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Review

Plasma rich in growth factors (PRGF) in intraoral bone grafting procedures: A systematic review

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ABSTRACT

Purpose: This systematic review aimed at assessing the effects of PRGF in new bone formation, soft tissue healing and post-operative pain and swelling in sites that underwent ridge preservation, ridge augmentation and maxillary sinus augmentation procedures.
Materials and methods: A comprehensive literature search employing seven databases was conducted by two independent reviewers. Only randomized and non-randomized controlled clinical trials using PRGF alone or in combination with bone grafting materials were selected.
Results: Overall, 919 studies were identified, of which a total of 8 articles were included in the qualitative analysis. Two of the selected studies reported on ridge preservation, one on ridge augmentation and five on maxillary sinus augmentation. Positive results were recorded for soft tissue healing and post-operative pain and swelling following these procedures. However, outcomes of PRGF on new bone formation post extraction and on maxillary sinus augmentation when combined with other biomaterials were conflicting. Meta-analysis could not be conducted for any variables due to the heterogeneity of selected studies.
Conclusion: Limited evidence exists on the effects of PRGF in different intraoral bone grafting procedures, with some benefit reported on soft tissue healing and post-operative symptomatology. As this platelet concentrate is commonly used in clinical practice, further research is needed to fully assess its clinical indications and effectiveness.

1. Introduction

Management of severely deficient edentulous ridges oftentimes represents a significant challenge in the context of tooth replacement therapy via implant-supported prostheses. Multiple surgical techniques and grafting materials aimed at implant site development have been proposed in the literature over the past several decades. In recent years, platelet concentrates (PCs) have gained significant acceptance as potential regenerative materials. A variety of preparation protocols have been introduced, including Platelet-rich Plasma (PRP) (Marx et al., 1998), Platelet-Rich Fibrin (PRF) (Choukroun, 2001) and Plasma-rich Growth Factors (PRGF) (Anitua, 1999). PRGF is an autologous blood-derived product that was initially introduced by Anitua (1999) with the objective of enhancing wound healing and promoting a faster and more predictable regenerative response following intraoral surgical procedures, such as bone grafting (Anitua, 2001). PRGF preparation is based on a single centrifugation technique and requires the conjugation of anticoagulants with the freshly collected blood, as well as the subsequent addition of calcium chloride, in order to allow for the release of growth factors and the formation of a provisional adhesive matrix, which is primarily constituted by fibrin (Anitua et al., 2012a). Diverse forms of clinically applicable PRGF products, such as clots, fibrin membranes and liquid, may be derived from different fractions of the plasma column upon centrifugation (Anitua et al., 2007). Theoretically, the enmeshment of a supraphysiologic concentration of platelets within the matrix allows for the secretion of a high concentration of growth factors,

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including TGF-β1, PDGF, VEGF and IGF. Hence, the local application of this construct is expected to enhance wound healing following surgical trauma through stimulation of re-epithelialization, angiogenesis and extracellular matrix formation (Anitua et al., 2008). As opposed to other platelet concentrates, the preparation of PRGF intentionally involves the exclusion of leukocytes, with the purpose of minimizing the occurrence of local pro-inflammatory effects (Anitua et al., 2008). *In vitro* studies have shown that PRGF may enhance soft and hard tissue regeneration by stimulating both fibroblast and osteoblast migration and proliferation (Anitua et al., 2012c; Anitua et al., 2013; Anitua et al., 2016). In a pre-clinical study, the application of PRGF on a β-TCP carrier resulted in significant bone regeneration in peri-implant bone defects, irrespective of the use of a collagen membrane (Batas et al., 2016). Clinical studies from different fields of medicine have also reported that PRGF may contribute to the treatment of chronic ulcers and orthopedic lesions (Anitua et al., 2007). Over the past two decades, PRGF has been extensively applied in oral surgery and oral implantology. Its application in extraction sockets has been claimed to improve healing by accelerating epithelialization, tissue maturation and bone regeneration (Anitua, 1999). Beneficial outcomes have also been reported in the wound healing of extraction sockets of diabetic patients (Mozzati et al., 2014) and patients with history of head and neck radiation (Mozzati et al., 2014). Incorporation of PRGF in maxillary sinus augmentation has also rendered positive outcomes in terms of reduced inflammation and post-operative pain, as well as amount of new bone formation (Anitua et al., 2012b). There is also evidence that the application of PRGF in ridge augmentation procedures is associated with positive outcomes, although the absence of a control in these studies does not allow for a proper evaluation of its effects (Anitua et al., 2011, Anitua et al., 2015). Interestingly, other clinical studies failed to demonstrate any substantial benefits associated with the use of PRGF in similar applications (Farina et al., 2013; Taschieri et al., 2015). Thus, the aim of this systematic review was to critically evaluate the effects of PRGF in new bone formation, soft tissue healing and post-operative pain and swelling in dental implant-related interventions, including (a) ridge preservation, (b) ridge augmentation and (c) maxillary sinus augmentation procedures.

2. Materials and methods

This systematic review was structured and conducted according to the Preferred Reporting of Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009).

2.1. Focused PICO question

To formulate the focused research question, the following PICO components were established: Population (P): Systemically healthy patients in need of post-extraction ridge preservation, ridge augmentation and maxillary sinus augmentation; Intervention (I): Addition of PRGF; Comparison (C): No addition of PRGF, alone or in combination with other biomaterials; Outcomes (O): New bone formation, soft tissue healing and post-operative complications.

The research question was: “Does the addition of Plasma-rich in Growth Factors (PRGF) enhance new bone formation, soft tissue healing and reduce post-operative complications in systemically healthy patients undergoing ridge preservation (a), ridge augmentation (b) and/or maxillary sinus augmentation (c) procedures, as compared to surgical approaches that did not involve the application of this autologous product”?

In order to comprehensively address all the facets of the research question, four (4) specific surrogate questions were formulated:

1. Can PRGF be considered a substitute for (i) bone grafting materials and/or (ii) barrier membranes in (a), (b) and (c) procedures?
2. Does the addition of PRGF to bone grafting materials lead to enhanced bone quantity and bone quality outcomes in (a), (b) and (c) procedures?
3. Does the adjuvant use of PRGF improve soft tissue healing in (a), (b) and (c) procedures?
4. Does the use of PRGF contribute to the reduction of post-operative swelling and patient-reported post-operative pain in (a), (b) and (c) procedures?

2.1.1. Outcome variables

- Percent of newly formed bone (*bone quality*), alveolar ridge dimensional changes and socket bone fill (*bone quantity*) assessed through histology/histomorphometry, clinical measurements and radiographic analysis.
- Soft tissue healing reported as healing index scores that consider parameters such as tissue color, response to palpation, presence/absence of granulation tissue, and premature incision margin opening.
- Post-operative complications reported as post-operative swelling and patient-reported pain assessed through questionnaires and clinical evaluation.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

Randomized controlled trials (RCT) and non-randomized controlled clinical trials (CCT) were considered eligible for inclusion if they assessed the treatment of systemically healthy patients undergoing (a) ridge preservation, (b) ridge augmentation and/or (c) maxillary sinus augmentation procedures with and without the use of PRGF, applied either alone or in combination with bone grafting materials. PRGF is a product associated with a specific preparation protocol as established by Anitua (1999), Anitua et al. (2012b, 2015). For inclusion, studies must have used a method that agreed with PRGF preparation protocols. Thus, studies were included if they reported venous blood collected in citrated tubes, centrifuged at 160g $\times$ 6 min (Anitua, 1999), 460g $\times$ 8min (Anitua et al., 2009) or 580g $\times$ 8 min (Anitua et al., 2012b, Anitua et al., 2015), with PRGF fractions (plasma above red blood cells, not including buffy coat) being activated with $CaCl_2$ (Anitua, 1999, Anitua et al., 2015) producing PRGF fibrin clots, membranes and/or liquid. All PRGF preparation protocols established by Anitua et al. have been described in relative centrifugal force (g). As centrifugation protocols for platelet concentrates in general can be described either in relative centrifugal force (g) or rounds per minute (rpm), with the equivalence between the two being dependent on variable parameters, it was decided to also include studies reporting PRGF preparation protocols in rpm.

2.2.2. Exclusion criteria

- Studies including the use of other biologic healing enhancers, such as fibrin glue, Platelet Rich Fibrin, Platelet Rich Plasma prepared not according to Anitua's protocol (Anitua, 1999, Anitua et al. 2009, 2012), recombinant human Platelet-derived Growth factors (rh-PDGF), Enamel Matrix Derivative (EMD) and bone morphogenic proteins (BMPs).
- Studies on regeneration of periodontal intrabony and furcation defects or periodontal plastic surgery.

- Studies on 3rd molar extraction sockets, as these are not normally related to site preparation for future dental implant placement.
- Inclusion of a total of less than five patients per study arm in the final analysis.
- Prospective and retrospective cohort studies and case series
- *In vitro* studies.
- Preclinical (animal) studies.

2.3. Search strategy

A literature search was conducted employing seven databases: Ovid MEDLINE, Scopus, Embase, Central (Cochrane Library), Web of Science, ProQuest (Dissertations and Theses and Nursing and Allied Health Database) and Google Scholar in an attempt to capture the grey literature up to April 23, 2018. No date limitations were used on the search and only studies published in English were included. MeSH and key terms included plasma rich growth factor, platelet rich growth factor, platelet rich plasma, PRGF, PRP, alveolar ridge preservation, tooth socket preservation, dental implants, dental implantation, maxillary sinus, sinus floor augmentation, and alveolar ridge augmentation. The MEDLINE search was adapted for use in searching the other databases. The search was supplemented by hand searches, citation screening and scanning of all reference lists of selected papers.

2.4. Screening and selection of studies

Titles and abstracts obtained were independently screened by two authors (P.D. and T.K.) on the basis of the eligibility criteria described above. If insufficient information was provided, the full text article was obtained. Full-text versions of all the eligible articles upon initial screening were obtained and independently examined by both reviewers for final selection. Disagreements, if any, were resolved by open discussion. In case that a disagreement was not resolved, an arbiter (G.A.) was consulted. All the selected studies were processed for data extraction.

2.5. Data extraction and assessment of heterogeneity

All selected publications were subdivided according to the procedure performed in three separate tables: (a) ridge preservation, (b) ridge augmentation, and (c) maxillary sinus augmentation. Two reviewers (P.D., T.K.) independently extracted relevant data into evidence tables. Data extraction included (1) first author, year of publication and study design (2) population characteristics, (3) parameters recorded and methodology, (4) PRGF preparation protocol, (5) surgical intervention details, (6) comparison/control (if any), (7) treatment outcomes, complications and patient-reported outcomes.

2.6. Quality assessment of selected clinical trials

For the interventional studies, the methodological quality of the trials was evaluated per the Cochrane Collaboration's tool for assessing risk of bias (Higgins, 2011) as adapted by Chambrone et al. (2009, 2010) to permit qualification of non-randomized trials. Concisely, the randomization and allocation methods, blinding of patients and examiners, completeness of follow-up, selective reporting and other sources of bias were classified as adequate (+), inadequate (−), unclear (?), or not applicable (NA). Based on this tool, the risk of bias was classified as follows: (1) low risk of bias if all criteria were met; (2) unclear risk of bias if one or more criteria were partly met; (3) high risk of bias if one or more of the criteria were not met.

3. Results

3.1. Study selection

The article selection process is depicted in Fig. 1. A total of 919 potentially eligible articles were identified following removal of duplicates. After application of the eligibility criteria, 903 articles were excluded based on title, abstract assessment and preparation protocol used. After review of the remaining full-text articles, 8 articles were excluded for multiple reasons (Table 1). A total of 8 publications were included in the qualitative analysis. Characteristics of all included studies on alveolar ridge preservation (two studies), ridge augmentation (one study), and maxillary sinus augmentation (five studies) are presented on Tables 2–4 respectively. All the data presented high heterogeneity across studies, so a meta-analysis was not feasible.

3.2. Risk of bias and quality assessment of included studies

The quality assessment of all included RCTs and CCTs is presented in Table 5. No studies with high risk of bias were identified. Four (4) out of the eight studies (50.0%) were identified as having low risk of bias and four (4) as having unclear risk of bias (50.0%).

3.3. Can PRGF be considered a substitute for (i) bone grafting materials and/or (ii) barrier membranes in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

3.3.1. Bone grafting materials

Ridge preservation: Two RCTs (Farina et al., 2013, Anitua et al., 2015) compared the healing outcomes in extraction sockets either filled with PRGF or allowed to heal with a natural clot. Anitua et al. (2015) used a PRGF fibrin clot in extraction sockets of mandibular molars with a PRGF fibrin membrane on top. CBCT scans taken after 10–12 weeks of healing revealed a significantly greater % of regenerated bone volume in PRGF-treated sites (96.7 ± 8.0 vs. 74.6 ± 15.3), as well as increased bone density (450 ± 106.7 vs. 318.2 ± 113 HU). Histologic analysis of bone core biopsies also revealed greater % of new bone regeneration in the test sites (63.1 ± 13.8 vs. 35.6 ± 35.3). The authors concluded that PRGF was significantly more effective in promoting bone regeneration than natural healing. Farina et al. (2013) in another controlled study, assessed early bone deposition in extraction sockets either treated with PRGF or allowed to heal naturally at two different time points (T1: 4–6 weeks, T2: 7–10 weeks). They reported no difference between groups for any of the parameters assessed through micro-CT and histologic analysis of bone core biopsies, which included bone volume, tissue mineral content, tissue mineral density and angiogenic potential, among others. It was concluded that PRGF did not enhance early bone deposition in this study.

Ridge augmentation and Maxillary sinus augmentation: No studies addressing that question were found.

3.3.2. Barrier membranes

Ridge preservation, Ridge augmentation and Maxillary sinus augmentation: No studies addressing that question were found.

3.4. Does the addition of PRGF to bone grafting materials lead to enhanced bone quantity and bone quality outcomes in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

Ridge preservation and Ridge augmentation: No studies addressing that question were found.

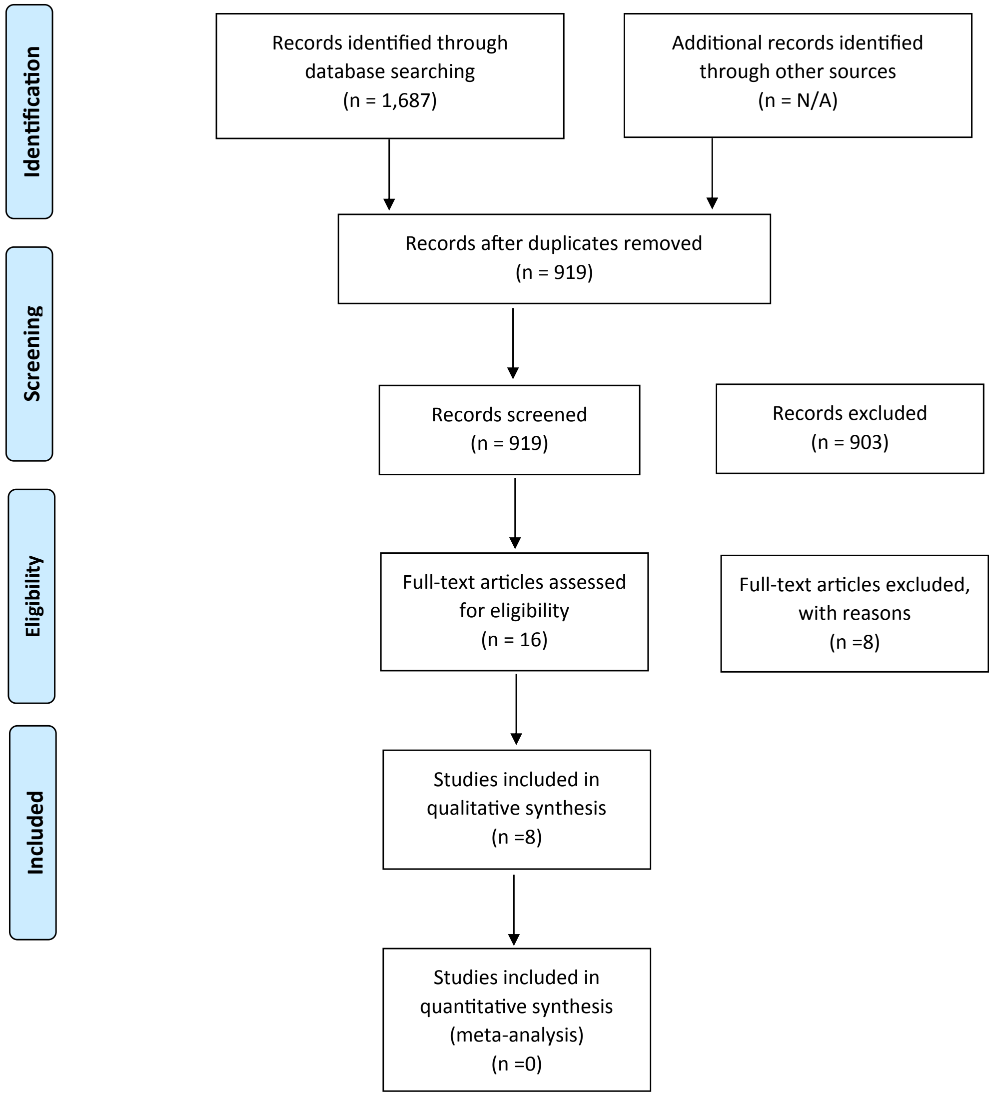

Fig. 1. Flow diagram of article selection process.

Maxillary sinus augmentation: Three controlled studies reported on histomorphometric outcomes after the use of bovine xenograft particles (Bio-Oss®, Geistlich, Wolhusen – Switzerland) (Torres et al., 2009; Taschieri et al., 2015) or β-TCP (Suprabone bone graft substitute BMT CALSIS Health Technology) (Comert Kilic et al., 2017) in combination with PRGF in direct sinus augmentation (DSA). Two of the studies had a split-mouth design with 5 patients included in each (Torres et al., 2009; Taschieri et al., 2015). Torres et al. (2009) reported higher percentage (%) of new bone (NB) formation in the PRGF-treated sites (31 ± 5 vs. 21.3 ± 4.5). On the contrary, Taschieri et al. (2015) found no statistically significant difference in % of NB between test and control sites, even if higher % of NB was noted for PRGF + xenograft (30.7 ± 7 vs. 22.72 ± 9.2). Similarly, Comert Kilic et al. (2017) also found no difference in terms of % NB, residual graft material and soft tissue between β-TCP and β-TCP + PRGF, and concluded that the addition of PRGF to DSA was not beneficial on new bone formation and regeneration. In terms of bone quantity post sinus augmentation, Kilic and Gungormus (2016), reported no difference in graft resorption between 10 days and 6 months post augmentation between β-TCP + PRGF and β-TCP alone.

Table 1
Studies excluded after full text reading and reasons for exclusion.

Study	Reasons for exclusion
Anitua (1999)	No quantitative results presented/description of biopsy outcomes
Anitua et al. (2012b)	Less than 5 patients included in the analysis
Inchingolo et al. (2012)	Peri-implant bone levels as primary outcome
Kassolis and Reynolds (2005)	Preparation protocol included use of coagulated whole blood
Khojasteh et al. (2012)	Effects of PRGF was not a primary outcome/Lack of statistics
Taschieri et al. (2014)	Perforation of sinus membrane during endodontic surgery
Taschieri et al. (2016)	Comparison between different bone grafting materials
Taschieri et al. (2017)	Immediate implants placed in post extraction sockets

3.5. *Does the adjuvant use of PRGF improve soft tissue healing in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?*

Ridge preservation: Anitua et al. (2015) assessed soft tissue healing in extraction sockets either filled with PRGF or allowed to

Table 2
Studies on PRGF and alveolar ridge preservation.

First Author, year of publication and study design	Population characteristics	Parameters recorded (P) and Methodology (M)	PRGF preparation protocol	Surgical Intervention Details	Comparison/Control	Treatment outcomes, complications and patient-reported outcomes
Farina et al. (2013) CCT	28 pts (13M/15F) –36 extraction sites – single rooted teeth 17 C–18 extraction sites 11 T–18 extraction sites	Early Bone deposition: Bone Volume (BV) Tissue Mineral Content (TMC) Tissue Mineral Density (TMD) Number of: CD68 + stained cells (macrophage, giant cells) vWF + stained cells (vasculature endothelial cells) Osteocalcin (Osteoblasts/bone matrix synthesis) At T1 (4–6 wks) or T2 (7–10 wks) post extraction **(M):** Bone Biopsy from extraction sockets at T1 and T2 Micro-computed tomography (micro-CT) HIS/HMP	20 cc of blood in tubes with 3.8% trisodium citrate as anticoagulant. 580g for 8 minutes PRGF activated with 10% Calcium Chloride (50 μL added per 1-ml fraction of PRGF)	Graft: PRGF clot	Natural Blood clot	C: NSSD in BV, TMC, TMD, CD68 + cells and vWF + cells in T1 vs. T2 T: NSSD in BV, TMC, TMD, CD68 + cells and vWF + cells in T1 vs. T2 SS decrease in osteocalcin from T1 to T2 in both C and T NSSD in BV, TMC, TMD, CD68 + cells, vWF + cells, osteocalcin in T vs. C. at T1 or T2 Extraction sites suitable for microCT analysis: 18C and 18T Suitable for HMP: 5C and 6T at T1 7C and 5T at T2.
Anitua et al. (2015) RCT	60 pts (31F/29M)/Smokers included 60 molars 90% 1st and 2nd molars in T and 96% on the C group 36 T (30 completed) 24 C (22 completed)	% of patients with Regenerated Bone volume (RBV) ≥ 75% at 10–12 wks post extraction % RBV % of new regenerated bone Bone density (HU) Pain, inflammation and soft tissue healing at day 3, 7 and 15 Gingival Thickness Complications **(M):** CBCT Bone core biopsy HIS/HMP 10-point VAS (Pain) 3-point Scale (Inflammation) Soft tissue healing: Epithelialization of wound boundaries, color, presence of bleeding on palpation, granulation, suppuration. Soft tissue biopsy	36 cc of blood in tubes with 3.8% trisodium citrate as anticoagulant. 580g for 8 minutes 8cc of Fraction 2 activated with 400 μL of 10% calcium chloride added (50 μL per 1-ml fraction) which produced fibrin clot. Fraction 1 was activated as above and formed a fibrin membrane.	PRGF Clot on socket PRGF fibrin membrane on top of the clot	Natural blood clot	96.7%T vs. 45.5%C (SS) of sites with ≥75% of RBV %RBV 96.5 ± 8.0T vs. 74.6 ± 15.3C (SS) Bone density in T vs. C (450.0 ± 106.7 vs. 318.2 ± 113) (SS) (HU) % of new bone regeneration 63.1 ± 13.8 in T vs. 35.6 ± 35.3 (SS) Increased keratinized Gingival thickness in T vs. C (415.4 ± 140.7 vs. 274.8 ± 36.0 μm) (SS) SS lower pain, inflammation at day 3 and 7 in T vs. C. No difference at day 15. Pain Day 3: 0.17 ± 0.5 (T) vs. 0.79 ± 0.7 (C) (SS) Day 7: 0.0 ± 0.0 (T) vs. 0.13 ± 0.3 (C) (SS) Inflammation Day 3: 0.19 ± 0.5 (T) vs. 0.88 ± 0.7 (C) (SS) Day 7: 0.0 ± 0.0 (T) vs. 0.38 ± 0.5 (C) (SS) SS enhanced soft tissue healing at day 3, 7 and 15 in T vs. C. No infections reported for either T or C

Abbreviations: CCT: Controlled clinical trial, RCT: Randomized Controlled trial, CBCT: Cone-Beam Computed Tomography, HIS: Histology, HMP: Histomorphometry, HU: Hounsfield unit VAS: Visual analog scale, SS: Statistically significant, NSSD: Non-statistically significant, C: Control, T: Test.

Table 3
Studies on PRGF and ridge augmentation.

First Author, year of publication and study design	Population characteristics	Parameters recorded (P) and Methodology (M)	PRGF preparation protocol	Surgical Intervention Details	Comparison/Control	Treatment outcomes, complications and patient-reported outcomes
Torres et al. (2010) RCT	30 pts (17F/13M) 15 T 15 C 97 implants placed (51 T/46C)	T-mesh exposure during healing Implant survival with 2 year follow up Bone volume increase **(M):** Clinical and radiographical (CBCT) evaluation	"PRP was prepared according to Anitua's method" (Anitua, 1999) 10–20 cc of blood in tubes with 3.8% sodium citrate as anticoagulant. Centrifuge: (BTI PRGF System II centrifuge) Activated with 30% $CaCl_2$.	PRGF membranes over T-mesh prior to closure	No PRGF membrane over T- mesh prior to closure.	No T-mesh exposure on T 6/15 T-mesh exposure on C Vertical and horizontal bone volume augmentation were SS Higher in T vs. C. One graft failure on the C group (T-mesh exposure) No SS difference in implant survival between T vs. C. (100% T vs. 97.3% C)

Abbreviations: T-mesh: Titanium mesh, CBCT: Cone-Beam Computed Tomography, SS: Statistically significant, T: Test, C: Control.

heal naturally according to the score described by Landry and Howley (1988) (range 1–5, with 1 described as "very poor" and 5 as "excellent" looking into epithelialization of wound boundaries, tissue color, presence of bleeding on palpation, granulation and suppuration). Soft tissue healing scores were significantly higher in the PRGF group until the 15th post-operative day (4.97 vs. 3.96). Gingival biopsy outcomes also showed increased keratinized gingiva for the PRGF group at 10–12 weeks post extraction (415.4 ± 140.7 vs. 274.8 ± 36.0 μm).

Ridge augmentation: Torres et al. (2010) evaluated whether PRGF membranes contribute to prevention of titanium mesh (Ti-mesh) exposure following ridge augmentation. In patients where PRGF membranes were placed on top of the Ti-Mesh, no exposures were registered (0/15), whereas in the control group, 40% of the cases (6/15) had a Ti-mesh exposure, with the majority of them within the first month. The average bone width and height gained in the PRGF group was significantly greater compared to control sites, which was attributed to the lack of Ti-mesh exposure. The authors concluded that PRGF may prevent the incidence of Ti-mesh exposure, by improving soft tissue healing.

Maxillary sinus augmentation: No studies addressing that question were found.

3.6. Does the use of PRGF contribute to the reduction of post-operative swelling and patient-reported post-operative pain in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

Ridge preservation: Anitua et al. (2015) assessed post-operative inflammation (3-point scale) and pain (10-point VAS) at days 3, 7 and 15 after extraction of mandibular molars, with sockets either filled with a PRGF fibrin clot and a PRGF fibrin membrane on top or allowed to heal naturally. Significantly less pain and inflammation for the PRGF group was reported at days 3 and 7 with no difference at day 15.

Ridge augmentation: No studies addressing that question were found.

Maxillary sinus augmentation: Del Fabbro et al. (2015) assessed post-operative swelling and pain in 30 patients undergoing DSA with xenograft + PRGF vs. xenograft alone (Bio-Oss®, Geistlich, Wolhusen – Switzerland), using questionnaires. On the test group, a PRGF membrane was placed over the lateral window and in the sinus membrane in case of perforation. Significant reduction in patient perceived pain was noted for the PRGF group during 2nd and 3rd day, with no difference from day 4. Less swelling was also reported during week 1 for the PRGF group. In general, limitations in daily functions were fewer for the PRGF vs. control group during the initial post-operative period.

4. Discussion

4.1. Study selection

As PRGF is considered a type of platelet rich plasma (PRP) that follows a specific preparation protocol, we included PRP as a MeSH term in the initial study screening in order to avoid excluding articles that may have not used a specific terminology when describing this platelet concentrate. We included studies that used as a reference, preparation protocols for PRP/PRGF as described by Anitua (1999), Anitua et al. (2009), Anitua et al. (2015), who initially introduced this particular product. However, two studies (Torres et al. 2009, 2010) used a 30% concentration of $CaCl_2$ for activation of PRGF which is different than the 10% concentration that was originally described by Anitua, (1999). Whether this difference affects the nature and

Table 4
Studies on PRGF and maxillary sinus augmentation.

First Author, year of publication and study design	Population characteristics	Parameters recorded (P) and Assessment Methodology (M)	PRGF preparation protocol	Surgical Intervention Details	Comparison/Control	Treatment outcomes, complications and patient-reported outcomes
Torres et al. (2009) RCT	87 pts (47F/40M) 35% smokers 144 DSA and 286 DI 1-stage (4–7 mm of RBH): 87 DSA's + 187 DI's 2-stage (<4 mm of RBH): 57 DSA's + 112 DI's 5 patients in need for bilateral DSA and 2-stage DI's recruited for **split-mouth RCT.**	**(P):** Implant survival with 2 year follow up period **Split-mouth RCT:** Bone quality/Bone volume/Bone density in 5 pts **(M):** Bone biopsy from osteotomy site. HIS/HMP CBCT Bone density (HU)	"According to Anitua's method"(Anitua, 1999) 10–20 cc of blood in tubes with 3.8% sodium citrate as anticoagulant. Centrifuge: (BTI PRGF System II centrifuge) Activated with 30% $CaCl_2$.	Graft: Xenograft + PRGF PRGF membrane for sinus membrane perforation. No membrane on lateral wall.	Graft: Xenograft Collagen membrane for sinus membrane perforation No membrane on lateral wall.	97.5% implant survival (7/286) 96.2% C vs. 98.6%T (NSSD) 94.6% when RBH<4 mm vs. 99.4% when RBH was 4–7 mm (SSD) 5/7 DI's were lost in smokers (SSD) **Split mouth RCT:** NSSD in bone density and bone volume in T vs. C NB: 31 ± 5 T vs. 21.3 ± 4.5 C. (SS) RG: NSSD CT: NSSD Sinus membrane perforations in 5 pts (3 in the C group and 2 on the T group) No infections reported in either groups
Del Fabbro et al. (2015) RCT	30 pts (18F/12M) 4 smokers <10 cigarettes a day) 15T 15C	**(P):** Post-op Pain, swelling, bleeding, nausea, bad taste/ breath and Limitations in daily functions: Mouth opening, Chewing, Speaking Sleeping, daily routine, missed work/school. For 1 week (assessed on daily basis) **(M):** Questionnaire: VAS for pain (0–100) 5-point Likert Type Scale (0 –4 – none to very much) for all others.	For protocol ref to Del Fabbro et al. (2012) Venous blood collected in citrated tubes. 580g for 8 minutes Fraction above red cells, not including the buffy coat was collected and activated with CaCl2.	Graft: Xenograft + PRGF PRGF membrane over lateral window. PRGF membrane in case of sinus membrane perforation	Graft: Xenograft No membrane over lateral window. Further detaching and folding the sinus membrane in case of perforation. No membranes used.	SS reduction of the perceived pain during 2nd and 3rd post-op pain in T. vs. C. From Day 4, NSSD between groups. Less swelling, less hematoma, less discomfort regarding chewing and speaking during 1st week in T vs. C (SSD) Mouth opening and sleeping improved in T vs. C in first 3–4 days (SSD). Bleeding was lower in the first 2 days in T vs. C (SSD) Less patients took analgesics in the T group vs. control in the first 3 days (SSD) One sinus membrane perforation in T group and two (2) in C.
Taschieri et al. (2015) CCT	5 pts (3F/2M) 10 DSA (Split mouth design) No smoking	**(P):** Bone quality Implant success and survival at 1 year post placement Complications (acute sinusitis, infection, dispersion of bone grafting material into the sinus, inadequate bone quantity, density) **(M):** Bone core biopsy from lateral wall HS/HMP PA's	For protocol authors reference Taschieri et al. (2012): "followed manufacturer's instructions (PRGF System IV, BTI Biotechnology institute") for PRGF preparation" Citrated tubes 580g for 8 min. Supernatant separated in two fractions that are both activated with calcium chloride.	Graft: Xenograft Membranes on lateral window/membranes in perforations (?)	Graft: Xenograft + PRGF liquid Membranes on lateral window/ membranes in perforations (?)	NB: 22.72% ± 9.21 C vs. 30.70% ± 7.89 T (NSSD) Residual bone height statistically correlated with % of vital bone formation No complications reported in either C or T 100% implant success and survival

(*continued on next page*)

Table 4 (*continued*)

First Author, year of publication and study design	Population characteristics	Parameters recorded (P) and Assessment Methodology (M)	PRGF preparation protocol	Surgical Intervention Details	Comparison/Control	Treatment outcomes, complications and patient-reported outcomes
Kilic and Gungormus (2016) RCT	18 pts (6F/12M) 18 DSA 9(C) 9(T)	**(P):** Vertical bone height gain at 10 days and 6 months **(M):** CBCT	For preparation protocol authors reference Anitua et al. (2004) 10 cc of blood in in tubes with 3.2% sodium citrate as anticoagulant. 1000 rpm for 10 min. PRGF activated with CaCl2.	Graft: β-TCP + PRGF Collagen membrane to cover lateral window	Graft: β-TCP Collagen membrane to cover lateral window	Vertical bone height gain at 10 days: 12.48 ± 2.99 mm (C) and 14.77 ± 2.97 mm (T) (NSSD) Vertical bone height gain at 6 months: 11.59 ± 3.02 mm (C) and 13.19 ± 3.32 (T) (NSSD) Graft resorption: 0.89 ± 0.79 mm (C) and 1.58 ± 1.01 mm (T) NSSD
Comert Kilic et al. (2017) [a] RCT	18 patients (6F/12M) 18 DSA 9(C) 9(T)	**(P):** Bone quality at 6 months **(M):** Bone biopsy from osteotomy site HIS/HMP	For protocol ref to Kilic and Gungormus (2016) 10 cc of blood in in tubes with 3.2% sodium citrate as anticoagulant. 1000 rpm for 10 min. PRGF activated with CaCl2.	Graft: β-TCP (2 cc) + PRGF (2 −2.4 ml) CM over lateral window and perforations if occurring	Graft: β-TCP (2 cc) CM over lateral window and perforations if occurring	NB: 33.40 ± 10.43 (C) vs. 34.83 ± 10.12 (T) (NSSD) Soft tissue: 36.21 ± 10.59 (C) vs. 36.19 ± 13.94 (T) (NSSD) REMN: 30.39 ± 10.29 (C) vs. 28.98 ± 7.94 (T) (NSSD) NSSD in mean density of osteoblasts, osteoclasts, osteocytes, capillary vessels, inflammatory cells and osteoprogenitor cells.

Abbreviations: RCT: Randomized controlled trial, CCT: Controlled Clinical trial, DSA: Direct Sinus augmentation, T: Test, C: Control DI: Dental Implant, HIS: Histology, HMP: Histomorphometry, RBH: Residual bone height, rpm: rounds per minute, β-TCP: beta-tricalcium phosphate, CM: Collagen membrane, NSSD: Non-statistically significant, SS: Statistically significant, NB: New bone, REMN: remnants/residual graft material, VAS: Visual analog scale, RG: residual graft, CT: Connective tissue, CBCT: Cone-Beam Computed Tomography.

[a] Data for leukocyte-platelet-rich fibrin (L-PRF) are not presented.

Table 5
Qualitative analysis of the included controlled clinical trials.

	Farina et al. (2013)	Anitua et al. (2015)	Torres et al. (2010)	Torres et al. (2009)	Del Fabbro et al. (2015)	Taschieri et al. (2015)	Kilic and Gungormus (2016)	Comert Kilic et al. (2017)
Method of randomization	N/A	+	+	+	+	N/A	?	?
Allocation Concealment	N/A	+	+	+	+	N/A	?	?
Blinding of participants, personnel and outcome assessors	+	?	+	+	?	+	?	?
Completeness of follow up	+	+	+	+	+	+	+	+
Selective reporting	+	+	+	+	+	+	+	+
Other bias	+	?	+	+	+	+	+	+

effectiveness of the product is unclear. Also, in the methodology of two studies by Kilic and Gungormus (2016); Comert Kilic et al. (2017), they reported that “In the present study, a one-step centrifugation procedure as described by Anitua et al. was used”. However, they used a centrifugation rate of 1000 rpm for 10 minutes which is substantially different than PRGF preparation protocols described elsewhere (Anitua, 1999; Anitua et al., 2009, Anitua et al., 2015). The equivalence of 1000 rpm to relative centrifugal force (g) is dependent, among other parameters, on the radius of the centrifugation machine. Thus, the similarity of this product to PRGF produced via other preparation protocols that follow a different centrifugation rate may be under question, but it could not be precisely determined. Variation in preparation protocols and the effect it may have on the final product was pointed out in a recent study looking into L-PRF, which concluded that the centrifuge characteristics and centrifugation protocols significantly alter cell viability, growth factor expression and fibrin architecture of L-PRF products (Dohan Ehrenfest et al., 2017). Whether that is also applicable to PRGF constructs has not been demonstrated. It is also unknown if differences in the composition of PRGF product translate into a patent clinical effect. Thus, it was decided to include studies with protocol variability to avoid excluding articles that may provide evidence on the clinical effects of PRGF.

4.2. Can PRGF be considered a substitute for (i) bone grafting materials and/or (ii) barrier membranes in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

Ridge preservation: Two controlled studies comparing PRGF-treated extraction sockets with natural healing were identified (Farina et al., 2013, Anitua et al., 2015). Interestingly, these studies report discrepant outcomes. Anitua et al. (2015) observed enhanced bone regeneration in the PRGF group at 10–12 weeks, whereas Farina et al. (2013) did not observe enhanced bone deposition on the PRGF group at 4 and 8 weeks post extraction, concluding that PRGF may not have an impact on early bone healing. Since the timing of assessment was different between the two studies (10–12 wks. vs. 4/8 wks), it is possible that the effect of PRGF on bone regeneration may become more evident at later stages of healing. Also, as none of the studies assessed dimensional changes of extraction sockets treated with or without PRGF, no conclusions could be drawn in this regard. Overall, the lack of controlled studies between PRGF and bone grafts in ridge preservation does not allow for the extraction of conclusions regarding its validity as a substitute for bone grafting materials. In summary, only limited evidence (i.e. one study) supports its use to enhance qualitative bone characteristics at later stages of healing (~12 weeks) as compared to natural clot, although this premise is not supported by the findings of a separate similar clinical trial.

Maxillary sinus augmentation: Cohort studies have reported favorable outcomes in terms of survival rates for implants placed in conjunction with PRGF in crestal sinus augmentation (Taschieri and Del Fabbro, 2011, Taschieri et al., 2014). However, no controlled studies could be identified reporting on outcomes of PRGF when used as a sole grafting material in the sinus, thus, firm conclusions on whether PRGF could be used as a bone graft substitute cannot be made. However, based on the promising outcomes reported in long-term controlled studies for implant placement with no grafting in sinus augmentation procedures (Nedir et al., 2016), PRGF could be another alternative to bone grafting, providing also the potential advantage of assisting in the repair of membrane perforations (Taschieri et al., 2012).

4.3. Does the addition of PRGF to bone grafting materials lead to enhanced bone quantity and bone quality outcomes in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

A common approach in contemporary clinical practice is mixing platelet concentrates with bone grafting materials with the goal of enhancing treatment outcomes. Following preparation of PRGF, a fraction is usually mixed with a biomaterial in order to improve its handling properties and regeneration properties. In this systematic review, such application was only identified in studies on maxillary sinus augmentation. Three controlled studies (Torres et al., 2009; Taschieri et al., 2015; Comert Kilic et al., 2017) assessing bone quality outcomes with or without PRGF were included, with two of them reporting only on 5 patients (Torres et al., 2009; Taschieri et al., 2015). Only in one study, % of new bone formation was higher in the PRGF vs. control group (Torres et al., 2009), whereas in the other two, using either β-TCP (Comert Kilic et al., 2017) or xenograft (Taschieri et al., 2015), no significant differences were noted. Higher % of new bone formation has been associated with a PRGF-enhanced vascularization of the grafted area during healing period (Anitua et al., 2012b) and increased proliferation, migration and chemotaxis of osteoblasts (Anitua et al., 2013). However, other clinical and pre-clinical studies have failed to report any difference in density of osteoblasts and capillary vessels (Comert Kilic et al., 2017) or density and quantity of *de novo* bone matrix (Hatakeyama et al., 2008), whether PRGF was applied or not. In terms of bone quantity outcomes, the use of PRGF does not seem to have an effect either, as demonstrated by both Kilic and Gungormus (2016) and Torres et al. (2009). Finally, the use of PRGF in maxillary sinus augmentation does not seem to be associated with superior implant outcomes. Two controlled studies (Torres et al., 2009; Taschieri et al., 2015) reported no difference in implant success and survival between treatment modalities. Therefore, there is no tangible evidence to date supporting the application of PRGF in maxillary sinus augmentation with the objective of enhancing bone quantity and/or bone quality outcomes.

4.4. Does the adjuvant use of PRGF improve soft tissue healing in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

Platelet concentrates, including PRP, PRF and PRGF, in the form of membranes are commonly used over biomaterials in augmentation procedures with the purpose of enhancing soft tissue healing and to reduce the incidence of premature wound dehiscence. However, there is limited available evidence supporting the effectiveness of such therapeutic strategies (Arora et al., 2010; Miron et al., 2017). In this systematic review, only two studies could be identified reporting on the effects of PRGF on soft tissue healing in ridge preservation (Anitua et al., 2015) and ridge augmentation (Torres et al., 2010). No studies could be found on maxillary sinus augmentation procedures. In one of the included studies, Anitua et al. (2015) reported thicker keratinized tissue and improved healing index in extraction sockets of mandibular molars that were treated with a PRGF fibrin clot and a fibrin membrane on top. Likewise, Torres et al. (2010) reported improved soft tissue healing in ridge augmentation cases involving the use of a Ti-mesh in which PRGF fibrin clots were placed below the flaps prior to closure, with no observed incidence of T-mesh exposure. They reported however, that the presence of PRGF fibrin clots demanded more extensive periosteal release compared to control sites, which may have had an impact on the reduced incidence of wound dehiscence during healing. Nonetheless, the addition of PRGF appeared to improve horizontal and vertical bone augmentation outcomes through maintenance of tissue closure during the healing period. Wound dehiscence and membrane exposure is one of the most frequent complications during ridge augmentation with negative effects on treatment outcomes (von Arx et al., 1996; Garcia et al., 2018), therefore the addition of this platelet concentrate may be advantageous in these procedures. Overall, the limited number of studies, as well as the limited number of patients included in them, does not allow for the extraction of conclusions that may be conducive to the establishment of clinical practice guidelines. Further, well-conducted studies assessing the effect on soft tissue healing of PRGF are warranted.

4.5. Does the use of PRGF contribute to the reduction of post-operative swelling and patient-reported post-operative pain in ridge preservation, ridge augmentation and maxillary sinus augmentation procedures?

In the two studies that were included in this systematic review, favorable outcomes in terms of post-operative inflammation and pain after maxillary sinus augmentation (Del Fabbro et al., 2015) and ridge preservation (Anitua et al., 2015) procedures were observed in association with the application of PRGF. According to Del Fabbro et al. (2015), reduction of post-surgical symptoms might be related with the absence of leukocytes in the PRGF fibrin membrane, thus reducing a leukocyte-induced exacerbated local inflammatory reaction. Nonetheless, whether the presence or absence of leukocytes in the platelet concentrates influences the initial healing response is still debatable. While some studies have suggested a protective effect of leukocytes against infections (Cieslik-Bielecka et al., 2007; Moojen et al., 2008) some others have reported on the negative effects of leukocytes in the early stages of healing (McCarrel et al., 2012). Studies on post-operative inflammation and pain using leukocyte platelet rich fibrin (L-PRF) have also reported improvement compared to controls (Marenzi et al., 2015; Ozgul et al., 2015; Temmerman et al., 2016), attributing it to a possible supportive effect of L-PRF on the immune system. Limited available evidence supports a marginally positive effect of PRGF in post-operative swelling and pain, mainly during the first week. Whether that is mediated through the absence of leukocytes is unclear and further specific research to answer that question is necessary.

5. Conclusion

Limited evidence exists regarding the effect of PRGF in ridge preservation, ridge augmentation and maxillary sinus augmentation. Some of the studies included in this systematic review report a marginally beneficial effect of this platelet concentrate in soft tissue healing and post-operative symptomatology following these procedures. On the contrary, its effect on bone regeneration, whether it is used alone or in combination with bone grafting materials, in both ridge preservation and maxillary sinus augmentation procedures is still questionable. Given its autologous nature and biological properties, the effect of PRGF in bone augmentation procedures should be further investigated in well conducted RCTs with larger populations on the basis of relevant and standardized outcomes of interest in order to expand our understanding of the clinical applicability of this product.

Conflicts of interest

The authors report no conflicts of interests.

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References

Anitua E: Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. Int J Oral Maxillofac Implants 14(4): 529–535, 1999

Anitua E: The use of plasma-rich growth factors (PRGF) in oral surgery. Pract Proced Aesthet Dent 13(6): 487–493, 2001 quiz 487-493

Anitua E, Aguirre JJ, Algorta J, Ayerdi E, Cabezas AI, Orive G, et al: Effectiveness of autologous preparation rich in growth factors for the treatment of chronic cutaneous ulcers. J Biomed Mater Res B Appl Biomater 84(2): 415–421, 2008

Anitua E, Alkhraisat MH, Orive G: Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J Control Release 157(1): 29–38, 2012a

Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT: Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 91(1): 4–15, 2004

Anitua E, Begona L, Orive G: Two-stage split-crest technique with ultrasonic bone surgery for controlled ridge expansion: a novel modified technique. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 112(6): 708–710, 2011

Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G: Clinical, radiographical, and histological outcomes of plasma rich in growth factors in extraction socket: a randomized controlled clinical trial. Clin Oral Invest 19(3): 589–600, 2015a

Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G: Implant-Guided vertical bone augmentation around extra-short implants for the management of severe bone atrophy. J Oral Implantol 41(5): 563–569, 2015b

Anitua E, Pino A, Orive G: Plasma rich in growth factors promotes dermal fibroblast proliferation, migration and biosynthetic activity. J Wound Care 25(11): 680–687, 2016

Anitua E, Prado R, Orive G: A lateral approach for sinus elevation using PRGF technology. Clin Implant Dent Relat Res 11(Suppl 1): e23–e31, 2009

Anitua E, Prado R, Orive G: Bilateral sinus elevation evaluating plasma rich in growth factors technology: a report of five cases. Clin Implant Dent Relat Res 14(1): 51–60, 2012b

Anitua E, Sanchez M, Orive G, Andia I: The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials 28(31): 4551–4560, 2007

Anitua E, Tejero R, Zalduendo MM, Orive G: Plasma rich in growth factors promotes bone tissue regeneration by stimulating proliferation, migration, and autocrine secretion in primary human osteoblasts. J Periodontol 84(8): 1180–1190, 2013

Anitua E, Troya M, Orive G: Plasma rich in growth factors promote gingival tissue regeneration by stimulating fibroblast proliferation and migration and by blocking transforming growth factor-beta1-induced myodifferentiation. J Periodontol 83(8): 1028–1037, 2012c

Arora NS, Ramanayake T, Ren YF, Romanos GE: Platelet-rich plasma in sinus augmentation procedures: a systematic literature review: Part II. Implant Dent 19(2): 145–157, 2010

Batas L, Stavropoulos A, Papadimitriou S, Nyengaard JR, Konstantinidis A: Evaluation of autogenous PRGF+beta-TCP with or without a collagen membrane on bone formation and implant osseointegration in large size bone defects. A preclinical in vivo study. Clin Oral Implants Res 27(8): 981–987, 2016

Chambrone L, Chambrone D, Lima LA, Chambrone LA: Predictors of tooth loss during long-term periodontal maintenance: a systematic review of observational studies. J Clin Periodontol 37(7): 675–684, 2010

Chambrone L, Chambrone D, Pustiglioni FE, Chambrone LA, Lima LA: The influence of tobacco smoking on the outcomes achieved by root-coverage procedures: a systematic review. J Am Dent Assoc 140(3): 294–306, 2009

Choukroun J: Une opportunite en paroimplantologie: le PRF. Implantodontie 42: 55–62, 2001

Cieslik-Bielecka A, Gazdzik TS, Bielecki TM, Cieslik T: Why the platelet-rich gel has antimicrobial activity? Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103(3): 303–305, 2007 author reply 305-306

Comert Kilic S, Gungormus M, Parlak SN: Histologic and histomorphometric assessment of sinus-floor augmentation with beta-tricalcium phosphate alone or in combination with pure-platelet-rich plasma or platelet-rich fibrin: a randomized clinical trial. Clin Implant Dent Relat Res 19(5): 959–967, 2017

Del Fabbro M, Ceresoli V, Lolato A, Taschieri S: Effect of platelet concentrate on quality of life after periradicular surgery: a randomized clinical study. J Endod 38(6): 733–739, 2012

Del Fabbro M, Corbella S, Ceresoli V, Ceci C, Taschieri S: Plasma rich in growth factors improves patients' postoperative quality of life in maxillary sinus floor augmentation: preliminary results of a randomized clinical study. Clin Implant Dent Relat Res 17(4): 708–716, 2015

Dohan Ehrenfest DM, Pinto NR, Pereda A, Jimenez P, Corso MD, Kang BS, et al: The impact of the centrifuge characteristics and centrifugation protocols on the cells, growth factors, and fibrin architecture of a leukocyte- and platelet-rich fibrin (L-PRF) clot and membrane. Platelets: 1–14, 2017

Farina R, Bressan E, Taut A, Cucchi A, Trombelli L: Plasma rich in growth factors in human extraction sockets: a radiographic and histomorphometric study on early bone deposition. Clin Oral Implants Res 24(12): 1360–1368, 2013

Garcia J, Dodge A, Luepke P, Wang HL, Kapila Y, Lin GH: Effect of membrane exposure on guided bone regeneration: a systematic review and meta-analysis. Clin Oral Implants Res 29(3): 328–338, 2018

Hatakeyama M, Beletti ME, Zanetta-Barbosa D, Dechichi P: Radiographic and histomorphometric analysis of bone healing using autogenous graft associated with platelet-rich plasma obtained by 2 different methods. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 105(1): e13–e18, 2008

Higgins JPTG,S: Cochrane handbook for systematic reviews of interventions (serial on the internet). Available at: www.cochrane-handbook.org; 2011

Inchingolo F, Tatullo M, Marrelli M, Inchingolo AM, Inchingolo AD, Dipalma G, et al: Regenerative surgery performed with platelet-rich plasma used in sinus lift elevation before dental implant surgery: an useful aid in healing and regeneration of bone tissue. Eur Rev Med Pharmacol Sci 16(9): 1222–1226, 2012

Kassolis JD, Reynolds MA: Evaluation of the adjunctive benefits of platelet-rich plasma in subantral sinus augmentation. J Craniofac Surg 16(2): 280–287, 2005

Khojasteh A, Behnia H, Shayesteh YS, Morad G, Alikhasi M: Localized bone augmentation with cortical bone blocks tented over different particulate bone substitutes: a retrospective study. Int J Oral Maxillofac Implants 27(6): 1481–1493, 2012

Kilic SC, Gungormus M: Cone beam computed Tomography assessment of maxillary sinus floor augmentation using beta-tricalcium phosphate alone or in combination with platelet-rich plasma: a randomized clinical trial. Int J Oral Maxillofac Implants 31(6): 1367–1375, 2016

Landry RTR, Howley T: Effectiveness of benzydamine HCl in the treatment of periodontal post-surgical patients. Res Clin Forums 10: 105–118, 1988

Marenzi G, Riccitiello F, Tia M, di Lauro A, Sammartino G: Influence of leukocyte- and platelet-rich fibrin (L-PRF) in the healing of simple postextraction sockets: a split-mouth study. Biomed Res Int 2015: 369273, 2015

Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR: Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 85(6): 638–646, 1998

McCarrel TM, Minas T, Fortier LA: Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. J Bone Jt Surg Am 94(19): 141–148, 2012 e143

Miron RJ, Zucchelli G, Pikos MA, Salama M, Lee S, Guillemette V, et al: Use of platelet-rich fibrin in regenerative dentistry: a systematic review. Clin Oral Invest 21(6): 1913–1927, 2017

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10): 1006–1012, 2009

Moojen DJ, Everts PA, Schure RM, Overdevest EP, van Zundert A, Knape JT, et al: Antimicrobial activity of platelet-leukocyte gel against Staphylococcus aureus. J Orthop Res 26(3): 404–410, 2008

Mozzati M, Gallesio G, di Romana S, Bergamasco L, Pol R: Efficacy of plasma-rich growth factor in the healing of postextraction sockets in patients affected by insulin-dependent diabetes mellitus. J Oral Maxillofac Surg 72(3): 456–462, 2014a

Mozzati M, Gallesio G, Gassino G, Palomba A, Bergamasco L: Can plasma rich in growth factors improve healing in patients who underwent radiotherapy for head and neck cancer? A split-mouth study. J Craniofac Surg 25(3): 938–943, 2014b

Nedir R, Nurdin N, Abi Najm S, El Hage M, Bischof M: Short implants placed with or without grafting into atrophic sinuses: the 5-year results of a prospective randomized controlled study. Clin Oral Implants Res 18(1): 10–18. https://doi.org/10.1111/cid.12279, 2016 Feb

Ozgul O, Senses F, Er N, Tekin U, Tuz HH, Alkan A, et al: Efficacy of platelet rich fibrin in the reduction of the pain and swelling after impacted third molar surgery: randomized multicenter split-mouth clinical trial. Head Face Med 11: 37, 2015

Taschieri S, Corbella S, Del Fabbro M: Use of plasma rich in growth factor for schneiderian membrane management during maxillary sinus augmentation procedure. J Oral Implantol 38(5): 621–627, 2012

Taschieri S, Corbella S, Del Fabbro M: Mini-invasive osteotome sinus floor elevation in partially edentulous atrophic maxilla using reduced length dental implants: interim results of a prospective study. Clin Implant Dent Relat Res 16(2): 185–193, 2014a

Taschieri S, Corbella S, Tsesis I, Del Fabbro M: Impact of the use of plasma rich in growth factors (PRGF) on the quality of life of patients treated with endodontic surgery when a perforation of sinus membrane occurred. A comparative study. Oral Maxillofac Surg 18(1): 43–52, 2014b

Taschieri S, Corbella S, Weinstein R, Di Giancamillo A, Mortellaro C, Del Fabbro M: Maxillary sinus floor elevation using platelet-rich plasma combined with either biphasic calcium phosphate or deproteinized bovine bone. J Craniofac Surg 27(3): 702–707, 2016

Taschieri S, Del Fabbro M: Postextraction osteotome sinus floor elevation technique using plasma-rich growth factors. Implant Dent 20(6): 418–424, 2011

Taschieri S, Lolato A, Ofer M, Testori T, Francetti L, Del Fabbro M: Immediate post-extraction implants with or without pure platelet-rich plasma: a 5-year follow-up study. Oral Maxillofac Surg 21(2): 147–157, 2017

Taschieri S, Testori T, Corbella S, Weinstein R, Francetti L, Di Giancamillo A, et al: Platelet-rich plasma and deproteinized bovine bone matrix in maxillary sinus lift surgery: a split-mouth histomorphometric evaluation. Implant Dent 24(5): 592–597, 2015

Temmerman A, Vandessel J, Castro A, Jacobs R, Teughels W, Pinto N, et al: The use of leucocyte and platelet-rich fibrin in socket management and ridge preservation: a split-mouth, randomized, controlled clinical trial. J Clin Periodontol 43(11): 990–999, 2016

Torres J, Tamimi F, Alkhraisat MH, Manchon A, Linares R, Prados-Frutos JC, et al: Platelet-rich plasma may prevent titanium-mesh exposure in alveolar ridge augmentation with anorganic bovine bone. J Clin Periodontol 37(10): 943–951, 2010

Torres J, Tamimi F, Martinez PP, Alkhraisat MH, Linares R, Hernandez G, et al: Effect of platelet-rich plasma on sinus lifting: a randomized-controlled clinical trial. J Clin Periodontol 36(8): 677–687, 2009

von Arx T, Hardt N, Wallkamm B: The TIME technique: a new method for localized alveolar ridge augmentation prior to placement of dental implants. Int J Oral Maxillofac Implants 11(3): 387–394, 1996