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RESEARCH ARTICLE

Efficacy of Platelet-Rich Fibrin in Bone Regeneration of the Jaws: A Systematic Review

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Abstract

Objective: To analyze the effects of Platelet-rich fibrin (PRF) in bone regeneration procedures of the jaws.

Materials and methods: The search was conducted from 2012 to 2017 in databases (MEDLINE/PubMed, Cochrane, EMBASE, Epistemonikos). Randomized clinical trials (RCTs) were included for the qualitative analysis and systematic reviews (SRs) found in the search were analyzed independently with AMSTAR.

Results: 5 RCTs were selected and analyzed qualitatively, 4 articles (1 RCT and 3 SRs) evaluated results in maxillary sinus lift surgery not showing differences using PRF compared to the traditional technique. For bone regeneration of the alveolar ridge, 2 RCTs indicated that PRF in combination with autogenous bone improves bone volume. 3 articles evaluated alveolar preservation (1 RCT and 2 SRs) demonstrating that there may be an increase in the density of neoformed bone in the long term with a lower rate of buccal/lingual reabsorption. The articles also demonstrate that the use of PRF improves the healing of soft tissues during first 7 days as well as decreasing symptomatology.

Finally, 4 studies (1 RCT and 3 SRs) evaluated the effect on infra-osseous periodontal defects in which the PRF showed to be effective, improving parameters such as clinical attachment level and probing depth in comparison with the control. There was considerable heterogeneity between the studies; therefore, they could not be analyzed quantitatively.

Conclusions: The use of PRF appears to improve the local conditions of the grafts and soft tissues, reducing the healing times and symptoms. However, more RCTs and protocol standardization are required to obtain reproducible results.

Keywords

Platelet-rich fibrin, Platelet concentrates, Bone regeneration, Bone grafts

Introduction

In recent years, it has become clear the key role of platelets and their products in tissue regeneration, specifically in bone regeneration accelerate healing of both soft and hard tissues, mediated by the local release of growth factors.

There are two categories or generations of autologous platelets concentrate (APC). The first generation or gels rich in growth factors (GFs) are obtained using anticoagulants and require subsequent platelet activation through the addition of thrombin or calcium chloride. In this group is the platelet-rich plasma (PRP).

The other category, second generation APC, is naturally activated in their collection, which basically correspond to platelet-rich fibrin (PRF) and its obtaining protocols, without using activators or anticoagulants. Platelet counts in relation to an established sample of blood collected are similar between PRP and PRF, both values contained in a physiological range [1,2]. The PRF rich in leukocytes corresponds to standard L-PRF or Choukroun PRF at 2700 rpm × 12 minutes [2,3], which allows obtaining a fibrin concentrate with platelet content, its release products and leukocytes.

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The physical conformation of the concentrate corresponds to a three-dimensional matrix of fibrin containing platelets, leukocytes and GFs which are organized into three zones: The most caudal corresponds to a red thrombus in contact with the clot of erythrocytes, then in the area adjacent to the thrombus is found a radiated zone of whitish color where the cellular elements distributed in filaments are concentrated towards the uppermost zone which ends in an acellular fibrin mesh [3,4]. The PRF presents a peak of release of GFs, transforming growth factor beta (TGF-B) and platelet derived growth factor (PDGF) 14 days after its application. For the first 7 days, the minimum amounts are released and then increase up until the 14th day. After this, the release of GFs starts to decline [5-7]. Marx [8] reported that autologous growth factors have a direct influence on local cells for a period of 5 to 7 days, so platelets would favor bone regeneration in the recipient site after a surgical intervention. The PRF provides a local release of GFs, which associated with its three-dimensional architecture, could be able to integrate different cell groups acting as a scaffold. This favors cell migration and accelerates the process of bone regeneration [5,7,9].

The literature about PRF and its use as an adjuvant in alveolar bone regeneration therapies is extensive and presents heterogeneous results. Despite the evidence in favor of the proliferation and differentiation of osteoblasts *in vitro* using PRF membranes [5,10,11], the results at the clinical level are controversial. The objective of this review is to provide an up-to-date overview of the clinical scope and the results of the use of PRF in bone regeneration therapies in the oral and maxillofacial territory.

Materials and Methods

The method used in this systematic review was adapted from the Preferred Report Elements for Systematic Reviews and Meta-analysis (PRISMA) [12] and the guide prepared by Needleman [13]. The clinical questions were formulated and organized according to the PICO framework for practice based in the evidence [14,15].

Focused Question

The question formulated to define the search strategy is: 'What effects does platelet-rich fibrin have on bone regeneration procedures of the jaws compared to traditional techniques?'

Search Strategy

The search strategy was based on the PRISMA guidelines, from January 2012 to May 2017, a thorough electronic search was performed in MEDLINE/PubMed, Cochrane databases and EMBASE/Elsevier databases (Science-Direct, Ebsco-host and Clinical-Key), for relevant publications from indexed journals. The electronic search followed the strategy shown in Table 1. Search

Table 1: Systematic search strategy.

Focused question	What effects does platelet-rich fibrin have on bone regeneration procedures of the jaws compared to traditional techniques?
Search strategy	
Population	(1) MeSh terms: "bone regeneration" OR "alveolar ridge augmentation" OR "alveolar bone atrophy" OR "alveolar process atrophy" OR "maxillary sinus" OR "alveolar bone loss"
Intervention	(2) MeSh terms not applicable for "Platelet-rich fibrin". Keywords: Platelet-rich fibrin OR Platelet-rich fibrin OR PRF OR L-PRF OR PRGF
Outcome	(3) MeSh terms: Bone healing OR tissue healing OR bone regeneration. Keywords: Bone formation OR dimensional changes.
Search combination	1 AND 2 AND 3
Search in databases	
Language	English/Spanish
Electronic databases	MEDLINE/PubMed, Cochrane, EMBASE (Science-Direct, Ebsco-host, Clinical-key) y Epistemonikos
Selection criteria	
Inclusion criteria	RCT, CCT and prospective cohort studies with control group, with informed consent approved by patients and SRs which evaluate the same aspects. Studies that lead to quantitative or qualitative analysis of changes in bone volume and/or soft tissues post-regenerative therapy. Population (P): Systemically healthy human patients with a lack of alveolar bone and/or in need of bone grafts for implant therapies, without restriction due to age, time of follow-up or number of patients. Intervention (I): Use of PRF as a biomaterial alone or in combination with a graft material in different bone grafting techniques. Comparison (C): Traditional periodontal therapy or traditional grafting techniques using substitute bone or control site without intervention. Outcomes (O): Alveolar bone regeneration (evaluated clinically, radiographically and/or histologically).
Exclusion criteria	We excluded animal studies, case reports, case series, technical notes, non-systematic reviews, studies that included the use of PRF in applications other than bone regeneration and/or that used PRP instead of PRF, which included patients with systemic compromise, insufficient platelet count (< 200,000 Umm^3), pregnant/lactating or tobacco use.

filters were limited by language to articles in Spanish or English from journals between 2012 to May 2017.

Review and Selection

We included in this review randomized clinical trials (RCTs) that evaluated the effects of platelet-rich fibrin in bone regeneration as well as adjuvant to bone grafts or by itself. Systematic reviews (SRs) were also included, since the amount of clinical trials were too limited to evaluate the results of the use of PRF in different alveolar bone regeneration therapies and their clinical considerations.

Two reviewers performed the detection of titles and abstracts for possible inclusion (J.L., E.M.). The complete selected studies were carefully read and analyzed for eligibility criteria and data extraction. Differences between reviewers were resolved through discussion and consensus.

The studies were selected according to the following inclusion criteria: (i) Use of PRF in oral and maxillofacial territory, (ii) Human studies, (iii) PRF used as graft material (either alone or in combination with other materials), (iv) Results of the treatment and follow-up, (v) Protocol of centrifugation and preparation of the PRF, which should have been clearly reported by the authors in the case of RCT. For the SRs, all those evaluating the use of PRF in bone regeneration therapies associated with osseointegrated implants, oral and maxillofacial surgery and infra-osseous periodontal defects were included (Table 1).

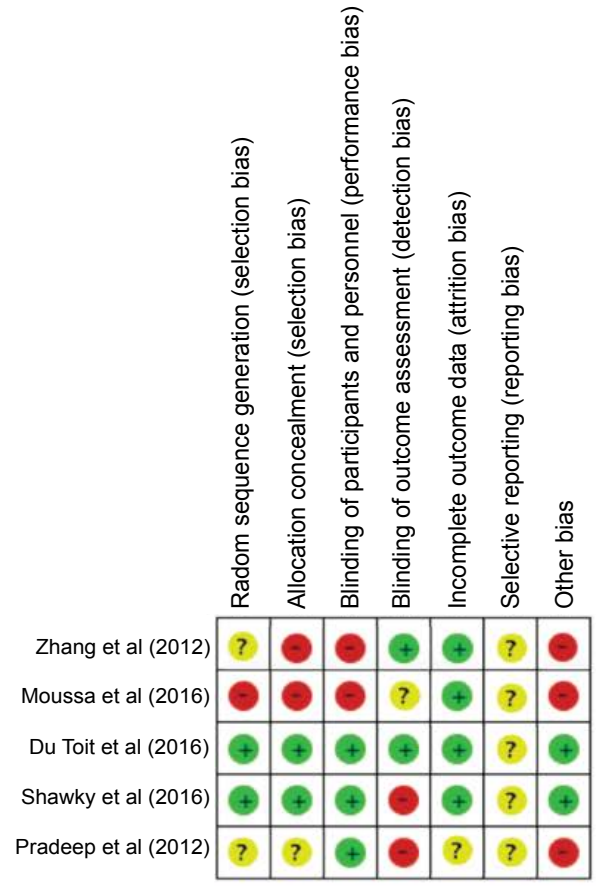

Figure 1: Risk of bias: Summary on each element of risk of bias for included studies; low risk (green), uncertain (yellow) and high risk (red) of bias according to the systematic review.

Evaluation of Heterogeneity

The heterogeneity of the primary results of this review were evaluated according to the following factors: Study design, follow-up time, number of participants, site to be intervened, PRF preparation protocol, surgical technique to be used and evaluation method.

Data Extraction and Quality Evaluation

Data extraction was performed for the included studies and all the variables analyzed in each study were processed. Both reviewers (J.L., E.M.) performed quality assessment independently using the Cochrane Collaboration tool to assess the risk of bias. Six quality criteria were verified: (1) Generation sequence or randomization component, (2) Concealment of allocation, (3) Blinding of participants, staff and outcome assessors, (4) Incomplete/missing outcome data, (5) Selective report of results and (6) Other sources of bias. Each study was classified into the following groups: low risk of bias, if all quality criteria were considered "present", moderate risk of bias, if one or more key domains were "unclear", and high risk of bias, if one or more domains key were "absent" (Figure 1).

For the SRs included, the tool used to assess the methodological quality of the systematic reviews was AMSTAR [16] (Figure 2).

Results

This systematic review aims to evaluate the effectiveness of the PRF in bone regeneration procedures. For this purpose, RCTs and SRs were evaluated separately, due to the methodological differences between the studies. A data presentation was made as a summary of the findings distributed in Table 2 and Table 3. 5 RCTs that clinically evaluated the use of the PRF according to the inclusion criteria were included in this review and 6 SRs were analyzed independently (Figure 3). 126 articles were identified, where 68 full-text were revised, of these 57 articles were excluded, among which 12 articles used PRP instead of PRF associated with bone regeneration techniques. Among the excluded studies, the largest number (n = 21) corresponded to articles where they evaluated the use of autologous platelet concentrates (both PRF and PRP) in other oral and maxillofacial procedures other than bone regeneration (e.g., treatment of osteonecrosis of the jaws, alveolar osteitis, healing of soft tissues, arthrocentesis, among others). Finally, the remaining excluded studies corresponded to case reports, case series, technical notes, non-systematic reviews, non-human studies and opinion articles (Supplementary Table 1).

Among the articles included in the review (Tables 2 and Table 3), only four describe results related to bone

Strengths and limitations of systematic reviews using AMSTAR

AMSTAR Item		Ali et al. (2015) [18]	Schliephake et al. (2017) [19]	Castro et al. (2017) [20]	Moraschini et al. (2015) [24]	Panda et al. (2015) [26]	Shah et al. (2017) [27]
Was a priori design provided?		+	+	+	+	+	+
Was there duplicate study selection and data extraction?	Selection	x	+	+	?	?	?
	Extraction	+	+	+	+	+	+
Was a comprehensive literature search performed?		+	+	+	+	+	+
Was the status of publication used as an inclusion criterion?		+	+	+	+	+	?
Was a list of studies (included and excluded) provided?	Included	+	+	+	+	+	+
	Excluded	x	+	+	+	+	x
Were the characteristics of the included studies provided?		+	+	+	+	+	+
Was the scientific quality of the included studies assessed and documented?		x	?	+	+	+	+
Was the scientific quality of the included studies used appropriately in formulating conclusion?		x	+	+	+	+	+
Were the methods used to combine the findings of studies appropriate?		?	x	+	+	+	+
Was the likelihood of publication bias assessed?		+	+	+	+	+	+
Was the coflict of interest included?		-	x	+	+	x	+

Figure 2: Critical evaluation of systematic reviews included in the study; + = Yes/x = No/? = It is not clear.

augmentation using maxillary sinus lift technique. Of these, only one was an RCT [17] with the rest corresponding to SRs [18-20].

For alveolar ridge grafting, 2 articles corresponded to RCTs [21,22], however, in the alveolar preservation technique, only one study corresponded to an RCT [23]. There were two SRs that evaluated this procedure [20,24].

Finally, four studies were selected in which they evaluated the PRF in bone regeneration techniques of infra-osseous periodontal defects. Of these, only one study corresponded to an RCT [25] with the rest being SRs [19,26,27]. The articles included are described below, listed according to clinical procedures.

PRF in bone augmentation procedures prior to the installation of osseointegrated implants

Maxillary sinus lift: Ali, et al. [18] conducted a review evaluating the use of PRF as a single filling material in maxillary sinus lift surgery with simultaneous installation of implants. The authors define it as a simple technique with promising results, however, they emphasize that their benefits compared to a natural blood clot have not yet been demonstrated in studies of significant evidence. On the other hand, they describe the use of PRF in combination with different types of grafts, evidencing a shorter time of graft maturation in the case of allografts, and reducing the healing period prior to the installation of dental implants. However, the use of PRF does not have any beneficial effect associated with xenografts.

Finally, they describe the successful use of PRF for the sinus membrane and bone window coating. These results were similar to those compiled by Schliephake, et al. [19], in which 224 articles were analyzed between the years 1994-2012. They don't describe benefits of PRF use in open or closed maxillary sinus lift with good documentation and reasonable evidence. Castro, et al. [20] summarised that there were no significant differences in bone apposition on the maxillary lateral window comparing PRF, collagen membrane and residual bone. Zhang, et al. [17] evaluated in an RCT the effect of PRF in combination with xenograft (Bio-Oss) and xenograft on its own in 11 maxillary sinuses, evaluating results radiographically and histologically at 6 months.

To the histomorphometric analysis, the percentage of new bone formation observed in the group with PRF

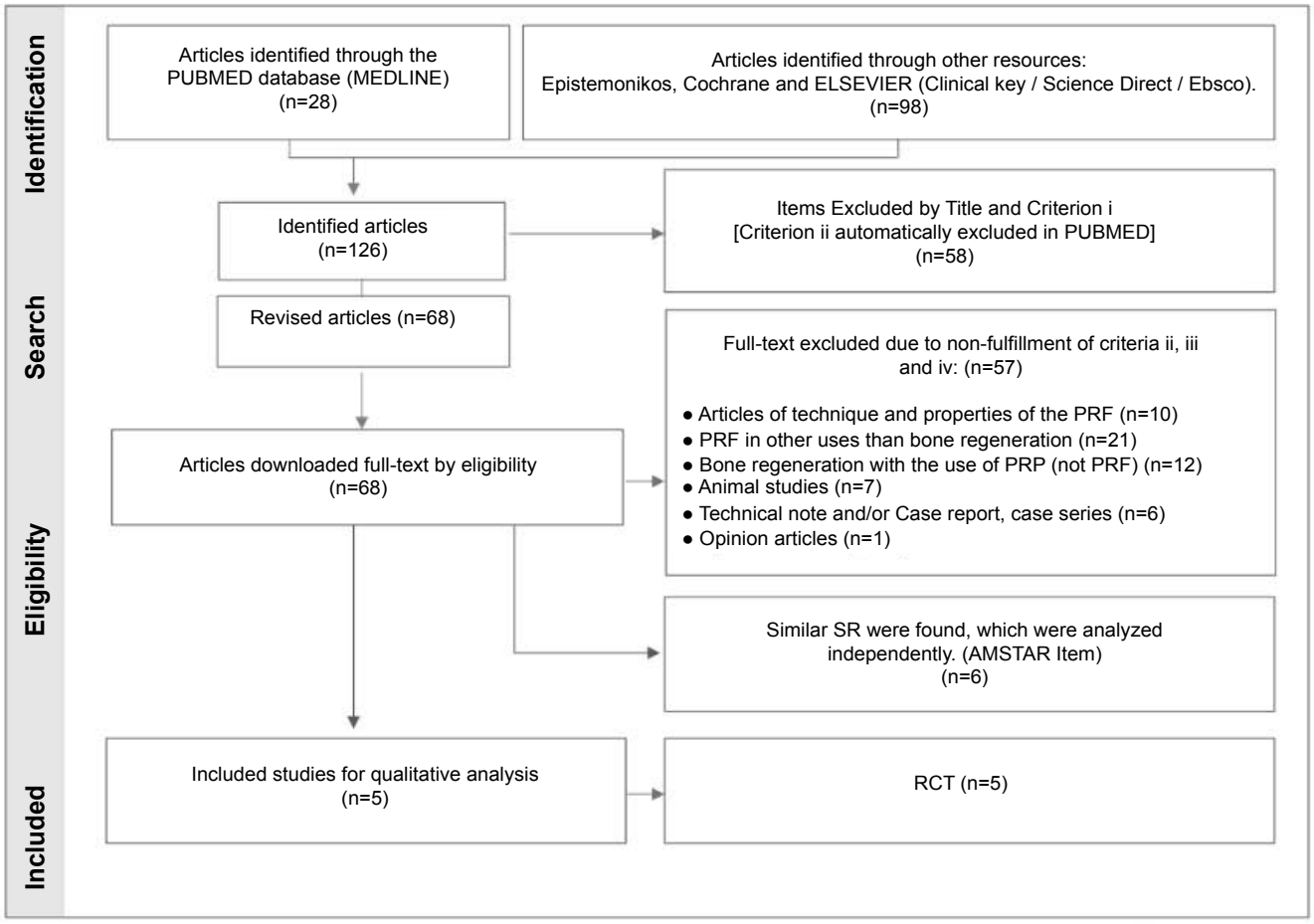

Figure 3: Flow diagram of the search strategy.

was approximately 1.4 times more than the control group (18.5 ± 5.62% vs. 12.95% ± 5.33%). Also, the percentage of contact area between the new bone and the bone graft in the group with PRF was 21.45% ± 14.57%, compared to the 18.5 ± 5.39% observed in the control group. Where as in the control group the residual bone graft percentage was approximately 1.5 times higher compared to the group with PRF (28.54% ± 12.01% vs. 19.16% ± 6.89%).

No statistically significant differences were observed between the two groups in the seen parameters, demonstrating that there is no advantage or disadvantage in the application of PRF in combination with xenograft for maxillary sinus elevation in a healing period of 6 months.

Bone graft in alveolar ridges: Moussa, et al. [21] described the benefits of using PRF in alveolar grafts through a clinical study with 12 patients in which they used autogenous intraoral graft associated with PRF and alone, evaluating results for 4 months clinically and radiographically. Results showed significantly lower reabsorption in the graft covered by PRF membranes compared to the control, however, the final volume in thickness and height does not differ greatly between the groups, considering both procedures to be successful.

Castro, et al. [20] describes the use of PRF associated with bone grafts, comparing it with PRP in alveolar ridges. He evidenced histologically significant differences in bone formation in a shorter period of time (106 days vs. 120-150 days).

Within the search, a single article by Shawky, et al. [22] evaluated the effects of PRF associated with autogenous anterior iliac crest graft on the quality and quantity of bone tissue formed for reconstruction in 24 patients with unilateral alveolar cleft. They evaluated clinically and imaged the amount of neoformed bone at 6 months using computed tomography, assessing Hounsfield units (Hu) and bone volume. They found a statistically significant increase in the percentage of newly formed bone (amount) in the group with PRF. However, the mean bone density (quality) of the neoformed bone was lower in the group with PRF than in the control group, but without significant differences. This concluded that the combination of PRF with autogenous bone was beneficial in bone neoformation, however, it would not improve the density of newly developed bone at 6 months postoperatively.

Alveolar preservation: For post-extraction bone preservation procedures, Moraschini, et al. [24] performed a comprehensive literature search analysing 102 extractions of 82 patients, using PRF in 55 of the extractions for alveolar preservation, evidencing that

the use of PRF accelerates the healing and epithelization of soft tissues in the post-extraction socket, as well as reducing post-operative pain and discomfort. These results are consistent with those described by Castro, et al. [20], in which they found significant differences in healing on the seventh day using PRF; however, there was no difference in the degree of trabecular bone formation, although after 12 weeks, the group with PRF presented significant differences in bone density, as well as in the percentage of buccal/lingual socket reabsorption. These differences were not significant at the soft tissue level.

The use of PRF in post third molar extraction socket reduces the probing depth (PD) at 3 months compared to that obtained by natural healing (1.5 mm and 0.5 mm respectively), but there were no significant differences in bone density.

From another point of view, Du Toit, et al. [23] verified histomorphometrically differences in bone tissue when using PRF in alveolar preservations prior to implants and socket healing alone in a series of a small number of patients with two sites to be treated per patient, one with PRF and another as control (n = 8). They concluded that the new bone formed does not differ from bone without intervention at 90 days, suggesting that even when PRF can rapidly stimulate bone formation, it should be evaluated by means of biopsies at 30, 60 and 90 days, therefore results can be compared, and the installation of implants allowed early compared to a control. However, taking biopsies in these periods is incompatible from an ethical point of view.

Infraosseous periodontal defects: Pradeep, et al. [25] conducted an RCT to evaluate the effects of surgical therapy with PRP and PRF in three wall infra-osseous periodontal defects. Both interventions were compared with conventional treatment without platelet concentrates in 50 patients, with a total of 90 intervened sites.

At 9 months postoperatively, they evaluated clinical and radiologic parameters such as probing depth (PD), clinical attachment level (CAL) and the percentage of bone neoformation in the treated defects radiographically. Their results showed that the use of PRF or autologous PRP was effective in the treatment of these bone defects achieving complete healing without complications in the surgical sites. Both treatments were based on autologous platelet concentrates and demonstrated a significant increase in PD reduction and compared to greater percentage of mean bone fill conventional therapy at 9 months. These parameters showed significant differences ($p < 0.05$) with control group, however, not significant between PRP and PRF.

In this context, they conclude that the use of platelet concentrates, both PRP and PRF improve the sites intervened, compared to conventional therapy without the need to use guided bone regeneration techniques (GBR), in addition to reducing treatment costs.

In a similar vein, Shah M, et al. [27] performed a SR and meta-analysis evaluating clinical and radiographic results of the use of PRF in open flap mechanical therapy, selecting 5 articles, with a total of 298 analyzed sites.

The meta-analysis showed a standard deviation difference of 0.95 mm in CAL (0.20 ± 1.71) and 2.33 mm for control (1.43 ± 3.23) after treatment of infra-osseous defects with PRF compared to conventional therapy.

They found clinically significant improvements in periodontal parameters such as CAL and PD in defects treated with PRF vs. control.

These results contrast those described by Panda, et al. [26], who evaluated the use of platelet concentrates associated with conventional debridement therapy without the use of grafts. They demonstrated that the use of PRF was effective by itself in infra-osseous defects associated with open flap debridement, however, there was no significant differences in PD decrease and CAL gain compared to control therapy without PRF.

Moreover, in a more recent review, Schliephake, et al. [19] showed better results with the use of PRF + autogenous grafts compared to conventional therapy with autogenous graft without PRF. These results are consistent with those described by Pradeep, et al. [25]. They also described that there were no real clinical benefits in furcation defects. The studies included in the review had reasonable evidence and good documentation.

Discussion

In recent years, platelet concentrates had a significant boom in the scientific literature and clinical practice in oral and maxillofacial surgery. However, the effects of the use of PRF on bone tissue in regenerative procedures are debatable. This is based on the lack of RCTs and evidence-based proof to support the use of this autologous platelet concentrate as an adjuvant in bone regeneration therapies or by itself as a filler. In addition to this, platelet concentrates were developed through a free access protocol so there are many variations of the original protocol. With the constant incorporation of platelet concentrates into clinical practice and the popularization of the use of PRF, different types of centrifuges and/or protocols developed by different clinicians have appeared [28]. This situation has resulted in variable outcomes making it difficult to compare different studies due to the large array of materials and methods used. This evidently results in a material with different qualities [4].

The fibrin architecture, the growth factors and specific contents of the PRF are key factors for its use in bone regeneration [3] and any modification of the protocol can lead to different biological characteristics and therefore alter the clinical result [29].

In the literature, the disparity of results can be found with respect to the effectiveness of PRF in different bone

regeneration techniques. One of the important aspects to consider when preparing PRF for clinical use is the centrifuge used, since, as a mechanical instrument, they present differences in specifications and models available on the market. Another aspect is the vibrations generated according to the type of centrifuge used, as well as the surface where it is located at the time of performing the procedure [28,29]. This aspect can be easily perceived just by listening and/or placing a hand on the centrifuge during the centrifugation process. Despite this observation, which in daily practice may be evident, in most articles the type of centrifuge, work surface, rotor radius, g force used, number of revolutions, among other aspects, are not specified, or they are simply not considered an important parameter in the preparation of autologous platelet concentrate.

Other important elements to consider in obtaining the PRF are the materials for the blood sample collection, the speed of blood extraction and centrifugation, all of which are critical in the quality of the resulting fibrin membrane. It is also considered important in relation to the clinical procedure the number of PRF membranes used by size of bone defect, as well as the extraction or not of plasma of the membranes (squeezing), and their compaction. Many articles published to date do not present this information clearly and sometimes it is not even mentioned. This generates results that are not replicable and makes it confusing to establish conclusions on the effectiveness of the interventions. Given its ease of preparation, low cost and biological properties, PRF could be considered as a valid treatment option as an adjuvant in regenerative therapies. However, the standardization of protocols and procedures by clinicians is necessary to obtain reproducible results [20].

To conduct studies using PRF it is suggested to use the centrifugation protocol of 3000 rpm x 10 minutes or 2700 rpm × 12 minutes as standard protocols. These protocols are the most widely used in the studies obtained in this review. The beneficial effects of PRF as a complement in bone regeneration are demonstrated especially in daily clinical practice. Since the PRF provides a local release of GFs which associated with its three-dimensional architecture, could be able to integrate different cell groups acting as a scaffold, thus favoring cell migration, leading to reduce healing times, postoperative symptomatology and improving healing in soft and hard tissues.

Although in this review the included articles presented good results with a reasonable degree of evidence, more studies are required in addition to other clinical modalities of treatment such as alveolar osteogenic distraction, reconstruction of extensive defects after resection or trauma, uses in orthognathic surgery and other techniques of reconstruction of alveolar ridges such as guided bone regeneration for vertical augmentation, not reported in the search performed.

Despite the limitations of this review, attributed mainly to the fact of including two types of different study designs, the limited number of clinical trials and the impossibility of analyzing and comparing statistically the results of the included RCTs, it is evident that the use of PRF could have a positive effect on bone regeneration in combination with biomaterials used as bone substitutes, accelerating the ossification of different types of grafts and decreasing the healing time of bone tissue.

Finally, the studies main limitations to evaluate the efficacy of PRF in bone regeneration are reduced to the technical and largely ethical difficulty to perform histological confirmation or CT imaging, checking the results in short intervals of time, rather than long-term results. This would be fundamental in making clinical decisions and reducing waiting times for second interventions, for example, in the case of the installation of osseointegrated implants.

Conclusion

The use of PRF as an adjuvant to bone grafts could be considered as a valid option in regenerative therapies in the oral and maxillofacial territory, improving the local grafts conditions and reducing the time of bone neoformation. However, more RCTs with detailed methodology are required which describe the quantity and manipulation of the fibrin membranes used in different procedures, in addition to the standardization of the protocol to obtain reproducible results. The use of PRF in clinical trials with bone regeneration techniques other than maxillary sinus lift, alveolar preservation and infra-osseous periodontal defects would also be promising.

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