–20.
- Hou X, Yuan J, Aisaiti A, Liu Y, Zhao J. The effect of platelet-rich plasma on clinical outcomes of the surgical treatment of periodontal intrabony defects: A systematic review and meta-analysis. *BMC Oral Health*. 2016;16(1):71.
- Preeja C, Arun S. Platelet-rich fibrin: Its role in periodontal regeneration. *Saudi J Dent Res*. 2014;4:117–22.
- Sander L, Karring T. Healing of periodontal lesions in monkeys following the guided tissue regeneration procedure. A histological study. *J Clin Periodontol*. 1995;22(4):332–7.
- Shah M, Deshpande N, Bharwani A, Nadig P, Doshi V, Dave D. Effectiveness of autologous platelet-rich fibrin in the treatment of intra-bony defects: A systematic review and meta-analysis. *J Indian Soc Periodontol*. 2014;18(6):698–704.
- Panda S, Ramamoorthi S, Jayakumar ND, Sankari M, Varghese SS. Platelet rich fibrin and alloplast in the treatment of intrabony defect. *J Pharm Bioallied Sci*. 2014;6(2):127–31.
- Chen FM, Zhang J, Zhang M, An Y, Chen F, Wu ZF. A review on endogenous regenerative technology in periodontal regenerative medi-

- ne. *Biomaterials*. 2010;31(31):7892–927.
8. Cochran DL, Wozney JM. Biological mediators for periodontal regeneration. *Periodontol* 2000. 1999;19:40–58.
 9. Mihaylova Z, Mitev V, Stanimirov P, Isaeva A, Gateva N, Ishkietiev N. Use of platelet concentrates in oral and maxillofacial surgery: an overview. *Acta Odontol Scand*. 2017;75(1):1–11.
 10. Darby IB, Morris KH. A systematic review of the use of growth factors in human periodontal regeneration. *J Periodontol*. 2013;84(4):465–76.
 11. Maeda H, Wada N, Tomokiyo A, Monnouchi S, Akamine A. Prospective potency of TGF- β 1 on maintenance and regeneration of periodontal tissue. *Int Rev Cell Mol Biol*. 2013;304:283–367.
 12. Babbush CA, Kevy SV, Jacobson MS. An in vitro and in vivo evaluation of autologous platelet concentrate in oral reconstruction. *Implant Dent*. 2013;12(1):24–34.
 13. Graves DT, Cochran DL. Periodontal regeneration with polypeptide growth factors. *Curr Opin Periodontol*. 1994:178–86.
 14. Prakash S, Thakur A. Platelet concentrates: past, present and future. *J Maxillofac Oral Surg*. 2011;10(1):45–9.
 15. Giannini S, Cielo A, Bonanome L, Rastelli C, Derla C, Corpaci F, Falisi G. Comparison between PRP, PRGF and PRF: lights and shadows in three similar but different protocols. *Eur Rev Med Pharmacol Sci*. 2015;19(6):927–30.
 16. Choukroun J, Adda F, Schoeffler C, Vervelle A. Une opportunité en paro-implantologie: Le PRF. *Implantodontie*. 2001;42:55–62.
 17. Urrútia G, Bonfill X. [PRISMA declaration: a proposal to improve the publication of systematic reviews and meta-analyses]. *Med Clin*. 2010;135(11):507–11.
 18. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. UK: The Cochrane Collaboration; 2011.
 19. Sezgin Y, Uraz A, Taner IL, Çulhaoğlu R. Effects of platelet-rich fibrin on healing of intra-bony defects treated with anorganic bovine bone mineral. *Braz Oral Res*. 2017;31:e15.
 20. Galav S, Chandrashekar KY, Mishra R, Tripathi V, Agarwal R, Galav A. Comparative evaluation of platelet-rich fibrin and autogenous bone graft for the treatment of infrabony defects in chronic periodontitis: Clinical, radiological, and surgical reentry. *Indian J Dent Res*. 2016;27(5):502–7.
 21. Chadwick JK, Mills MP, Mealey BL. Clinical and Radiographic Evaluation of Demineralized Freeze-Dried Bone Allograft Versus Platelet-Rich Fibrin for the Treatment of Periodontal Intrabony Defects in Humans. *J Periodontol*. 2016;87(11):1253–60.
 22. Chandradas ND, Ravindra S, Rangaraju VM, Jain S, Dasappa S. Efficacy of platelet rich fibrin in the treatment of human intrabony defects with or without bone graft: A randomized controlled trial. *J Int Soc Prev Community Dent*. 2016;6(Suppl 2):S153–9.
 23. Kanoriya D, Pradeep AR, Singhal S, Garg V, Guruprasad CN. Synergistic Approach Using Platelet-Rich Fibrin and 1% Alendronate for Intrabony Defect Treatment in Chronic Periodontitis: A Randomized Clinical Trial. *J Periodontol*. 2016;87(12):1427–35.
 24. Chatterjee A, Pradeep AR, Garg V, Yajamanya S, Ali MM, Priya VS. Treatment of periodontal intrabony defects using autologous platelet-rich fibrin and titanium platelet-rich fibrin: a randomized, clinical, comparative study. *J Investig Clin Dent*. 2016:[Epub ahead of print].
 25. Aydemir Turkal H, Demirel S, Dolgun A, Keceli HG. Evaluation of the adjunctive effect of platelet-rich fibrin to enamel matrix derivative in the treatment of intrabony defects. Six-month results of a randomized, split-mouth, controlled clinical study. *J Clin Periodontol*. 2016;43(11):955–64.
 26. Martande SS, Kumari M, Pradeep AR, Singh SP, Suke DK, Guruprasad CN. Platelet-Rich Fibrin Combined With 1.2% Atorvastatin for Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Controlled Clinical Trial. *J Periodontol*. 2016;87(9):1039–46.
 27. Agarwal A, Gupta ND, Jain A. Platelet rich fibrin combined with decalcified freeze-dried bone allograft for the treatment of human intrabony periodontal defects: a randomized split mouth clinical trial. *Acta Odontol Scand*. 2016;74(1):36–43.
 28. Gamal AY, Abdel Ghaffar KA, Algezhwy OA. Crevicular Fluid Growth Factors Release Profile Following the Use of Platelet-Rich Fibrin and Plasma Rich Growth Factors in Treating Periodontal Intrabony Defects: A Randomized Clinical Trial. *J Periodontol*. 2016;87(6):654–62.
 29. Panda S, Sankari M, Satpathy A, Jayakumar D, Mozzati M, Mortellaro C, Gallesio G, Taschieri S, Del Fabbro M. Adjunctive Effect of Autologous Platelet-Rich Fibrin to Barrier Membrane in the Treatment of Periodontal Intrabony Defects. *J Craniofac Surg*. 2016;27(3):691–6.
 30. Ajwani H, Shetty S, Gopalakrishnan D, Kathariya R, Kulloli A, Dolas RS, Pradeep AR. Comparative evaluation of platelet-rich fibrin biomaterial and open flap debridement in the treatment of two and three wall intrabony defects. *J Int Oral Health*. 2015;7(4):32–7.
 31. Shah M, Patel J, Dave D, Shah S. Comparative evaluation of platelet-rich fibrin with demineralized freeze-dried bone allograft in periodontal infrabony defects: A randomized controlled clinical study. *J Indian Soc Periodontol*. 2015;19(1):56–60.
 32. Pradeep AR, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad CN. Platelet-rich fibrin with 1% metformin for the treatment of intrabony defects in chronic periodontitis: a randomized controlled clinical trial. *J Periodontol*. 2015;86(6):729–37.
 33. Mathur A, Bains VK, Gupta V, Jhingran R, Singh GP. Evaluation of intrabony defects treated with platelet-rich fibrin or autogenous bone graft: A comparative analysis. *Eur J Dent*. 2015;9(1):100–8.
 34. Gupta SJ, Jhingran R, Gupta V, Bains VK, Madan R, Rizvi I. Efficacy of platelet-rich fibrin vs. enamel matrix derivative in the treatment of periodontal intrabony defects: a clinical and cone beam computed tomography study. *J Int Acad Periodontol*. 2014;16(3):86–96.
 35. Bansal C, Bharti V. Evaluation of efficacy of autologous platelet-rich fibrin with demineralized-freeze dried bone allograft in the treatment of periodontal intrabony defects. *J Indian Soc Periodontol*. 2013;17(3):361–6.
 36. Rosamma Joseph V, Raghunath A, Sharma N. Clinical effectiveness of autologous platelet rich fibrin in the management of infrabony periodontal defects. 2012;33(1):5–12.
 37. Pradeep AR, Rao NS, Agarwal E, Bajaj P, Kumari M, Naik SB. Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of 3-wall intrabony defects in chronic periodontitis: a randomized controlled clinical trial. *J Periodontol*. 2012;83(12):1499–507.
 38. Pradeep AR, Rao NS, Agarwal E, Bajaj P, Kumari M, Naik SB. Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of 3-wall intrabony defects in chronic periodontitis: a randomized controlled clinical trial. *J Periodontol*. 2012;83(12):1499–507.
 39. Smaïl-Faugeron V, Fron-Chabouis H, Courson F, Durieux P. Comparison of intervention effects in split-mouth and parallel-arm randomized controlled trials: a meta-epidemiological study. *BMC Med Res Methodol*. 2014;14:64.
 40. Shah M, Deshpande N, Bharwani A, Nadig P, Doshi V, Dave D. Effectiveness of autologous platelet-rich fibrin in the treatment of intra-bony defects: A systematic review and meta-analysis. *J Indian Soc Periodontol*. 2014;18(6):698–704.
 41. Castro AB, Meschi N, Temmerman A, Pinto N, Lambrechts P, Teughels W, Quirynen M. Regenerative potential of leucocyte- and platelet-rich fibrin. Part A: intra-bony defects, furcation defects and periodontal plastic surgery. A systematic review and meta-analysis. *J Clin Periodontol*. 2017;44(1):67–82.