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Platelet-rich plasma for periodontal regeneration in the treatment of intrabony defects: a meta-analysis on prospective clinical trials

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Objective. The aim of this systematic review and meta-analysis was to assess the influence of platelet-rich plasma (PRP) on the regeneration of periodontal intrabony defects by means of evaluating clinical and radiographic outcomes in prospective human clinical trials.

Background. PRP is a high concentration of platelets suspended in a small volume of plasma and has been used for periodontal tissue regeneration. However, although it has been broadly studied, there is much controversy on its efficacy when used to treat intrabony periodontal defects.

Methods. An electronic literature search was conducted by two reviewers (AR and AM) in several databases up to February 2014. The PICO question was: Does PRP have a higher or similar efficacy of regenerating periodontal intrabony defects compared with other conventional periodontal regeneration treatments (e.g., bone grafts, barrier membranes)? Articles were included in this systematic review if they were prospective clinical trials with 10 or more human patients, reporting the radiographic and/or clinical outcomes PRP for regeneration intrabony periodontal defects. Random effects meta-analyses of the selected studies were applied to avoid any bias being caused by methodologic differences among studies.

Results. Twenty-two papers were obtained and reviewed. Of these, 21 articles fulfilled the inclusion criteria and subsequently were qualitatively analyzed. Eighteen of these could be meta-analyzed. Fourteen articles were included for evaluating of probing pocket depth (PPD). The weighted mean difference (WMD) was 0.55 mm, with a 95% CI = -0.09 to 1.20 mm ($P = .09$). For bone level (BL), 2 articles measured BL in millimeters, and the other two articles measured BL in percentage. The WMD was 0.76 mm (95% CI = 0.21-1.31 mm; $P = .007$) and 47.41% (95% CI = 32.48%-62.33%; $P < .0001$), respectively. For attachment level (AL) changes, 12 articles were included. The WMD was 0.58 mm, with a 95% CI = 0.24 to 0.91 mm ($P = .0008$). Sixteen articles were included for evaluation of marginal gingival level (MGL). The WMD -0.10 mm, with a 95% CI = -0.19 to -0.01 ($P = .03$).

Conclusions. High heterogeneity among studies made it difficult to draw clear conclusions. Nonetheless, within the limitations of this review, PRP might offer some beneficial effects on clinical and radiographic outcomes for regeneration of periodontal intrabony defects. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:562-574)

Regeneration of lost periodontal structures, characterized by formation of new cementum, new bone, and new periodontal ligament (PDL), has been a challenge for clinicians. Common procedures employed for periodontal regeneration include the use of barrier membranes alone,¹ bone substitutes with²⁻⁴ or without membranes,⁵ and root conditioning with chemical agents (e.g., citric acid or tetracycline).⁶ Although these procedures have shown more or less satisfactory results,^{1,7-9} a high degree of variability in clinical outcomes has been observed.¹⁰ The application of growth

factors (GFs) recently has shown to promote periodontal regeneration¹¹⁻¹⁷ is another promising approach for regeneration.

New materials that enhance and accelerate healing and regeneration of hard and soft tissues are being constantly study in the field of medicine. One of these is platelet-rich plasma (PRP). Matras et al. in 1982¹⁸ pioneered the use of a fibrin clot to promote tissue healing in oral surgery-related procedures. Subsequently, GFs were studied in autologous fibrin glue (AFG).¹⁹ As researchers focused on obtaining a

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Statement of Clinical Relevance

High heterogeneity among studies made it difficult to draw clear conclusions. Nonetheless, within the limitations of this review, platelet-rich plasma (PRP) may offer some beneficial effects on clinical and radiographic outcomes for guided tissue regeneration (GTR) of intrabony defects.

higher concentration of GFs, the capability of PRP to promote cell formation was realized. The positive effects of PRP are attributed to the angiogenic, mitogenic, and proliferative abilities of GFs, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF).^{20,21} PRP is defined as a high concentration of platelets suspended in a small volume of plasma. Blood is extracted from the patient and centrifugally processed to produce PRP. The platelets contain α -granules that are released during the first minutes after activation. The granules contain, among other molecules, the aforementioned GFs.²⁰

Osteoinduction stimulates the division, differentiation, and secretion of the bone cells present and the undifferentiated mesenchymal cells to synthesize new bone.²² The most common mediators are the bone morphogenetic proteins (BMPs), which promote the differentiation of mesenchymal pluripotent stem cells around the graft.²³ PRP contains no BMP, and hence it does not have osteoinductive potential itself. However, once the osteoconductive grafts have facilitated the formation of osteoblasts, the mitogenic capacity of GFs accelerates bone formation.²⁰ In 1997, Whitman et al.²⁴ were the first to refer to PRP in the field of oral surgery. Later on, Marx et al.²⁵ introduced the PRP for alveolar bone regeneration. They found better bone maturation and radiographic density in autologous grafts combined with PRP compared with autologous grafts alone. Since then, many clinical trials have been carried out in order to determine the benefit of using PRP in guided bone regeneration (GBR) and guided tissue regeneration (GTR).

All in all, the aim of this systematic review and meta-analysis was to assess the influence of PRP on the regeneration of periodontal intrabony defects by means of evaluating clinical and radiographic outcomes in prospective human clinical trials.

MATERIAL AND METHODS

Information sources and development of focused question

An electronic literature search was conducted by two reviewers (AR and AM) in several databases, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register databases for articles written in up to February 2014. The PICO (Patient, Intervention, Comparison, and Outcome) question was: Does PRP has a higher or similar efficacy in regenerating periodontal intrabony defects compared with other conventional periodontal regeneration treatments (e.g., bone grafts, barrier membranes)? The reporting of these meta-analyses followed the PRISMA (Preferred

Reporting Items for Systematic Review and Meta-Analyses) guidelines for adequate conductance of systematic reviews.

Screening process

Combinations of controlled terms (MeSH and Emtree) and keywords were used whenever possible. The search terms used, where “[mh]” represented the MeSH terms and “[tiab]” represented title and/or abstract, are listed below: (“platelet-rich plasma”[mh] OR “platelet-rich growth factor”[ti]) AND (periodontal defect [tiab]) OR (intrabony defect [tiab]) or (infrabony defect [tiab]) OR (clinical attachment loss [tiab]) AND English [la] NOT (letter [pt] OR comment [pt] OR editorial [pt]) NOT (“animals”[mh]). Additionally, a manual search of periodontology-related journals, including *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, and *The International Journal of Periodontics & Restorative Dentistry*, from October 2013 up to February 2014, was also performed to ensure a thorough screening process. References in the excluded articles were also checked seeking for studies that fulfilled our inclusion criteria.

Eligibility criteria

Articles were included in this systematic review if they met the following inclusion criteria: prospective clinical trials with 10 or more human patients, reporting the radiographic and clinical outcomes of PRP for regeneration of periodontal defects. Accordingly, several factors, such as the study design, number of patients included at the last follow-up assessment, number of defect sites, test/control groups, characteristics of the material (i.e., concentration, time of centrifugation), and type of bone grafting material/membrane were extracted from the articles. Moreover, in order to address the aim of this study more comprehensively, other parameters related to the technique were further extracted: probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing, radiographic analysis, suppuration, and recession (Table 1). These were subgrouped by initial, final, and reduction in percentage or millimeters, depending on the parameter to be studied. Case reports or case series with less than 10 patients, systematic reviews, preclinical studies, and human retrospective trials or randomized trials with missing information were excluded.

Data analyses

The primary outcome was probing PPD, and the secondary outcomes included CAL changes, radiographic bone level (BL), and changes of marginal

Table I. Eligibility criteria

Author (year)	Study design	Group (T/C)	Patients (n°)	Defects (n°)	Age (SD)	Smokers (Y/N)	Other systemic considerations	Type of defect
Lekovic et al. (2002)	RCT	T (PRP + ABBM + BCM)	21 (6 females & 15 males)	21	40 ± 11 years	9 smokers & 12 non-smokers	N	ND
		C (PRP + ABBM)		21			N	ND
Camargo et al. (2002)	RCT	T (PRP + ABBM + BCM)	18 (10 females & 8 males)	18	39 ± 9 years	6 smokers & 12 non-smokers	N	ND
		C (ABBM + BCM)		18			N	ND
Hanna et al. (2004)	RCT	T (PRP + BDX)	13 (8 females & 5 males)	13	37 to 74 years (55.5±?)	ND	N	2 or 3 WD
		C (BDX alone)		13		ND	N	2 or 3 WD
Sammartino et al. (2005)	RCT	T (PRP)	18 (8 females & 10 males)	18	21 to 26 years (23.5±?)	N	N	1WD
		C (Empty)		18		N	N	1WD
Okuda et al. (2005)	RCT	T (PRP + HA)	70 (49 females & 21 males)	35	55.5 ± 8.2 years	N	N	1WD=7 / 2WD=6 / 3WD=22
		C (Saline + HA)		35		N	N	1WD=5 / 2WD=4 / 3WD=26
Ouyang & Qiao (2006)	RCT	T (PRP + ABBM)	10 (5 females & 5 males)	9	27 to 45 years (36.0±?)	N	N	2WD=4 / 3WD=5
		C ABBM alone		8		N	N	2WD=3 / 3WD=5
Papli & Chen (2007)	PCS	T (APC)	5 (4 females & 1 male)	5	33 ± 10.23 years	N	N	2WD=3 / 3WD=2
		C (MEM)		5		N	N	2WD=3 / 3WD=2
Döri et al. (2007)	RCT	T (PRP + ABBM + ePTFE)	24 (14 females & 10 males)	12	26 to 55 years (40.5±?)	N	N	1 to 2WD=10 / 2WD=2
		C (ABBM + ePTFE)		12		N	N	1 to 2WD=9 / 2WD=3
Döri et al. (2007)	RCT	T (PRP + ABBM + GTR)	30 (16 females & 14 males)	15	28 to 56 years (40.5±?)	N	N	1 to 2WD=9 / 2WD=4 / 3WD=2
		C (ABBM + GTR)		15		N	N	1 to 2WD=10 / 2WD=3 / 3WD=2
Demir et al. (2007)	RCT	T (PRP + BG)	29 (16 females & 13 males)	15	37.87 ± 14.16	9 smokers (5 T group & 4 C group) & 20 non-smokers	N	1WD=5 / 2WD=8 / 3WD=3
		C (BG)		14	34.07 ± 09.34		N	1WD=3 / 2WD=8 / 3WD=3
Piemontese et al. (2008)	RCT	T (DFDBA + PRP)	60 (29 females & 31 males)	30	47 to 72 years (58.4 ± 10.0)	N	N	2WD= 8 / 3WD= 22
		C (DFDBA + Saline)		30		N	N	2WD= 10 / 3WD= 20
Döri et al. (2008)	RCT	T (PRP + β-TCP + ePTFE)	28 (16 females & 12 males)	14	28 to 56 years (42±?)	N	N	1 to 2WD=3 / 2WD=9 / 3WD=2
		C (β-TCP + ePTFE)		14		N	N	1 to 2WD=3 / 2WD=8 / 3WD=3
Döri et al. (2008)	RCT	T (PRP + ABBM + EMD)	26 (14 females & 12 males)	13	32 to 56 years (44±?)	N	N	1 to 2WD=7 / 2WD=6
		C (ABBM + EMD)		13		N	N	1 to 2WD=8 / 2WD=5
Camargo et al. (2009)	RCT	T (PRP + BPBM + GTR)	23 (14 females & 9 males)	23	34 to 67 years (47 ± 10.00)	11 Y	N	2WD=19 / 3WD=4
		C (BPBM + GTR)		23		12 N	N	2WD=17 / 3WD=6
Yilmaz et al. (2010)	RCT	Smokers (PRP + BDX)	24 (12 smokers & 12 non-smokers)	56	ND	Y	N	1 to 3WD=15 / 2WD=23 / 2 to 3WD=18
		Non-Smokers (PRP + BDX)		57		N	N	1 to 3WD=13 / 2WD=24 / 2 to 3WD=20
Yilmaz et al. (2011)	RCT	T (PRP + BDX)	20 (8 females & 12 males)	41	ND	ND	N	1 to 3WD=10 / 2WD=23 / 2 to 3WD=3 / 3WD=5
		C (PPP + BDX)		38		ND	N	1 to 3WD=10 / 2WD=19 / 2 to 3WD=5 / 3WD=4
Özdemir et al. (2012)	RCT	C (β-TCP)	14 (5 females & 9 males)	14	48.9 ± 6.6 years	N	N	3WD=14
		T (PPP + β-TCP)		14		N	N	3WD=14
Hassan et al. (2012)	RCT	C (AB)	12 (5 females & 7 males)	12	41.4 ± 2.61 years	N	N	2 or 3 WD
		T (AB + PRP)		12		N	N	2 or 3 WD
Pradeep et al. (2012)	RCT	T (PRF)	54 (27 females & 27 males)	33	(36.8 ± ??)	N	N	3WD
		T (PRP)		32		N	N	3WD
		C (OFD)		33		N	N	3WD
Bajaj et al. (2013)	RCT	T (PRF)	42 (20 females & 22 males)	24	(39.4 ± ??)	N	N	2FD
		T (PRP)		25		N	N	2FD
		C (OFD)		23		N	N	2FD
Döri et al. (2013)	RCT	T (EMD + ABBM + PRP)	24 (13 females & 11 males)	12	32 to 56 years	N	N	1 to 2WD=6 / 2WD=6
		C (EMD + ABBM)		12		N	N	1 to 2WD=7 / 2WD=5

β-TCP, beta tricalcium phosphate; AB, autologous bone; ABBM, anorganic bovine bone mineral (Bio-Oss, Geistlich, Switzerland); ACD-A, anticoagulant citrate dextrose A; APC, autologous platelet concentrate; B, Buccal; BCM, bioabsorbable collagen membrane (BioGide, Geistlich Pharma, Wolhusen, Switzerland); BDX, bovine-derived xenograft; BG, bioactive glass; DBX, allogeneic demineralized bone matrix (DBX, Synthes, USA); DFDBA, demineralized freeze-dried bone allograft (Musculoskeletal Transplant Foundation, Adison, N.J.); EMD, enamel matrix derivative (Emdogain, Institute Straumann); ePTFE, non-resorbable expanded polytetrafluoroethylene (W.L. Gore & Associates, Flagstaff, AZ); FD, furcation defects; GTR, guided tissue regeneration (BioGide Perio, Geistlich, Wolhusen, Switzerland); HA, hydroxyapatite; L, Lingual; MBC, bioabsorbable collagen membrane (ACE Surgical supply, Inc., USA); MEM, bioabsorbable barrier membrane (Resolut, W.L. Gore & Associates, Flagstaff, AZ); N, no; NB, synthetic calcium hydroxyapatite (Novabone Porex Surgical Inc, MTF, USA); NC, not clear; ND, not determined or reported; OFD, open-flap debridement; PCS, prospective case series; PDCM, porcine-derived collagen membrane (Bio-Gide, Geistlich); PID, periodontal intrabony defects; PRF, platelet rich fibrin; PRP, platelet rich-plasma; PRP M1, platelet rich-plasma method 1; RCT, Randomized controlled trial; PRP M2, platelet rich-plasma method 2; Scale 1-5 (1=minimal or radiopaque bone formation; 5=maximal or radiopaque bone formation); TCAS, trisodium citrate anticoagulant solution; TMBG, torus mandibular bone graft; WD, Wall defect.

Concentration of PRP	First Centrifugation	Second Centrifugation	Grafting material	Type of membrane	Follow-up (months)
10ml of blood + 1ml ACD-A	5,600rpm - 6min	N	ABBM	BCM	6
10ml of blood + 1ml ACD-A	5,600rpm - 6min	N	ABBM	BCM	6
10ml of blood + 1ml ACD-A	5,600rpm - 6min	N	ABBM	BCM	6
10ml of blood + 1ml ACD-A	5,600rpm - 6min	N	ABBM	BCM	6
60ml of blood + 7ml ACD-A (7ml of PRP)	ND	N	BDX	N	6
N	N	N	BDX	N	6
40ml of blood + 10% TCAS	1,220rpm - 15min	N	N	N	4.5
N	N	N	N	N	4.5
8.5ml of blood + 1ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	HA	N	12
N	N	N	HA	N	12
10ml of blood + 1ml ACD-A	1,220rpm - 15min	3,600rpm - 15min	ABBM	N	12
N	N	N	ABBM	N	12
55ml of blood + 6ml ACD-A (5 to 7 ml of APC was collected)	ND	ND	N	MEM	12
N	N	ND	N	MEM	12
7ml of blood + 1ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	ABBM	ePTFE (removed after 6 weeks)	12
N	N	N	ABBM	ePTFE (removed after 6 weeks)	12
7ml of blood + 1ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	ABBM	GTR	12
N	N	N	ABBM	GTR	12
9ml of blood + 0.105mol/l ACD-A	200g - 10min	250g - 10min	BG	N	9
9ml of blood + 0.105mol/l ACD-A	N	N	BG	N	9
60ml of blood + 7ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	DFDBA	N	12
N	N	N	DFDBA	N	12
7ml of blood + 1ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	β-TCP	ePTFE (removed after 6 weeks)	12
N	N	N	β-TCP	ePTFE (removed after 6 weeks)	12
7ml of blood + 1ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	EMD + ABBM	N	12
N	N	N	EMD + ABBM	N	12
10ml of blood + 1ml ACD-A	5,600rpm - 6min	N	BPBM	PDCM	6
N	N	N	BPBM	PDCM	6
30ml of blood	ND	N	BDX	N	12
30ml of blood	ND	N	BDX	N	12
20ml of blood + 2ml ACD-A	ND rpm - 14min	N	BDX	N	12
20ml of blood + 2ml ACD-A	ND rpm - 14min	N	BDX	N	12
8ml of blood + 0.5ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	β-TCP	N	6
8ml of blood + 0.5ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	β-TCP	N	6
N	N	N	AB	MBC	12
10ml of blood + 0.5ml ACD-A	200 × g for 20min	400 × g for 10min	AB	MBC	12
30ml of blood	3,000rpm - 10min	N	N	N	9
20ml of blood + 2.8ml ACD-A	3,000rpm - 10min	N	N	N	9
N	N	N	N	N	9
30ml of blood	400g - 10min	N	N	N	9
20ml of blood + 2.8ml ACD-A	400g - 10min	N	N	N	9
N	N	N	N	N	9
7ml of blood + 1ml ACD-A	2,400rpm - 10min	3,600rpm - 15min	EMD + ABBM	N	60
N	N	N	EMD + ABBM	N	60

Table I. Continued

Author (year)	Mean probing depth			Mean clinical attachment level			Radiographic analysis		
Lekovic et al. (2002)	<i>Initial (mm)</i> B: 7.81 ± 1.32 L: 7.92 ± 1.40 B: 7.96 ± 1.41 L: 7.90 ± 1.38	<i>Final (mm) (6 months)</i> B: 3.62 ± 1.12 L: 3.71 ± 1.06 B: 3.98 ± 1.16 L: 3.96 ± 1.15	<i>Reduction (mm)</i> B: 4.19 ± 0.88 L: 4.21 ± 0.92 B: 3.98 ± 1.02 L: 3.94 ± 0.94	<i>Initial (mm)</i> B: ND L: ND B: ND L: ND	<i>Final (mm) (6 months)</i> B: ND L: ND B: ND L: ND	<i>Reduction (mm)</i> B: 4.12 ± 0.78 L: 4.16 ± 0.83 B: 3.78 ± 0.72 L: 3.84 ± 0.76	<i>Initial (mm)</i> ND ND ND ND	<i>Final (mm) (6 months)</i> ND ND ND ND	<i>Reduction (mm)</i> ND ND ND ND
Camargo et al. (2002)	<i>Initial (mm)</i> B: 7.87 ± 1.38 L: 7.76 ± 1.42 B: 7.78 ± 1.46 L: 7.67 ± 1.28	<i>Final (mm) (6 months)</i> B: 2.89 ± 1.36 L: 2.83 ± 1.41 B: 4.16 ± 0.83 L: 4.13 ± 0.99	<i>Reduction (mm)</i> B: 4.98 ± 0.96 L: 4.93 ± 0.92 B: 3.62 ± 0.81 L: 3.54 ± 0.88	<i>Initial (mm)</i> B: ND L: ND B: ND L: ND	<i>Final (mm) (6 months)</i> B: ND L: ND B: ND L: ND	<i>Reduction (mm)</i> B: 4.37 ± 1.31 L: 4.28 ± 1.33 B: 2.62 ± 1.23 L: 2.44 ± 1.21	<i>Initial (mm)</i> ND ND ND ND	<i>Final (mm) (6 months)</i> ND ND ND ND	<i>Reduction (mm)</i> ND ND ND ND
Hanna et al. (2004)	<i>Initial (mm)</i> B: 6.92 ± 1.50 L: 7.15 ± 1.46 B: 6.08 ± 0.95 L: 6.92 ± 1.11	<i>Final (mm) (6 months)</i> B: 3.38 ± 0.50 L: 3.61 ± 1.04 B: 4.15 ± 0.89 L: 4.23 ± 1.16	<i>Reduction (mm)</i> B: 3.54±?? L: 3.54±?? B: 1.93±?? L: 2.69±??	<i>Initial (mm)</i> B: 6.92 ± 1.70 L: 6.76 ± 1.42 B: 6.38 ± 1.19 L: 6.92 ± 1.38	<i>Final (mm) (6 months)</i> B: 3.69 ± 1.03 L: 3.46 ± 1.50 B: 4.31 ± 0.85 L: 4.38 ± 1.32	<i>Reduction (mm)</i> B: 3.23±?? L: 3.30±?? B: 2.07±?? L: 2.54±??	<i>Initial (mm)</i> ND ND ND ND	<i>Final (mm) (6 months)</i> ND ND ND ND	<i>Reduction (mm)</i> ND ND ND ND
Sammartino et al. (2005)	<i>Initial (mm)</i> 8.89 ± 1.01 8.90 ± 0.71	<i>Final (mm) (4.5 months)</i> 3.65 ± 0.47 7.18 ± 0.95	<i>Reduction (mm)</i> 5.24±?? 1.72±??	<i>Initial (mm)</i> 6.89 ± 1.01 6.80 ± 0.78	<i>Final (mm) (4.5 months)</i> 2.42 ± 1.38 5.84 ± 0.90	<i>Reduction (mm)</i> 4.47±?? 0.96±??	<i>Initial (mm)</i> ND ND	<i>Final (mm) (4.5 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Okuda et al. (2005)	<i>Initial (mm)</i> 7.7 ± 1.5 7.9 ± 1.8	<i>Final (mm) (12 months)</i> 3.0 ± 0.8 4.2 ± 1.9	<i>Reduction (mm)</i> 4.7 ± 1.6 3.7 ± 2.0	<i>Initial (mm)</i> 8.4 ± 1.8 8.8 ± 1.8	<i>Final (mm) (12 months)</i> 5.0 ± 1.8 6.8 ± 1.7	<i>Reduction (mm)</i> 3.4 ± 1.7 2.0 ± 1.2	<i>Initial (mm)</i> 5.0 ± 1.6 4.8 ± 1.7	<i>Final (mm) (12 months)</i> 1.4 ± 1.3 2.1 ± 1.7	<i>Reduction (mm)</i> 3.5 ± 1.5 2.7 ± 1.6
Ouyang & Qiao (2006)	<i>Initial (mm)</i> 8.22 ± 1.31 7.78 ± 1.16	<i>Final (mm) (12 months)</i> 3.44 ± 0.47 4.30 ± 0.81	<i>Reduction (mm)</i> 4.78 ± 0.95 3.48 ± 0.41	<i>Initial (mm)</i> 16.67 ± 2.19 16.33 ± 1.57	<i>Final (mm) (12 months)</i> 12.16 ± 1.97 13.48 ± 1.17	<i>Reduction (mm)</i> 4.52 ± 1.14 2.85 ± 0.80	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Papli & Chen (2007)	<i>Initial (mm)</i> 8.0 ± 1.41 7.0 ± 2.05	<i>Final (mm) (12 months)</i> 5.0 ± 2.0 3.6 ± 1.14	<i>Reduction (mm)</i> 3.0 ± 1.41 3.6 ± 1.67	<i>Initial (mm)</i> 7.6 ± 2.07 7.2 ± 1.1	<i>Final (mm) (12 months)</i> 5.4 ± 3.05 4.2 ± 1.3	<i>Reduction (mm)</i> 2.2 ± 1.79 3.0 ± 1.0	<i>Initial (mm)</i> 8.78 ± 2.48 7.34 ± 1.59	<i>Final (mm) (12 months)</i> 5.54 ± 3.59 4.64 ± 1.74	<i>Reduction (mm)</i> 3.24±?? 2.70±??
Döri et al. (2007)	<i>Initial (mm)</i> 8.6 ± 1.7 8.8 ± 1.7	<i>Final (mm) (12 months)</i> 3.1 ± 1.7 3.1 ± 1.0	<i>Reduction (mm)</i> 5.5 ± 1.2 5.7 ± 1.2	<i>Initial (mm)</i> 10.3 ± 1.4 10.4 ± 2.6	<i>Final (mm) (12 months)</i> 5.7 ± 1.6 5.9 ± 1.8	<i>Reduction (mm)</i> 4.7 ± 1.1 4.6 ± 0.8	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Döri et al. (2007)	<i>Initial (mm)</i> 8.9 ± 2.3 8.9 ± 2.5	<i>Final (mm) (12 months)</i> 3.4 ± 2.0 3.4 ± 2.3	<i>Reduction (mm)</i> 5.5 ± 1.3 5.5 ± 1.7	<i>Initial (mm)</i> 10.9 ± 2.2 11.1 ± 2.5	<i>Final (mm) (12 months)</i> 6.4 ± 1.8 6.5 ± 2.3	<i>Reduction (mm)</i> 4.5 ± 1.1 4.6 ± 1.1	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Demir et al. (2007)	<i>Initial (mm)</i> 7.80 ± 0.28 8.36 ± 0.53	<i>Final (mm) (9 months)</i> 4.20 ± 0.49 5.07 ± 0.45	<i>Reduction (mm)</i> 3.60 ± 0.51 3.28 ± 0.45	<i>Initial (mm)</i> 8.53 ± 0.42 9.07 ± 0.57	<i>Final (mm) (9 months)</i> 5.40 ± 0.50 6.21 ± 0.58	<i>Reduction (mm)</i> 3.13 ± 0.46 2.86 ± 0.42	<i>Initial (mm)</i> ND ND	<i>Final (mm) (9 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Piemontese et al. (2008)	<i>Initial (mm)</i> 8.4 ± 1.9 8.0 ± 1.5	<i>Final (mm) (12 months)</i> 3.8 ± 0.9 4.5 ± 2.7	<i>Reduction (mm)</i> 4.6 ± 1.3 3.5 ± 1.9	<i>Initial (mm)</i> 8.8 ± 1.8 8.5 ± 2.4	<i>Final (mm) (12 months)</i> 5.2 ± 2.4 6.1 ± 2.1	<i>Reduction (mm)</i> 3.6 ± 1.8 2.4 ± 2.2	<i>Initial (mm)</i> 9.2 ± 1.4 9.0 ± 1.7	<i>Final (mm) (12 months)</i> 5.9 ± 1.6 6.4 ± 1.9	<i>Reduction (mm)</i> 3.3 ± 1.5 2.6 ± 1.8
Döri et al. (2008)	<i>Initial (mm)</i> 9.1 ± 0.6 9.0 ± 0.8	<i>Final (mm) (12 months)</i> 3.3 ± 0.5 3.6 ± 0.9	<i>Reduction (mm)</i> 5.8 ± 0.6 5.4 ± 0.7	<i>Initial (mm)</i> 10.1 ± 1.3 9.9 ± 1.0	<i>Final (mm) (12 months)</i> 5.7 ± 1.1 5.9 ± 1.2	<i>Reduction (mm)</i> 4.1 ± 0.7 3.9 ± 0.9	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Döri et al. (2008)	<i>Initial (mm)</i> 8.8 ± 1.9 8.8 ± 2.0	<i>Final (mm) (12 months)</i> 3.1 ± 0.9 2.8 ± 1.6	<i>Reduction (mm)</i> 5.8 ± 1.8 5.9 ± 1.3	<i>Initial (mm)</i> 10.8 ± 2.0 10.5 ± 1.6	<i>Final (mm) (12 months)</i> 6.0 ± 1.5 5.5 ± 1.4	<i>Reduction (mm)</i> 4.8 ± 1.3 5.0 ± 0.9	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND
Camargo et al. (2009)	<i>Initial (mm)</i> B: 8.19 ± 1.56 L: 8.21 ± 1.62 B: 8.11 ± 1.48 L: 8.23 ± 1.52	<i>Final (mm) (6 months)</i> B: 3.31 ± 1.38 L: 3.49 ± 1.46 B: 3.95 ± 1.46 L: 4.41 ± 1.49	<i>Reduction (mm)</i> B: 4.88 ± 1.08 L: 4.72 ± 1.12 B: 4.16 ± 1.11 L: 3.82 ± 0.98	<i>Initial (mm)</i> B: ND L: ND B: ND L: ND	<i>Final (mm) (6 months)</i> B: ND L: ND B: ND L: ND	<i>Reduction (mm)</i> B: 4.38 ± 1.22 L: 4.12 ± 1.18 B: 3.56 ± 1.21 L: 3.34 ± 1.18	<i>Initial (mm)</i> ND ND ND ND	<i>Final (mm) (6 months)</i> ND ND ND ND	<i>Reduction (mm)</i> ND ND ND ND
Yılmaz et al. (2010)	<i>Initial (mm)</i> 6.72 ± 1.03 6.89 ± 0.95	<i>Final (mm) (12 months)</i> 2.75±??? 2.26±???	<i>Reduction (mm)</i> 3.97 ± 0.76 4.63 ± 0.52	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND	<i>Initial (mm)</i> 5.80 ± 1.88 4.54 ± 0.53	<i>Final (mm) (12 months)</i> 8.78±?? 8.21±??	<i>Gain (mm)</i> 2.98 ± 0.38 3.67 ± 0.48
Yılmaz et al. (2011)	<i>Initial (mm)</i> 6.93 ± 1.13 6.57 ± 1.16	<i>Final (mm) (12 months)</i> 3.06±??? 2.81±???	<i>Reduction (mm)</i> 3.87 ± 0.86 3.76 ± 0.80	<i>Initial (mm)</i> ND ND	<i>Final (mm) (12 months)</i> ND ND	<i>Reduction (mm)</i> ND ND	<i>Initial (mm)</i> 9.08 ± 2.32 8.91 ± 2.29	<i>Final (mm) (12 months)</i> 11.19±?? 11.10±??	<i>Gain (mm)</i> 2.11 ± 0.87 2.19 ± 0.96
Özdemir et al. (2012)	<i>Initial (mm)</i> 7.0 ± 1.25 7.0 ± 1.00	<i>Final (mm) (12 months)</i> 4.0 ± 1.25 4.0 ± 1.00	<i>Reduction (mm)</i> 3.00 ± 1.25 3.00 ± 1.25	<i>Initial (mm)</i> 7.0 ± 2.00 7.5 ± 1.25	<i>Final (mm) (6 months)</i> 6.0 ± 2.25 5.0 ± 3.00	<i>Reduction (mm)</i> 1.0±??? 2.5±???	<i>Initial (mm)</i> 27.0±?? 28.0±??	<i>Final (mm) (6 months)</i> 17.0±?? 20.0±??	<i>Reduction (mm)</i> 10.0±??? 8.00±???
Hassan et al. (2012)	<i>Initial (mm)</i> 7.19 ± 0.71 7.28 ± 0.53	<i>Final (mm) (12 months)</i> 2.81 ± 0.64 2.31 ± 0.48	<i>Reduction (mm)</i> 4.38±?? 4.97±??	<i>Initial (mm)</i> 5.14 ± 0.77 5.24 ± 0.57	<i>Final (mm) (12 months)</i> 2.20 ± 0.79 1.43 ± 0.51	<i>Reduction (mm)</i> 2.94±?? 3.81±??	<i>Initial (mm)</i> 3.87 ± 0.28 3.57 ± 0.35	<i>Final (mm) (12 months)</i> 3.54 ± 0.27 2.25 ± 0.36	<i>Reduction (mm)</i> 0.33±?? 1.32±??
Pradeep et al. (2012)	<i>Initial (mm)</i> 7.83 ± 1.44 7.90 ± 1.56 7.76 ± 1.22	<i>Final (mm) (9 months)</i> 4.06 ± 0.83 4.13 ± 1.04 4.80 ± 0.66	<i>Reduction (mm)</i> 3.77 ± 1.19 3.77 ± 1.07 2.97 ± 0.93	<i>Initial (mm)</i> 6.20 ± 1.49 6.16 ± 1.53 6.26 ± 1.17	<i>Final (mm) (9 months)</i> 3.03 ± 0.76 3.23 ± 1.22 3.43 ± 0.89	<i>Reduction (mm)</i> 3.17 ± 1.29 2.93 ± 1.08 2.83 ± 0.91	<i>Initial (%)</i> ND ND ND	<i>Final (%) (9 months)</i> ND ND ND	<i>Reduction (%)</i> 55.41 ± 11.39 56.85 ± 14.01 1.56 ± 15.12
Bajaj et al. (2013)	<i>Initial (mm)</i> 7.29 ± 0.95 7.17 ± 1.01 6.87 ± 0.90	<i>Final (mm) (9 months)</i> 3.0 ± 0.51 3.25 ± 0.68 5.29 ± 0.99	<i>Reduction (mm)</i> 4.29 ± 1.04 3.92 ± 0.93 1.58 ± 1.02	<i>Initial (mm)</i> NC NC NC	<i>Final (mm) (9 months)</i> NC NC NC	<i>Reduction (mm)</i> NC NC NC	<i>Initial (%)</i> ND ND ND	<i>Final (%) (9 months)</i> ND ND ND	<i>Reduction (%)</i> 44.01 ± 9.98 42.83 ± 11.15 2.78 ± 0.68
Döri et al. (2013)	<i>Initial (mm)</i> 8.7 ± 1.7 8.8 ± 2.0	<i>Final (mm) (60 months)</i> 3.8 ± 1.1 3.8 ± 1.3	<i>Reduction (mm)</i> 4.9±?? 5.0±??	<i>Initial (mm)</i> 10.5 ± 1.6 10.6 ± 1.7	<i>Final (mm) (60 months)</i> 6.2 ± 1.5 6.3 ± 1.4	<i>Reduction (mm)</i> 4.3±?? 4.3±??	<i>Initial (mm)</i> ND ND	<i>Final (mm) (60 months)</i> ND ND	<i>Reduction (mm)</i> ND ND

Bleeding on probing			Supuration			Recession (mm)
<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	B: 1.72 ± 0.37
ND	ND	ND	ND	ND	ND	L: 1.78 ± 0.36
ND	ND	ND	ND	ND	ND	B: 1.68 ± 0.41
						L: 1.75 ± 0.38
<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	B: 0.67 ± 0.41
0.66 ± 0.26	0.53 ± 0.23	0.13±??	ND	ND	ND	L: 0.71 ± 0.44
0.68 ± 0.27	0.56 ± 0.22	0.12±??	ND	ND	ND	B: 0.94 ± 0.38
						L: 1.02 ± 0.36
<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	B: -0.30 ± 1.09
ND	ND	ND	ND	ND	ND	L: 0.15 ± 1.09
ND	ND	ND	ND	ND	ND	B: -0.15 ± 0.89
						L: -0.15 ± 1.06
<i>Initial (%)</i>	<i>Final (%) (4.5 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (4.5 months)</i>	<i>Reduction (%)</i>	0.80 ± 0.37
0.73 ± 0.45	0.61 ± 0.27	0.16±??	ND	ND	ND	
0.81 ± 0.39	0.68 ± 0.29	0.19±??	ND	ND	ND	0.82 ± 0.51
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	-1.3 ± 1.2
0.9 ± 0.2	0.2 ± 0.4	0.7±??	ND	ND	ND	
1.0 ± 0.2	0.3 ± 0.5	0.7±??	ND	ND	ND	-1.8 ± 1.6
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	0.8 ± 0.4
0.89 ± 1.05	0.89 ± 0.78	0.00±??	ND	ND	ND	
0.88 ± 0.64	1.00 ± 0.93	-0.12±??	ND	ND	ND	0.95 ± 0.45
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	0.8 ± 1.01
10.8 ± 8.53	9.5 ± 4.59	1.3±??	ND	ND	ND	
			ND	ND	ND	0.6 ± 1.14
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	1.2 ± 1.1
41%	15%	26%	ND	ND	ND	
42%	14%	28%	ND	ND	ND	1.2 ± 0.9
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	1.1 ± 0.7
52%	18%	34%	ND	ND	ND	
54%	19%	35%	ND	ND	ND	1.3 ± 0.8
<i>Initial (%)</i>	<i>Final (%) (9 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	-0.47 ± 0.19
80%	26.66%	53.34%	ND	ND	ND	
78.57%	28.57%	50%	ND	ND	ND	-0.43 ± 0.25
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	-1.0 ± 1.3
1.2 ± 0.3	0.2 ± 0.4	1.0±??	ND	ND	ND	
1.4 ± 0.5	0.1 ± 0.6	1.3±??	ND	ND	ND	-1.1 ± 2.1
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	1.4 ± 0.8
38%	11%	27%	ND	ND	ND	
40%	12%	28%	ND	ND	ND	1.5 ± 0.7
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	1.0 ± 1.0
58%	19%	39%	ND	ND	ND	
60%	18%	42%	ND	ND	ND	0.9 ± 1.3
<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	B:0.69 ± 0.66
ND	ND	ND	ND	ND	ND	L: 0.72 ± 0.71
ND	ND	ND	ND	ND	ND	B: 0.88 ± 0.72
						L: 0.79 ± 0.76
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	-0.76 ± 0.44
0.50 ± 0.18	0.31 ± 0.10	0.19±??	ND	ND	ND	
0.75 ± 0.27	0.41 ± 0.15	0.34±??	ND	ND	ND	-0.50 ± 0.12
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	1.35 ± 0.68
ND	ND	ND	ND	ND	ND	
ND	ND	ND	ND	ND	ND	1.58 ± 0.54
<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (6 months)</i>	<i>Reduction (%)</i>	ND
78.6%	7.1%	71.5%	ND	ND	ND	
71.4%	7.1%	64.3%	ND	ND	ND	ND
<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (12 months)</i>	<i>Reduction (%)</i>	ND
ND	ND	ND	ND	ND	ND	
ND	ND	ND	ND	ND	ND	ND
<i>Initial (%)</i>	<i>Final (%) (9 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (9 months)</i>	<i>Reduction (%)</i>	0.20 ± 0.71
NC	NC	NC	ND	ND	ND	
NC	NC	NC	ND	ND	ND	0.1 ± 0.61
NC	NC	NC	ND	ND	ND	-0.27 ± 0.58
<i>Initial (%)</i>	<i>Final (%) (9 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (9 months)</i>	<i>Reduction (%)</i>	0.17 ± 0.76
NC	NC	NC	ND	ND	ND	
NC	NC	NC	ND	ND	ND	0.04 ± 0.62
NC	NC	NC	ND	ND	ND	-0.25 ± 0.61
<i>Initial (%)</i>	<i>Final (%) (60 months)</i>	<i>Reduction (%)</i>	<i>Initial (%)</i>	<i>Final (%) (60 months)</i>	<i>Reduction (%)</i>	2.4 ± 1.4
57%	25%	32%	ND	ND	ND	
59%	25%	34%	ND	ND	ND	2.5 ± 1.2

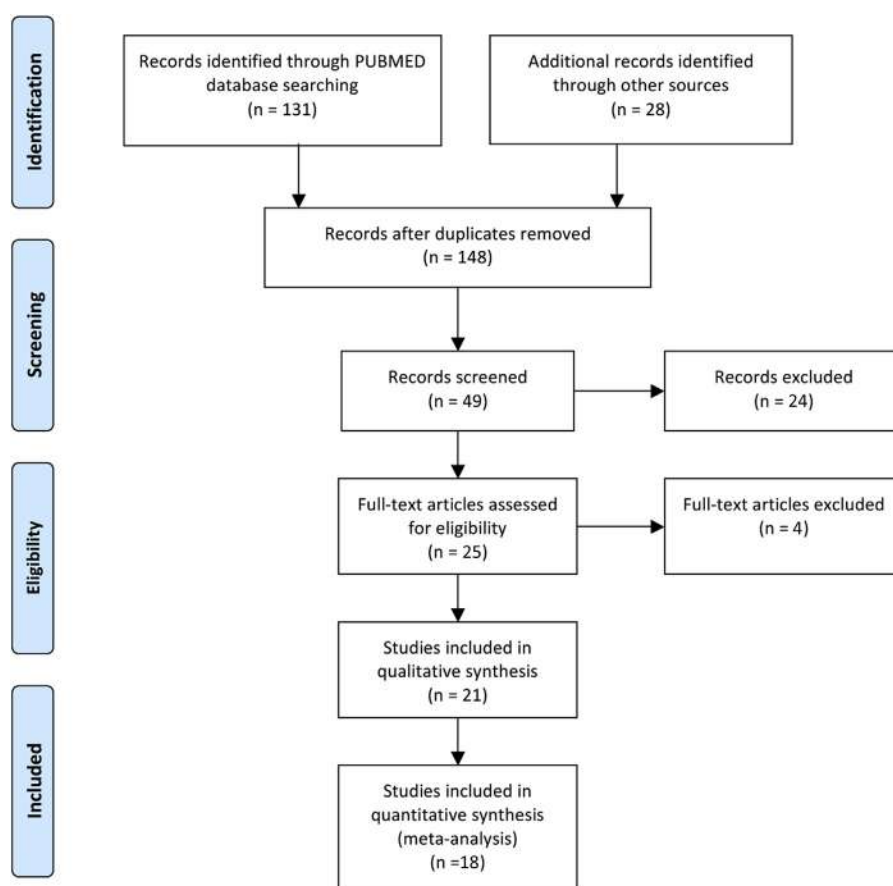


Fig. 1. Flow chart of the screening process for the qualitative and quantitative analysis.

gingival level (MGL). The pooled weighted mean difference (WMD) and the 95% confidence interval (CI) were estimated using a computer program.* The contributions of each article to the primary outcome and the secondary outcome were weighed on the basis of the sample size. Random effects meta-analyses of the selected studies were applied to avoid any bias being caused by the methodologic differences between studies. Forest plots were produced to graphically represent the differences in the outcomes of the PRP group and the control group for all included studies, using the number of treated defects as the analysis unit. A *P* value of .05 was used as the level of significance. Heterogeneity, assessed with chi-square test and I^2 test, ranged between 0% and 100%, with lower values representing less heterogeneity. In addition, a funnel plot was also used to assess the presence of the publication bias. The reporting of these meta-analyses adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement.

Study quality

The criteria used to evaluate the quality of the selected randomized controlled trials (RCTs) were modified

from the randomized clinical trial checklist of the Cochrane Center and the CONSORT (Consolidated Standards of Reporting Trials) statement, which provided guidelines for the following parameters: (1) sequence generation; (2) allocation concealment method; (3) blinding of the examiner; (4) addressing incomplete outcome data; and (5) being free of selective outcome reporting. The degree of bias was categorized as low risk if all the criteria were met, moderate risk when only one criterion was missing, and high risk if two or more criteria were missing.^{26,27} Two independent reviewers (AR & AM) evaluated all the included articles.

RESULTS

Study selection

An initial screening yielded a total of 148 articles, of which 49 potentially relevant articles were selected after evaluation of their abstracts. The full texts of 25 of these articles were then obtained and reviewed. Of these, 21 articles²⁸⁻⁴⁸ fulfilled the inclusion criteria and subsequently were qualitatively analyzed (Figure 1). The reasons for exclusion from the systematic review were as follows: (1) Although presumably (based on

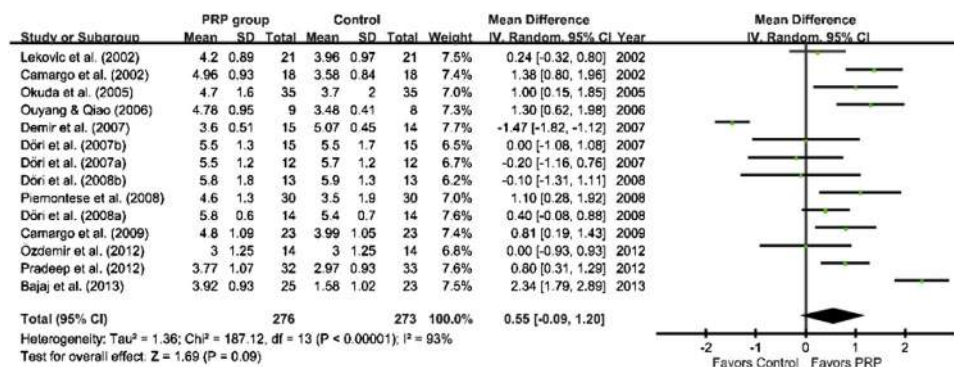


Fig. 2. Meta-analysis for the comparison of probing pocket depth (PPD). The weighted mean difference in PPD between the platelet-rich plasma (PRP) group and the control group was 0.55 mm (95% CI = -0.09-1.20 mm), presenting no statistically significant difference between the two groups.

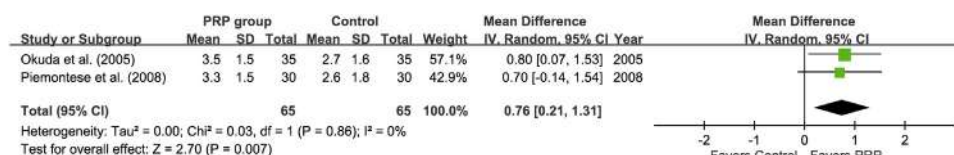


Fig. 3. Meta-analysis for the comparison of bone level (BL0 measured in millimeters). The weighted mean difference in BL between the platelet-rich plasma (PRP) group and the control group was 0.76 mm (95% CI = 0.21-1.31 mm), favoring the PRP group with statistical significance ($P = .007$).

the review of title/abstract) might be potentially included in the qualitative assessment, the study did not evaluate PRP⁴⁹; and (2) clear results were not shown.⁵⁰⁻⁵² For quantitative analysis, 18 articles were appraised. Reasons for exclusion in the meta-analysis were as follows: (1) The article did not provide standard deviation⁴²; (2) the test groups used other biologic agent (i.e., APC or PRF) instead of PRP³⁴ or the control group used PPP,⁴⁰ to avoid risk of bias; and (3) the test and control groups used PRP.³⁹

Results of the meta-analyses

The statistical results from each of the selected studies were converted into effect sizes and combined in the meta-analyses. Three of the four periodontal parameters (BL, MGL, and CAL) showed significant differences between the PRP group and the control group, all favoring the PRP group. However, most comparisons presented a considerable heterogeneity between studies; only BL measured in millimeters and marginal gingival recession (GR) showed low heterogeneity. The meta-analysis of PPD reduction did not show any statistically significant difference between the test and control groups. The results and forest plots of meta-analyses for each clinical parameter are demonstrated in Figures 2 to 6. For the funnel plots, refer to Table 1.

Fourteen articles were included for evaluating of PPD. The WMD was 0.55 mm, with a 95% CI = -0.09 to 1.20 mm ($P = .09$; see Figure 2). For BL, 2 articles

measured BL in millimeters, and the other two articles measured BL in percentage. The WMD was 0.76 mm (95% CI = 0.21-1.31 mm; $P = .007$; see Figure 3) and 47.41% (95% CI = 32.48%-62.33%; $P < .0001$; see Figure 4), respectively. For AL, 12 articles were included. The WMD was 0.58 mm, with a 95% CI = 0.24 to 0.91 mm ($P = .0008$; see Figure 5). Sixteen articles were included for evaluation of MGL. The WMD -0.10 mm, with a 95% CI = -0.19 to -0.01 ($P = .03$; see Figure 6).

Study quality

Figure 7 shows the risk of bias according to the Cochrane Library CONSORT. Overall, low risk of bias was present (>85% bias-free), particularly for sections “free of suggestion of selective outcome reporting,” incomplete of suggestion of selective outcome reporting,” “allocation concealment method,” and “sequence generation.”

DISCUSSION

Since Whitman described the benefit of PRP in 1997, its efficacy in promoting the outcomes of regenerative procedures has been extensively studied^{28-30,32,33,53-58} Conflicting results have been reported, and these might be due to (1) conflict of interest by some companies and (2) the subjective appraisal of outcomes by clinicians. Therefore, we recognized the need for performing a current and thorough systematic review to

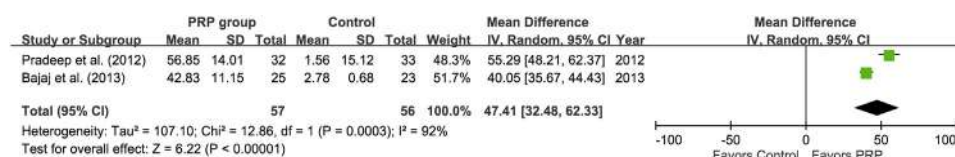


Fig. 4. Meta-analysis for the comparison of bone level (BL) measured in percentage. The weighted mean difference in BL between the platelet-rich plasma (PRP) group and the control group was 47.41% (95% CI = 32.48%-62.33%), favoring the PRP group with statistical significance ($P < .0001$).

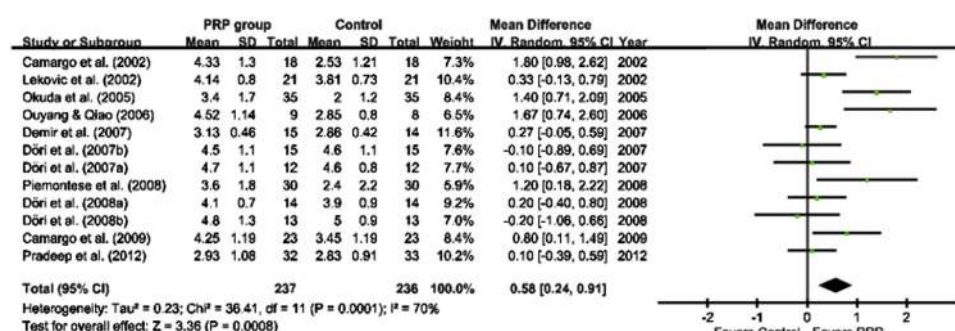


Fig. 5. Meta-analysis for the comparison of attachment level (AL). The weighted mean difference in AL between the platelet-rich plasma (PRP) group and the control group was 0.58 mm (95% CI = 0.24-0.91 mm), favoring the PRP group with statistical significance ($P = .0008$).

study the true effects of PRP on regeneration of periodontal intrabony defects. This systematic review has obtained results with a substantial heterogeneity among different studies. This heterogeneity was found in the experimental designs, surgical techniques, graft materials, patient populations, follow-up, durations, and types and methods of preparation of the platelet concentrate. Therefore, although the analyses of clinical and radiographic parameters showed a significant effect for the test groups, it was difficult to draw any conclusion with regard to its superiority compared with other techniques/biologic materials. Certainly, more systematic reviews on the topic of bone and tissue regeneration have been conducted. Plaschokova et al. showed the beneficial, but not conclusive, effects of PRP on GBR.⁵⁹ Subsequently, the effectiveness of PRP for root coverage was pointed out. However, its efficacy to gain CAL could not be demonstrated.⁶⁰ Two other systematic reviews have stressed the limitations of this biomaterial as a result of the heterogeneity of the reviewed studies.^{54,61} Nonetheless, both reviews presented positive results for PRP in GTR. Indeed, Del Fabbro et al. recently conducted a comprehensive systematic review focusing on the CAL and GR primarily.⁵⁴ We used PPD as the primary goal, as PRP might have a relevant role in promoting bone formation but might promote the formation of new connective tissue attachment to procure healing by repair. We did not find any statistical significance favoring PRP in GTR for all the parameters; unfortunately, BL gain was

only analyzed from two studies. Thus its beneficial effect on bone regeneration cannot be stated with certainty. Our findings demonstrated the overall need for cautiousness in interpreting results favoring PRP due to the considerable heterogeneity that existed among the studies.

Topical delivery of PRP resulted in statistically significant higher CAL gain (0.58 mm) than in the control groups, supporting the claim that PRP is beneficial in promoting periodontal regeneration. However, PPD reduction (0.55 mm) did not show statistical significance, so the effectiveness of PRP remained debatable. It is arguable that this difference is of little clinical value. Nonetheless, the GFs of PRP might induce more favorable histologic outcomes, and the nonsignificance may have been caused by the difference in healing patterns between the PRP and control groups. Probing would not be able to distinguish between fibrous attachment and epithelial attachment, and the healing pattern cannot be reflected in the amount of CAL gain. However, this hypothesis can be validated only with histologic findings.

Included studies had reported contrasting result in terms of the efficacy of PRP when coupled with bone grafts. Some reported a significant enhancement for PRP,^{30,32,33} whereas others showed lack of effectiveness.⁴⁷ The conflicting results were attributed to differences in the methodologies employed to obtain the PRP preparations, which, in turn, might have had an effect on the concentration of GFs and the content

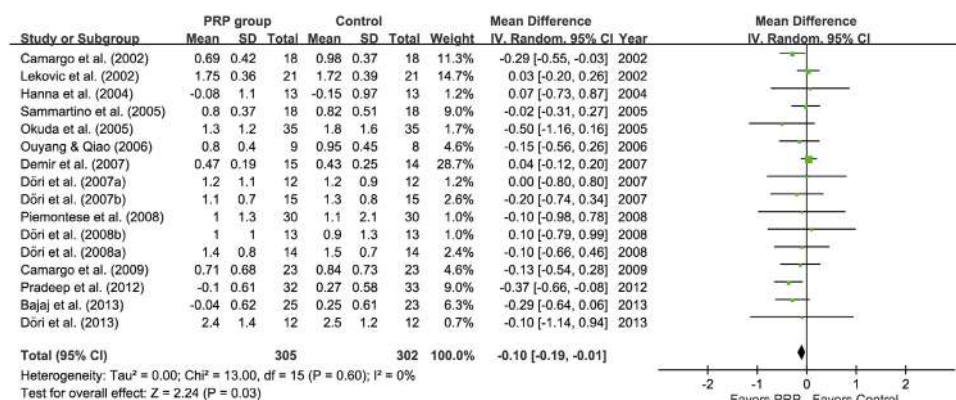


Fig. 6. Meta-analysis for the comparison of marginal gingival level (MGL). The weighted mean difference in MGL between the platelet-rich plasma (PRP) group and the control group was -0.10 mm (95% CI = -0.19 mm to -0.01 mm), favoring the PRP group with statistical significance ($P = .03$).

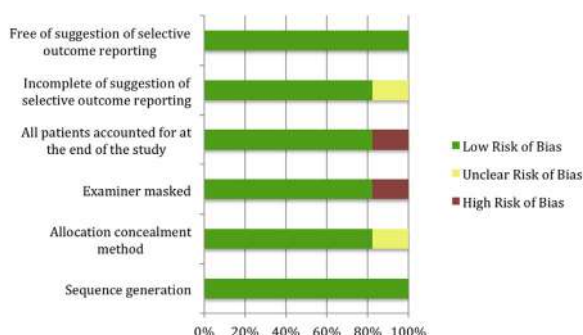


Fig. 7. Risk of bias graph according to the Cochrane guidelines.

of platelets and inflammatory cytokines, besides contamination of the platelet preparation with leukocytes and erythrocytes. Another explanation might be the potential synergistic effect that might exist between PRP and specific types of bone substitutes.⁵

No adverse events have been reported following topical delivery of PRP in the regeneration of periodontal intrabony defects. In fact, the included clinical trials suggested a more rapid healing and less postoperative pain in PRP-treated sites compared with controls.³⁴ Additionally, postoperative healing was uneventful when PRP was used in conjunction with grafting materials. This might be explained by the use of a number of different GFs, including PDGF, TGF- β , and insulin-like growth factor (IGF),³² which could potentially exert a positive effect on cell lines involved in periodontal wound healing.⁵ Moreover, when the adjunctive use of PRP with both grafts and GTR was evaluated, non-PRP-grafted sites demonstrated a higher incidence of membrane exposure compared with PRP-grafted sites, which highlights the role of PRP in promoting postoperative soft tissue healing. With regard to the amount of

platelets, there is no protocol to indicate which concentration is necessary to obtain PRP.³⁵ The activation of platelets during centrifugation could liberate the α -granules before their application in the recipient area.³⁵ The great majority of the studies do not demonstrate the use of any marker to control the precipitated degranulation of the α -granules. A precipitated liberation of the GFs before the placement of the product could reduce their effectiveness. Since GFs generally suffer from instability and quick dilution soon after local delivery, for optimizing the bioavailability of GFs,^{62,63} primary wound closure might play a key role in increasing the effect of PRPs.

Other possible confounding factor might be the regenerative technique/biologic materials utilized. The vast majority of the studies included did not merely use PRP versus the placebo group. As known from earlier studies on periodontal regeneration, the placement of membrane to accomplish GTR may cause a 3.2-mm CAL gain.⁶⁴ In addition, when this is supplemented by the placement of grafting material, vertical PD, vertical and horizontal CAL gain can be enhanced.⁶⁵ In this situation, defect morphology also potentially affects the final outcome. Steffensen and Weber showed statistically better results for defects angled less than 45 degrees. In fact, wider defects showed radiographic bone loss.⁶⁶ Likewise, Cortellini and Tonetti demonstrated that in scenarios of radiographic angulation of 25 degrees or less and presence of deep infrabony defect (≥ 3 mm) with at least 1 mm of gingival thickness over the site, the most consistent clinical attachment and bone gains were achieved, regardless of the number of bony walls.⁶⁷ Thus, many factors contribute to the results of any regenerative procedure, and as such, precautions must be taken when interpreting results about the benefits of biologic agents for regeneration.

As it has been mentioned, there is no standard method to obtain PRP. In addition, normal values of platelets in blood are in wide range, usually between 150,000 and 400,000 units/mm³. For example, blood can be obtained from two different patients with normal platelets values, and one could have double the number of platelets, indicating higher concentration of PRP. This implies that when in studies on PRP, authors should perform a blood analysis to determine the quantity of cells present in blood. However, there are many ways to obtain PRP,^{28,31,43,44,58} which could lead to finding different concentrations even in the same individual. For example, Sammartino et al.³¹ extracted 40 mL, Lekovic et al.^{28,58} extracted 10 mL, and Pradeep et al.⁴³ and Bajaj et al.⁴⁴ extracted 30 mL. Furthermore, Sammartino et al. commented that the centrifuge they performed was 1200 rpm/15 min, whereas Lekovic et al.^{28,58} centrifuged at 5600 rpm/6 min and Pradeep et al.⁴³ at 3000 rpm/10 min. Other authors have used two centrifuges to obtain PRP^{32,33,35-37,46,48,68} extracted from 7 mL to 60 mL. Some^{32,35-37,46,48,68} did a first centrifuge at 2400 rpm/10 min and another at 3600 rpm/15 min, and Ouyang and Qiao³³ performed their first centrifugation at 1220 rpm/15 min and a second at 3600 rpm/15 min. Also, some authors do not explain how they obtained PRP.³⁰ Due to the methodologic differences in obtaining PRP, it is very difficult to compare the results of the studies.

CONCLUSIONS

High heterogeneity among studies made it difficult to draw any clear conclusions. Nonetheless, within the limitations of this review, PRP may confer some beneficial effects on the clinical and radiographic outcomes for GTR of intrabony defects. Standardized models should be used to test its effectiveness in vivo as well as the regenerative effect with different biomaterials in comparison with other biologic agents (i.e., PDGF-BB).

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