

Regeneration Efficacy of Platelet-rich Fibrin in Patients Undergoing Periodontal Surgery: A Systematic Review and Meta-analysis

Eficacia de la Regeneración con Plasma Rico en Fibrina en Pacientes Sometidos a Cirugía Periodontal: Una Revisión Sistemática y Meta-análisis

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ABSTRACT: Periodontal surgery seeks for tissue regeneration. There is a new grafting material called platelet-rich fibrin (PRF), with multiple properties and one of them is regeneration. This study aimed to assess the regeneration efficacy of Platelet-rich fibrin in periodontal surgery. Were performed several computerized literature searches for randomized controlled trials (RCTs). That evaluated regeneration efficacy in hard and/or soft tissues of autologous PRF in periodontal surgery were used, the methodological quality of them was assessed. The concept of efficacy for soft tissue were considered the outcome of mean gain of probing depth (PD) and mean gain of clinical attachment level (CAL) and for hard tissues the outcome of percentage of bone fill. The data was obtain from the included original articles and entered in the Review Manager (RevMan). There were only 11 RCTs that meet the inclusion criteria assessing clinical efficacy in maxillofacial area in human, of those only 6 studies were able to do the meta-analysis. The articles show an increased of 1.02 mm with a CI (0.85, 1.19) of PD over the control, an increased of 0.73 mm with a CI (0.58, 0.89) of CAL over the control, and a 44.15% with a CI (42.37, 45.93) over the control group. The regeneration efficacy of Platelet-rich fibrin in periodontal surgery is real. We recommend it use, however further research is necessary in order to obtain more information about this biomaterial.

KEY WORDS: platelet-rich fibrin, periodontal surgery, periodontal regeneration.

INTRODUCTION

In the field of dental surgery there are challenges proper of any surgical procedure, but there are also some others that are exclusive from the oral cavity. Most of the time dental surgery does not seek for cicatrization, it is a requirement that the regeneration must be the goal, in periodontal regenerative therapy the objective is the reconstitution of the architecture and function of the periodontium (Thorat *et al.*, 2011). It is important to have a predictable method for the appearance of new attachment apparatus including bone, cement, and periodontal ligament (Sharma & Pradeep, 2011a). Although there are a wide variety of options for periodontal regenerative therapy (Lekovic *et al.*, 2012) there is not a single one that can be considered as a gold standard because complete regeneration of the periodontium have not been accomplish yet (Pradeep *et al.*, 2012a).

A new grafting material called platelet-rich fibrin (PRF) developed by Choukroun *et al.* (2001), come to fill this gap, why is so revolutionary is due it's a second generation platelet concentrate, this mean a preparation method that doesn't need biochemical blood handing (neither anticoagulant nor bovine thrombin) and only using own blood centrifugation, making it an advantage versus the already known first generation platelet-rich plasma (PRP) (Dohan *et al.*, 2006a). PRF is a autologous fibrin clot that due a slow fibrin polymerization traps in their fibrin meshes glycanic chains and platelet cytokines grown factors such as TGF-b-1, PDGFs and IGF allowing progressive release of them during fibrin matrix remodeling (Dohan *et al.*, 2006b), a-Granules of platelets gives wound-healing properties on hard and soft tissues of grown factors presented in them, it has been probe experimental and

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clinical and is widely accepted their healing properties (Del Fabbro *et al.*, 2011) The use of PRF in the oral and maxillofacial has been reported in different areas especially in dental surgery: gingival recession (Aroca *et al.*, 2009), intra-bony defects (Thorat *et al.*), furcation defects (Sharma *et al.*, 2011a), filling and hemostatic biomaterial after dental extraction (Sammartino *et al.*, 2011), sinus floor augmentation (Mazor *et al.*, 2009), preimplantary and implant surgery (Simonpieri *et al.*, 2009a, 2009b), filling after parotidectomy for benign parotid tumors (Charrier *et al.*, 2008). However there are some others pioneer areas for its study related to ear, nose and even plastic surgery (Choukroun *et al.*, 2007; Braccini & Dohan, 2007). Due that we think that probably there are even others areas and functions still unexplored where this healing biomaterial may play an important role. A biomaterial with so many possibilities and uses should have a review to assess and compare its efficacy, because nowadays there isn't many clinical studies available on the efficacy of PRF, we considered that it would be important to collect all the knowledge and evaluated it.

The objective of this study aimed to assess the regeneration efficacy of Platelet-rich fibrin in periodontal surgery.

MATERIAL AND METHOD

Criteria for considering studies for this review

Types of studies. In our study were considered only randomized controlled trials (RCTs) that evaluated regeneration efficacy in hard and/or soft tissues of autologous PRF in periodontal surgery. Were used only RCTs with a score equal or over 3 in the Jadad scale, and CASP to assess the methodological quality of the clinical trial. Was included split-mouth-design RCTs and studies were they have a control and test site in the same patient regardless of the side, only if they were randomized. It excludes trials that have two test groups in which both used PRF. Only were used RCTs that had been approved by an ethical committee.

Types of participants. Were included Patients that were submitted to the use of PRF in the oral and maxillofacial region. Were excluded all patients with systemically illness, insufficient platelet count (<200,000/mm³), pregnancy/lactation or use of any form of tobacco. All RCTs declared to have a written informed consent obtained from patients agreed to participate.

Types of interventions. Were included interventions that assess the efficacy of autologous PRF for regeneration of hard and/ or soft tissues in the oral and maxillofacial area.

Types of outcome measures . Were evaluated hard and soft tissue regeneration efficacy. The concept of efficacy for soft tissue considered the outcome of mean gain of probing depth (PD) and mean gain of clinical attachment level (CAL) and for hard tissues the outcome of percentage of bone fill, were considered both outcomes as continuous outcomes.

Search methods for identification of studies. Were performed several computerized literature searches for trials using the following search terms and combining them: platelet rich fibrin, Choukroun prf, L-PRF autologous plasma, autologous platelet, Choukroun. This search was performed in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2012), MEDLINE (accessed via PubMed; 1966-2012), EMBASE (via OVID; 1974-2012), Science Citation Index (1945-2012), and Google scholar. No language restrictions were applied; Reference lists of the most relevant studies and engines search were checked for possible additional studies.

Data collection and analysis. To consider the articles for this review, two persons examined and read independently the full text of each article according to the inclusion and exclusion criteria (see criteria for considering studies for this review) and excluded them when they meet the exclusion criteria, if it was not discarded, the complete read of the article was performed. Only selection was performed of the papers that informed that were RCTs without confusion and meet the inclusion criteria.

Risk of bias. Two authors extracted the information independently, assessed the methodological quality and the risk of bias (Higgins & Green, 2008).

The assessment of risk of bias was an evaluation in six domains:

1. Sequence generation,
2. Allocation concealment,
3. Blinding,
4. Incomplete outcome data,
5. Selective outcome reporting
6. Other bias

Statistical analysis. The data was obtained from the included original articles and entered in the Review Manager® (RevMan) for the meta-analysis using fixed-effects statistical model. Were calculated mean differences (MD) for continuous outcomes and their 95 percent confidence intervals (95% CIs). Heterogeneity analysis was conducted by an I2 test considering values of 25, 50, and 75 percent as a sign of low, moderate, and high heterogeneity, respectively. When I2 values were 50 percent or greater, a sensitivity analysis was conducted to explore the cause of heterogeneity. The I2 describes the proportion of variability across studies and the importance depends on magnitude and direction of effects on strength of heterogeneity.

RESULTS

This systematic review aimed to assess the regeneration efficacy of Platelet-rich fibrin in periodontal surgery for this purpose we based on randomized controlled trials, due the differences between RCTs it is necessary to look for similarities between them in order to obtain conclusive information, the data of the different studies were described in Table I.

There were only 11 RCTs that meet the inclusion criteria assessing clinical efficacy in maxillofacial area in human. However is importance to notice that to do the meta-analysis is a required to have the same parameters allowing different kinds of procedures to compare them, due that of the 11RCTs, 1 study compared PRF with PRF with BPBM and it had not control group (Lekovic *et al.*), 1 evaluate bone, but did not percentage of bone fill (Zhang *et al.*, 2012), 2

studies did not have the mean change, just giving the mean of the time periods and for our meta-analysis we used mean changes (Jankovic *et al.*, 2010), Knowing that, only 6 RCTs were able to get into Revman to analyze (Fig. 1).

The results of the RCTs were taken from the last measurement, in the ones that evaluated the outcomes at different time periods. The risk of bias was assessed according to the items listed (Fig. 2).

PRF efficacy in soft tissue

Outcome: Mean gain of probing depth (PD) (mm): For this outcome we used only 5 studies with 122 sites in the PRF group as well in the control group, was discard Jankovic *et al.* (2012) because the result including this study is too heterogenic therefore is inconclusive. All of these 5 RCTs used open flap debridement (OFD) as the control group, and OFD with PRF as the test group, the follow up was at 9 months in all 5 of the studies. The articles show an increased of 1.02 mm with a CI (0.85, 1.19) over the control. The heterogeneity was 0% and it has not biases according to the funnel plot (Fig. 3).

For each study the size of treatment effect (squares) together with 95% confidence interval (CI, horizontal bars) is indicated. The diamond indicates overall estimate of treatment effect and its width indicates the overall 95% CI. The vertical line represents absence of treatment effect. IV= inverse variance; df= degrees of freedom; I=index for assessing heterogeneity in a meta-analysis.

Outcome: Mean gain of clinical attachment level (CAL) (mm): For this outcome we used all 6 selected

Table I. RCTs that were submitted to meta-analysis.

Author, Publication Year	Patients (n)	Number of sites		Intervention		Follow-up (Months)	Periodontal condition
		Test	Control	Test	Control		
Jankovic <i>et al.</i> (2012)	15	15	15	PRF+CAF	CTG+CAF	6	Gingival recession
Pradeep <i>et al.</i> (2012a)	57	30	30	PRF+OFD	OFD	9	Three-wall intra-bony defects
Pradeep <i>et al.</i> (2012b)	50	30	30	PRF+OFD	OFD	9	Three-wall intra-bony defects
Sharma & Pradeep (2011b)	35	28	28	PRF+OFD	OFD	9	Three-wall intra-bony defects
Sharma & Pradeep (2011a)	18	18	18	PRF+OFD	OFD	9	Degree II furcation defects
Thorat <i>et al.</i> , (2011)	32	16	16	PRF+OFD	OFD	9	Intra-bony defects

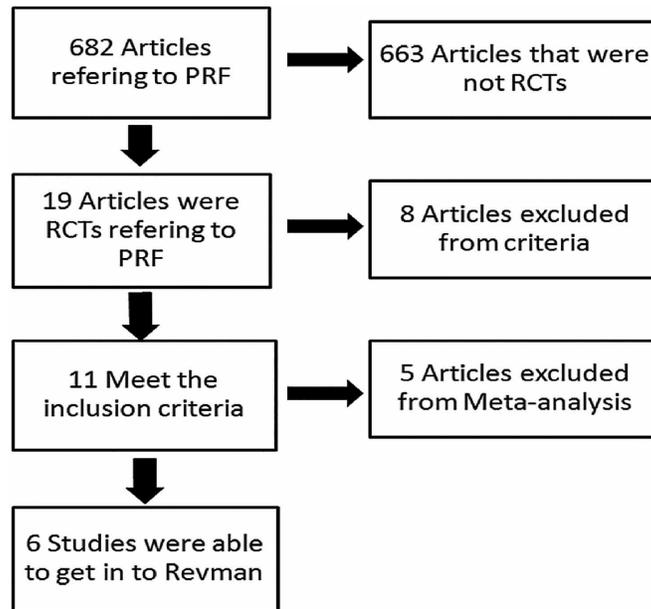


Fig. 1. Flowchart summarizing the articles selection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	(performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting data)	Other bias
Jankovic <i>et al.</i> (2012)	?	-	?	+	+	+
Pradeep <i>et al.</i> (2012b)	?	?	-	+	+	?
Pradeep <i>et al.</i> (2012a)	?	-	?	+	+	?
Sharma & Pradeep (2011b)	?	?	-	+	+	?
Sharma & Pradeep (2011a)	+	-	?	+	+	+
Thorat <i>et al.</i> (2011)	+	-	?	+	+	+

Fig. 2. Risk of Bias. Low (Green), unclear (yellow) and high (red) risk of bias according to the systematic review.

articles that meet the inclusion criteria with 137 sites in the PRF group as well in the control group. An increased of 0.73 mm with a CI (0.58, 0.89) over the control. The heterogeneity was high showing 93%, due that sensitivity analysis was conducted (Fig. 4).

For each study the size of treatment effect

(squares) together with 95% confidence interval (CI, horizontal bars) is indicated. The diamond indicates overall estimate of treatment effect and its width indicates the overall 95% CI. The vertical line represents absence of treatment effect. IV= inverse variance; df= degrees of freedom; I= index for assessing heterogeneity in a meta-analysis.

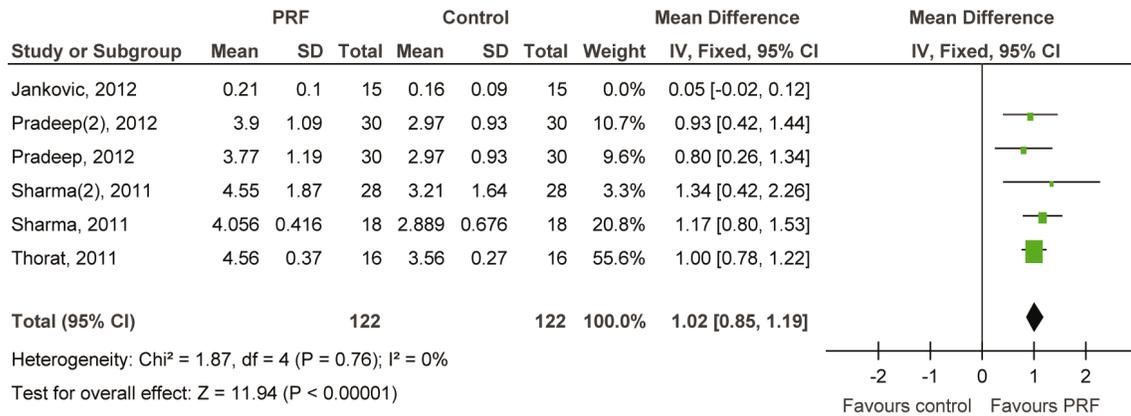


Fig. 3. Forest plot evaluation mean gain of PD (mm).

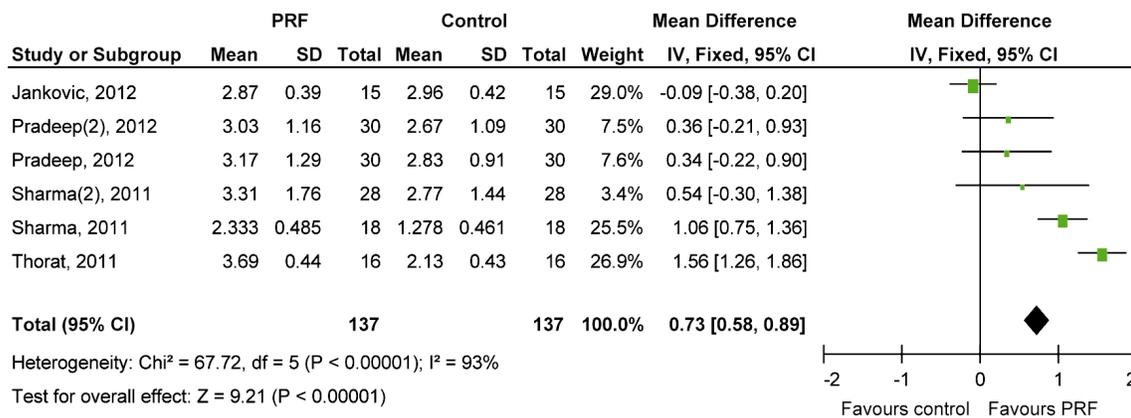


Fig. 4. Forest plot evaluation mean gain of CAL (mm).

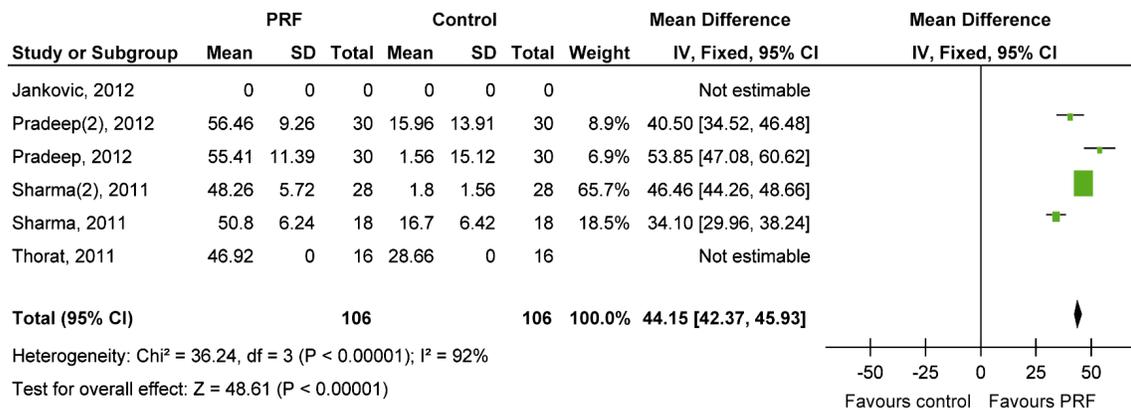


Fig. 5. Forest plot evaluation percentage of bone fill (%).

PRF efficacy in hard tissue

Outcome: Percentage of bone fill (%): Only 4 outcomes were used, Jankovic *et al.* (2012) was discarded because it did not assess percentage of bone fill and Thorat *et al.* that did not published the standard

deviation. The meta-analysis showed a 44.15% with a CI (42.37, 45.93) over the control group. The heterogeneity was high with 92% due that a sensitivity analysis was conducted (Fig. 5).

For each study the size of treatment effect (squares) together with 95% confidence interval (CI, horizontal bars) is indicated. The diamond indicates overall estimate of treatment effect and its width indicates the overall 95% CI. The vertical line represents absence of treatment effect. IV= inverse variance; df= degrees of freedom; I= index for assessing heterogeneity in a meta-analysis.

DISCUSSION

The quality of the selected RCTs were generally good and the results were accord to previous studies and what we expect, they showed an increased of probing depth, clinical attachment level and percentage of bone level. Periodontal surgery is a wide area however we believed that the concept of regeneration (for us considered in the outcomes of gain of probing depth, clinical attachment level and percentage of bone fill), should increase regardless of the technique, allowing us to compared them. PRF is a autologous platelet concentrate this gives it the attribute of been an unspecific technique, due that we can measured it efficacy for different periodontal conditions, this attribute of PRF along with the same outcomes measured for different procedures allowed us to compared them.

PRF efficacy in soft tissue. The mean gain of probing depth (PD) (mm) showed an increased in all 5 RCTs in favor of PRF over control group, meta-analysis show a substantial overall increased. The control used was Open flap debridement alone, a technique that showed an increased of PD, this effect seems to increase when it is used alongside PRF. When Jankovic *et al.* (2012) was used heterogeneity raised from 0% (low) to 96% (high), we believe that the difference in the results may be attributed to the difference in the study regarding intervention (it used coronally advanced flap and connective tissue graft), follow-up (6 months) and the type of surgery treatment (gingival recession), due that we did not considered this study for the meta-analysis

The Mean gain of clinical attachment level (CAL) (mm) showed and overall increased however there is one of 6 studies in favor of control group; this may be due the study type. Is important to notice that the results show an important gain in the control group as well, however we cannot tell if the CAL gain is due real regeneration or it is due a long junctional epithelium (Pradeep *et al.*, 2012b), this may look like the PRF is not so effective compare to control group, nevertheless

this discrepancy in CAL is still overall increased in the PRF group.

PRF efficacy in hard tissue. The percentage of bone fill show overall and individual effect in all 4 RCTs, filling procedures of the condition have shown to be substantial better including different procedures as bone replacements graft (Wang *et al.*, 2005), compare to a flap management technique as OFD, however the effectiveness of PRF is high achieving a great response around 50% in all studies.

Considerations. Despite the fact that we picked the regeneration efficacy, we know that is important to consider other specific variables depending of the periodontal procedure and the objective of it, when a technique is going to be chosen. It is necessary to analyze factors as esthetics, pain, objective of the procedure, and other variables for each individual procedure. Also is important some considerations for the proper use of this technique particularly about timing of the procedure for obtaining the clot of PRF, that may affect the quality of the clot, because this technique it is very sensitive to long time periods due is a biomaterial. However the benefits of this technique are many, is really simple and inexpensive protocol due does not require any biochemical modifications, making it safer for the patient (Dohan Ehrenfest *et al.*, 2009). There is still a lot of room for future research about PRF, about its application in different fields due its great potential, however further investigation in periodontal field still necessary although it is the area where we found more information in the form of RCTs. It is important and necessary to carry out more RCTs about PRF because this type of study is the best to objective analyze effectiveness.

The regeneration efficacy of Platelet-rich fibrin in periodontal surgery is effective according to present information of RCTs especially in hard tissues as a filling material. We recommend it use, however further research is necessary in order to obtain more information about this promising biomaterial.

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RESUMEN: La cirugía periodontal se enfoca en la regeneración de tejidos. Existe un nuevo material de injerto llamado plasma rico en fibrina (PRF), con múltiples propiedades y una de ellas es la regeneración. El objetivo fue eva-

lular la eficacia de la regeneración plasma rico en fibrina en cirugía periodontal. Se realizaron búsquedas bibliográficas electrónicas para identificar ensayos controlados aleatorios (ECA). Se evaluó la eficacia de la regeneración de tejidos duros o blandos con PRF autóloga en cirugía periodontal, se consideró la calidad metodológica de los mismos. Para el concepto de la eficacia de los tejidos blandos se analizó la ganancia media de profundidad de sondaje (PD) y la ganancia media de nivel de inserción clínica (NIC) para los tejidos duros. Los datos se obtienen a partir de los artículos originales incluidos en el Software Review Manager (RevMan). Hubo sólo 11 ECA que cumplan con los criterios de inclusión en el área maxilofacial en humanos, de los cuales sólo 6 estudios fueron sometidos al meta-análisis. Los artículos muestran un aumento de 1,02 con un IC (0,85, 1,19) de la EP sobre el control, un aumento de 0,73 mm con un CI (0;58, 0,89) de la CAL en el control, y un 44,15% con un IC (42,37, 45,93) en el grupo de control. La eficacia de la regeneración del plasma rico en fibrina en cirugía periodontal es real. Se recomienda el uso, sin embargo, se necesita más investigación para obtener información sobre de este biomaterial.

PALABRAS CLAVE: plasma rico en fibrina, cirugía periodontal, regeneración periodontal.

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