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Review

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

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Abstract: Introduction: One of the consequences of periodontitis is periodontal intrabony defects (PID). Various biomaterials have been used for its treatment, but there is still no biomaterial considered as the gold standard. Current research is focused on the use of platelet-rich plasma (PRP) for the treatment of PID. Objective: To determine the clinical effect of PRP in the treatment of PID through a systematic review with meta-analysis. Materials and Methods: A literature search was conducted until February 2017 in the biomedical databases: Pubmed, Embase, Scielo, Science Direct, SIGLE, LILACS, IBECS, and the Cochrane Central Register of Clinical Trials. The criteria for the selection of the studies, which were randomized clinical trials, were the following: articles or papers published in the last 5 years, reporting clinical effects, with a follow-up time equal to or greater than 6 months, and a sample size equal to or greater than 10 patients reporting the use of PRP 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 nine articles reporting a reduction in probing depth and gingival recession, and an increase in clinical insertion level when using PRP alone or in combination with another biomaterial. Conclusion: The reviewed literature suggests that the use of PRP in the treatment of PID has a positive clinical effect.

Keywords: platelet-rich plasma, periodontitis, review, meta-analysis.

INTRODUCTION.

Periodontal disease is a multifactorial and complex condition that affects the periodontium. It is characterized by the loss of collagen membrane with the subsequent destruction of the periodontal tissues.[1-3] If not treated, the condition will lead to a premature loss of teeth.[2,4]

The main objectives of periodontal treatment are to eliminate the inflammatory process, prevent the progression of periodontal disease, maintain natural dentition in optimal health and function, and regenerate the lost periodontal tissues.[1,5,6] The therapeutic modalities currently used to restore periodontal tissues, such as conventional open flap debridement (COFD), have shown limited potential to achieve the desired results. These techniques fail to regenerate the tissues affected by the disease. In addition, current regenerative procedures offer limited potential for complete periodontal restoration.[4,5]

One of the consequences of periodontal disease (periodontitis) is

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the appearance of periodontal intrabony defects (PID) (proximal and/or marginal bone loss). Various biomaterials, based on endogenous regenerative technology, have been used for treatment, in addition to using autogenous and allogeneic bone grafts. However, there is not any biomaterial considered as the gold standard yet for the treatment of PID.[3,5,7,8]

The key to tissue regeneration is to produce a cascade of coordinated curative events that can stimulate tissue formation. Such modulators include the use of growth factors (GFs), the application of extracellular matrix proteins, binding factors and the use of bone morphogenetic proteins.[2,9,10] The potential role of GFs in periodontal regeneration is currently the focus of research. In recent years, there has been an increase in the scientific evidence that demonstrates their effectiveness in periodontal regeneration.[2,5,11-14]

GFs are present in platelet alpha granules, which upon release allow the multiplication and development of vascular endothelial cells, smooth muscle cells and fibroblasts. In addition, they induce multiple effects on cellular remodeling and modulate the inflammatory reaction in the healing and tissue regeneration processes.[1,2,5,10,14-18]

GFs include the platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β). These factors are the most studied in terms of periodontal regeneration. They are known to facilitate bone regeneration after bone grafting by increasing neoangiogenesis, cellular chemotaxis, mitosis, promoting stem cell proliferation and increasing osteoconduction.[1,2,10,14,19] Other GFs, such as endothelial growth factor, vascular endothelial growth factor (VEGF), and type 1 insulin-growth factor, have been shown to have the potential to improve and accelerate the regeneration of hard and soft tissues.[1,5,10-15]

There is a growing interest in the use of platelet-rich plasma (PRP) for the treatment of PID since it is a concentrated source of autologous platelets enriched with several GFs.[2,5,10,14] However, there is a high heterogeneity among the studies that have evaluated the effect of PRP in the treatment of PID.[2,14,20-22]

The aim of this article was to evaluate the clinical effect of PRP in the treatment of periodontal intrabony defects.

MATERIALS AND METHODS.

This review was carried out according to a research protocol previously developed following the guidelines established in the PRISMA standards.[23]

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 high impact journals of periodontology such as: *Periodontology 2000, Journal of Clinical Periodontology* and *Journal of Periodontology* up to February 2017; using a combination of topic or thematic headings with the following keywords: ("plasma rico en plaquetas" OR "platelet rich plasma" OR "PRP" OR "plasma rich in growth factors") AND ("defecto intraóseo" OR "defecto periodontal" OR "intrabony defect" OR "infrabony defect" OR "periodontal defect").

Selection criteria.

The following inclusion criteria were considered: articles reporting the use of PRP in the treatment of PID; articles reporting clinical effects (reduction in probing depth, increase in clinical insertion level and reduction in gingival recession) when using PRP in the treatment of PID; articles published in the last 5 years, because the most current research is also the most rigorously conducted and contains the most relevant data; articles reporting a follow-up time equal to or greater than 6 months, whose sample sizes are equal to or greater than 10 patients, because the longer the follow-up period and the larger the sample size, the more representative the results will be, reducing the margin of error and increasing the level of confidence; articles reporting clinical trials without language restriction.

The following exclusion criteria were considered: articles reporting the use of PRP as a control group; articles published in non-indexed journals.

Process of selection and extraction of data.

The titles and abstracts of all the articles were reviewed. Full texts of the articles that appeared to meet the selection criteria were obtained.

A checklist was made in duplicate to evaluate the studies and to extract the information of interest. Two

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reviewers (LG and EI) independently performed the evaluation of the articles regarding title, author, year of publication, type of study, number of patients, age 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, activators 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.[24]

Analysis of results

Data from each study were placed and analyzed with RevMan 5.3 (Cochrane Group, UK).

RESULTS.

The initial search yielded a total of 112 titles; Figure 1 shows the selection flowchart.

Table 1 also shows the characteristics and variables considered in the nine selected articles. Figure 2 shows the analysis of the methodological quality and the risk of bias of the studies.

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

Figure 1. Article selection flowchart.

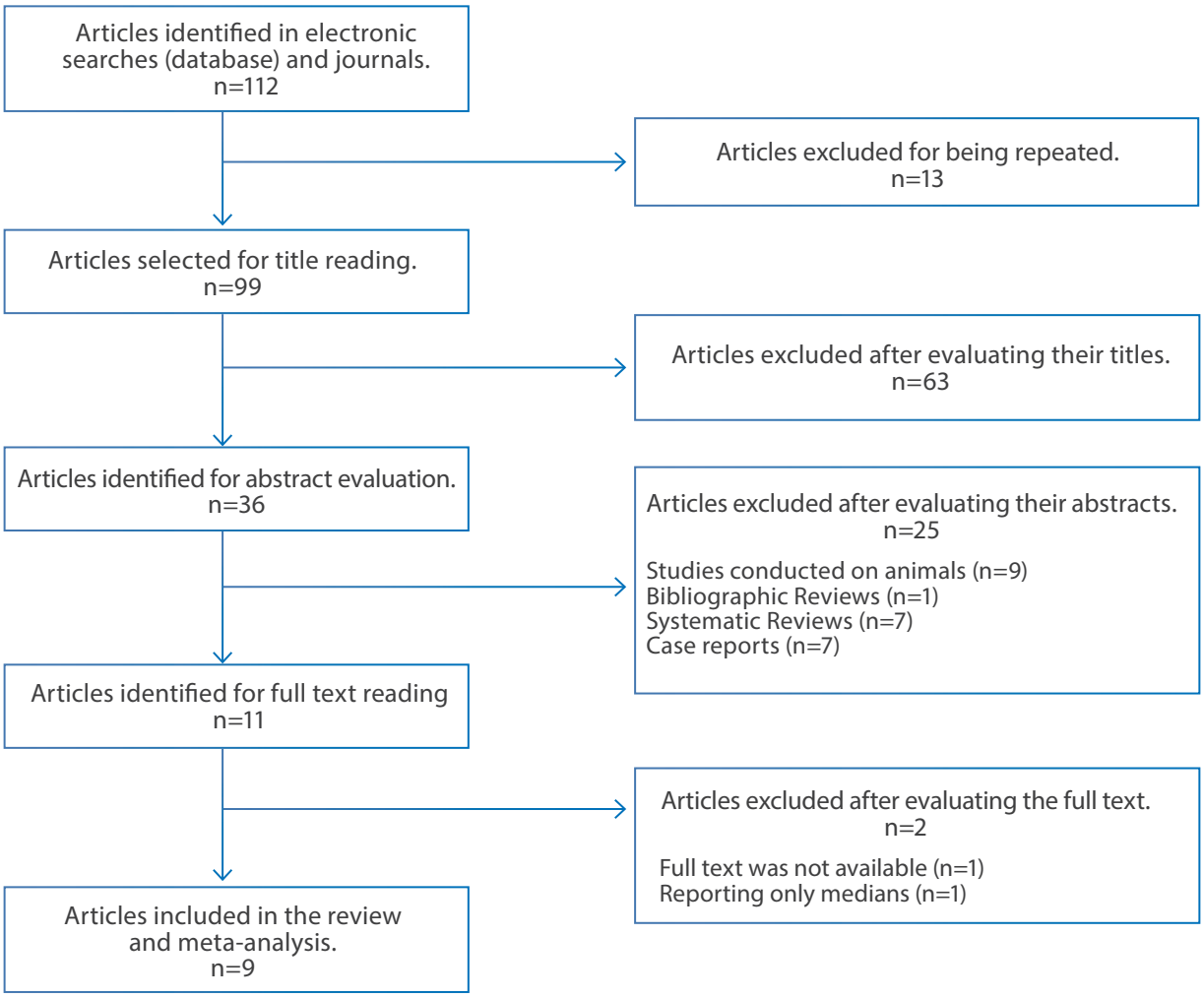


Table 1. Characteristics of included articles.

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 (walls)	N° of centrifugation cycles (rpm x m)	Primer	Post-surgical medication
Shukla *et al.*[25]	2016	RCT	20 (13/7)	40±10.5	9 months	India	Control (COFD+CPS) Test (COFD+CPS +PRP)	20 20	20 20	4.05±1.1 3.7±1	5.00±1.46 5.62±1.48	NR NR	NR	2 (2000rpm x 15m; 3000rpm x 15m)	Calcium Chloride	NR
Agarwal *et al.*[26]	2016	RCT	10 (7/3)	NA	1 year	India	Control (COFD) Test 1 (PRP) Test 2 (PRP+DFDBA)	10 10 10	9 10 9	2.69±1.37 4.86±2.12 4.88±1.12	1.27±0.89 4.10±1.47 4.26±1.85	-3.31±0.54 -2.04±1.15 -1.45±1.08	3 walls	1 (3000rpm x 10m)	10% Calcium Chloride gel+ autologous thrombin	Amoxicilin 500mg
Gamal *et al.*[27]	2016	RCT	30 (21/19)	39.6±3.9 (28–51)	9 months	Egipto	Control (Xenograft) Test 1 (PRP+Xenograft) Test 2 (PRF+Xenograft)	10 10 10	10 10 10	3.8±0.42 4.3±0.36 3.6±0.45	1.8±0.5 2.00±0.58 1.2±0.36	NR NR NR	2 and 3 walls	NR	NR	Amoxicilin 500mg or Clindamycin 300mg
Krosropanah *et al.*[28]	2015	RCT	12 (5/7)	45±10.7	6 months	Iran	Control (DFDBA) Test (DFDBA+PRP)	12 12	12 12	4.2 ± 1.22 4.6 ± 1.4	3.5±1.74 3.7±1.71	-0.9±1.06 -0.4±1.4	NR	1 (460g x 8m)	50 µL Calcium Citrate	Amoxicilin 500mg and Acetaminoph 500mg
Gupta [29]	2014	RCT	10	NA	1 year	India	Control (HA) Test (PRP+HA)	10 10	10 10	1.90±1.87 3.40±1.97	1.3±1.86 3.05±2.28	NR NR	NR	2 (1200rpm x 20m; 2000rpm x 15m)	10% Calcium Choloride gel+ human thrombin	Amoxicilin 500mg and Ibuprofen 400mg
Agarwal *et al.*[30]	2014	RCT	24 (14/10)	(30–65)	1 year	India	Control (DFDBA + Saline solution) Test (DFDBA+PRP)	24 24	24 24	3.65±0.52 3.65±0.63	2.40±0.61 3.15±0.50	-1.23±0.47 -0.54±0.59	1 and 2 walls and combined	2 (2400rpm x 10m; 3600rpm x 15m)	1mL of 10% Calcium Chloride with 1000 IU of topical thrombin	Amoxicilin 500 mg and Nimesulide
Döri *et al.*[31]	2013	RCT	26 (14/12)	(32–56)	5 years	Hungary	Control (NBM+EMB) Test (NBM+EMB+PRP)	13 13	12 12	5.0±2.39 4.9±2.03	4.3±2.2 4.3±2.19	-0.7±1.84 -0.6±1.91	1 and 2 walls	2 (2400rpm x 10m; 3600rpm x 15m)	Saline serum with 10% Calcium Chloride an 100U/ml sterile bovine thrombin	Amoxicilin 500mg
Hassan *et al.*[32]	2012	RCT	12 (7/5)	41.4±2.61	1 year	Arabia Saudita	Control (COFD+ABG) Test (COFD+ABG+PRP)	6 6	6 6	4.38±0.96 4.97±0.72	2.94±1.1 3.81±0.77	NR NA	2 walls	2 (200g x 20m; 400g x 10m)	10% Calcium Chloride +bovine thrombin	Amoxicilin 500mg
Pradeep *et al.*[33]	2012	RCT	54 (27/27)	36.8	9 months	India	Control (OFD) Test 1 (OFD+PRP) Test 2 (OFD+PRF)	18 18 18	17 17 16	2.97±0.93 3.77±1.07 3.77±1.19	2.83±0.91 2.93±1.08 3.17±1.29	-0.27±0.58 0.1±0.61 0.2±0.71	3 walls	1 (3000rpm x 10m)	10% Calcium Choloride	Amoxicilin 500mg and Ibuprofen 800mg

NR: Not reported, **RCT:** Randomized controlled trial; **COFD:** Conventional open-flap debridement; **PRP:** Platelet rich plasma; **CPS:** Calcium phosphosilicate; **DFDBA:** Demineralized Freeze Dried Bone Allograft; **ABG:** Autologous bone graft; **EMD:** Enamel Matrix Derivative; **HA:** Hydroxyapatite; **NBM:** Natural bone mineral; **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 2. Risk of bias of the articles.

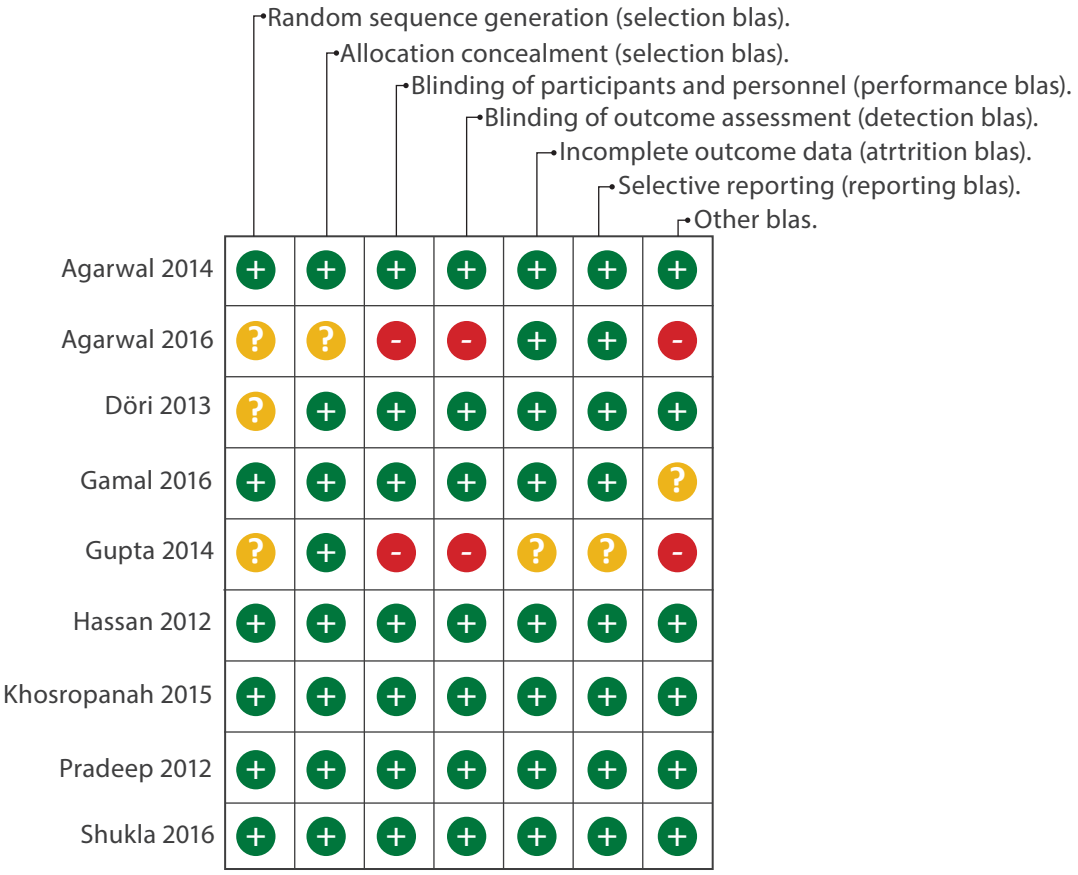


Figure 3. Forest plot of the event "Reduction of probing depth when using PRP in the treatment of periodontal intrabony defects".

Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV Random, 95% CI	Year
1.1.1 only PRP									
Pradeep 2012	3.77	1.07	17	2.97	0.93	17	12.8%	0.80 (0.13, 1.47)	2012
Agarwal 2016	4.86	2.12	10	2.69	1.37	9	5.2%	2.17 (0.58, 3.76)	2016
Subtotal (95% CI)			27			26	18.0%	**1.29 (0.00, 2.57)**	
Heterogeneity: Tau²=0.55; Chi²=2.42, d_f=1 (p=0.12); I²=59%									
Test for overall effect: Z=1.96 (p=0.05)									
1.1.2 PRP combined with another biomaterial									
Hassan 2012	4.97	0.72	6	4.38	0.96	6	9.6%	0.59 (-0.37, 1.55)	2012
Döri 2013	4.9	2.03	12	5	2.39	12	4.4%	-010 (-187, 167)	2013
Gupta 2014	3.4	1.97	10	1.9	1.87	10	4.8%	1.50 (-018, 3.18)	2014
Agarwal 2014	3.65	0.63	24	3.65	0.52	24	16.8%	0.00 (-0.33, 0.33)	2014
Khosropanah 2015	4.6	1.4	12	4.2	1.22	12	8.8%	0.40 (-065, 1.15)	2015
Gamal 2016	4.3	0.36	10	3.8	0.42	10	16.6%	0.50 (0.16, 0.84)	2016
Shukla 2016	3.7	1	20	4.05	1.1	20	13.0%	-0.35 (-1.00, 0.30)	2016
Agarwal 2016	4.88	1.12	9	2.69	1.37	9	7.9%	2.19 (1.03, 3.35)	2016
Subtotal (95% CI)			103			103	82.0%	**0.44 (-0.01, 0.89)**	
Heterogeneity: Tau²=0.22; Chi²=21.12, d_f=9 (p=0.004); I²=67%									
Test for overall effect: Z=1.91 (p=0.06)									
Total (95% CI)			130			129	100.0%	**0.59 (0.16, 1.01)**	
Heterogeneity: Tau²=0.26; Chi²=28.34, d_f=9 (p=0.0008); I²=68%									
Test for overall effect: Z=2.68 (p=0.007)									
Test for subgroup differences: Chi²=1.49, d_f=1 (p=0.22); I²=32.7%									

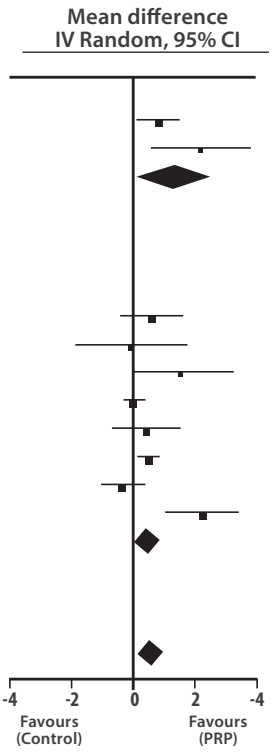


Figure 4. Forest plot of the event "Increase in clinical insertion level when using PRP in the treatment of periodontal intrabony defects"

Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV Random, 95% CI	Year
1.2.1 only PRP									
Pradeep 2012	2.93	1.08	17	2.83	0.91	17	12.8%	0.10 (-0.57, 0.77)	2012
Agarwal 2016	4.1	1.47	10	1.27	0.89	9	9.7%	2.83 (1.75, 3.91)	2016
Subtotal(95% CI)			**27**			**26**	**22.5%**	**1.43 (-1.24, 4.11)**	
Heterogeneity: Tau²=3.25; Chi²=17.69, d_f =1 (*p*=<0.0001); I²=94%									
Test for overall effect: Z=1.05 (*p*=0.29)									
1.2.2 PRP combined with another biomaterial									
Hassan 2012	3.81	0.77	6	2.94	1.1	6	9.7%	0.87(-0.20, 1.94)	2012
Döri 2013	4.3	2.19	12	4.3	2.2	12	5.9%	0.00 (-1.76, 1.76)	2013
Gupta 2014	3.05	2.28	10	1.3	1.86	10	5.6%	1.75 (-007, 3.57)	2014
Agarwal 2014	3.15	0.5	24	2.4	0.61	24	15.2%	0.00 (0.43, 1.07)	2014
Khosropanah 2015	3.7	1.71	12	3.5	1.74	12	7.8%	0.20 (-1.18, 1.58)	2015
Gamal 2016	2	0.58	10	1.8	0.5	10	14.3%	0.20 (-0.27, 0.67)	2016
Shukla 2016	5.62	1.48	20	5	1.46	20	11.0%	0.62 (-0.29, 1.53)	2016
Agarwal 2016	4.26	1.85	9	1.27	0.89	9	8.0%	2.99 (1.65, 4.33)	2016
Subtotal (95% CI)			**103**			**103**	**77.5%**	**0.80 (0.30, 1.30)**	
Heterogeneity: Tau²=0.25; Chi²=18.00, d_f =7 (*p*=0.01); I²=61%									
Test for overall effect: Z=3.13 (*p*=0.002)									
Total(95% CI)			**130**			**129**	**100.0%**	**0.94 (0.40, 1.47)**	
Heterogeneity: Tau²=0.46; Chi²=36.06, d_f =9 (*p*=<0.0001); I²=75%									
Test for overall effect: Z=3.43(*p*=0.0006)									
Test for subgroup differences: Chi²=0.21, d_f =1 (*p*=0.65); I²=0%									

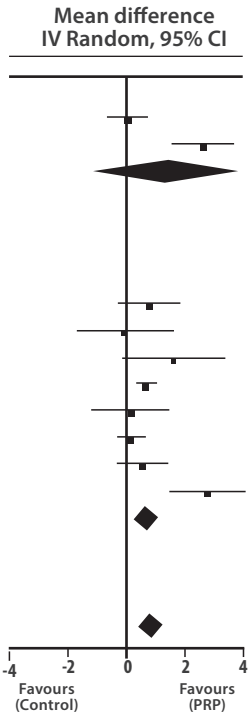
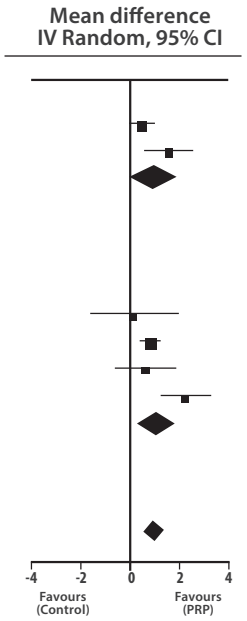


Figure 5. Forest plot of the event "Reduction in gingival recession when using PRP in the treatment of periodontal intrabony defects".

Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV Random, 95% CI	Year
1.3.1 only PRP									
Pradeep 2012	0.1	0.61	17	-0.27	0.58	17	24.4%	0.37 (-0.03, 0.77)	2012
Agarwal 2016	-2.04	1.15	10	-3.31	0.54	9	15.1%	1.27 (0.47, 2.07)	2016
Subtotal(95% CI)			**27**			**26**	**39.6%**	**0.75 (-0.12, 1.62)**	
Heterogeneity: Tau²=0.30; Chi²=3.93, d_f =1(*p*=0.05); I²=75%									
Test for overall effect: Z=1.69 (*p*=0.09)									
1.3.2 PRP combined with another biomaterial									
Döri 2013	-0.6	1.91	12	-0.7	1.84	12	6.6%	0.10 (-1.40, 1.60)	2013
Agarwal 2014	-0.54	0.59	24	-1.23	0.47	24	26.9%	0.69 (0.39, 0.99)	2014
Khosropanah 2015	-0.4	1.4	12	-0.9	1.06	12	11.8%	0.50 (-0.49, 1.49)	2015
Agarwal 2016	-1.45	1.08	9	-3.31	0.54	9	15.2%	1.86 (1.07, 2.65)	2016
Subtotal (95% CI)			**57**			**57**	**60.4%**	**0.88 (0.21, 1.55)**	
Heterogeneity: Tau²=0.28; Chi²=8.63, d_f =3 (*p*=0.03); I²=65%									
Test for overall effect: Z=2.56 (*p*=0.01)									
Total(95% CI)			**84**			**83**	**100.0%**	**0.82 (0.38, 1.25)**	
Heterogeneity: Tau²=0.16; Chi²=13.66, d_f =9(*p*=0.02); I²=63%									
Test for overall effect: Z=3.70(*p*=0.0002)									
Test for subgroup differences: Chi²=0.05, d_f =1(*p*=0.82); I²=0%									



DISCUSSION.

Results revealed that the use of PRP 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 the same if only PRP was used or if PRP was combined with another biomaterial.

In this study, a random effects model for the meta-analysis was used. It was found that there was no difference if the randomized controlled trial (RCT) had a parallel or cross-over design, since the studies showed positive clinical effects for the use of PRP in the treatment of PID. This is similar to the findings reported by Smail *et al.*,[34]

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who performed a meta-epidemiological 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 data. In contrast, Hou *et al.*,[2] stated that different study designs are not equally effective in assessing the clinical efficacy of PRP.

In relation to the use of PRP in the reduction of gingival recessions, there are conflicting results. Del Fabbro *et al.*[20] and Gao *et al.*[21] suggest that PRP does not produce significant results in gingival recessions. However, Fu *et al.*[35] report that the systematic review and meta-analysis performed by Del Fabbro *et al.*[20] contained a significant number of inconsistencies and therefore determined that their level of evidence was 2. The same observations are applicable for Gao *et al.*[21]. For this reason, one of the strengths of this review is to have taken into account the suggestions of Fu *et al.*,[35] for higher reliability results.

However, the present review also has limitations. Some RCTs with a high risk of bias were included. In addition, there is variability in obtaining PRP due to the different protocols currently in existence and to the different commercially available systems.

Despite these limitations, more than half of the studies showed a low risk of bias. Consequently, the results obtained from this systematic review and meta-analysis are reliable. The conclusions and the results of the systematic reviews that have been carried out on this topic,[2,14,20,21,36] confirm that using PRP produces a positive clinical effect in the treatment of PID, such reviews covered RCTs published in years prior to those included in this study.

However, these results cannot be generalized due to two reasons. First, most RCTs compared in all systematic reviews had high heterogeneity. Second, all RCTs are from European and Asian countries, but each continent and country has its own culture and type of food. These factors can significantly influence the PRP preparation and its clinical effects. It is recommended to carry out well-designed RCTs dealing with this issue in other countries.

CONCLUSION.

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

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