APPLICATION OF PLATELET-RICH PLASMA FOR ALVEOLAR RIDGE PRESERVATION. A REVIEW ARTICLE

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ABSTRACT

INTRODUCTION: Bone quality and quantity are key prerequisites for dental implant surgery. The methods of reducing tissue resorption after tooth extraction are called alveolar ridge preservation and have recently gained increasing popularity. One of them is the application of autologous platelet concentrates. They release an abundance of growth factors with the potential to accelerate the healing process.

AIM: The present review aims to observe the application of platelet-rich plasma in postextraction dental sockets and evaluate its efficacy for hard and soft tissue healing and preservation according to the literature. We carefully analyzed, compared, and summarized the collected data and found numerous research and methodological gaps that can explain the heterogeneity in the studies.

MATERIALS AND METHODS: The review is based on the existing scientific database and includes 222 studies. It provides a comparative analysis and guidelines for further research.

RESULTS: There is high heterogeneity among studies, regarding the effect of platelet concentrates and platelet-rich plasma in particular on alveolar ridge preservation. Most of them validate its beneficial impact on tissue healing and volumetric preservation, which facilitate the subsequent implant placement.

CONCLUSION: The scientific data about the efficacy of platelet concentrates for soft tissue healing and preservation of the alveolar ridge are not univocal. Further research, longitudinal studies, randomized controlled trials, systematic reviews, and meta-analyses are required to evaluate its efficacy and determine whether it is superior to other methods for socket preservation.

Keywords: alveolar ridge preservation, autologous platelet concentrates, platelet-rich plasma

INTRODUCTION

Successful dental implantation requires adequate bone quality and quantity and often necessitates additional procedures, called alveolar ridge preservation (ARP), to be performed before implant placement. The allografts used broadly in the clinical practice showed variable osteoinductive properties, which resulted in clinicians being in search of additional biologically active materials. Examples of such
materials are those, acting as growth factor delivery systems, used to facilitate tissue healing and regeneration in periodontal and intrabony defects (1–7). There is an accumulation of platelets during the cellular phase of healing. They contain α-granules with growth factors (GFs), which play an essential role in bone regeneration.

Recently, autologous platelet concentrates (APCs) have gained increasing attention in the fields of oral surgery and dental implantology due to the abundance of growth factors that they release. Growth factors have an osteoinductive capacity and guide the formation of periodontal tissues (8). These platelet-released factors are: platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), epidermal growth factor (EGF), platelet-derived angiogenesis factor (PDAF), insulin-like growth factor (IGF), platelet factor-4, etc. (9).

Along with GFs, APCs also provide delivery systems for cytokines, chemokines, and other proteins in the wound, which play a vital role in tissue repair mechanisms (10–13) and have chemostatic and mitogenic potential, affecting cell proliferation and differentiation, angiogenesis, and tissue regeneration (12–19).

Some authors have suggested that APCs facilitate and accelerate the process of hard and soft tissue healing (20–23), enhance bone formation around implants (24), and preserve the marginal bone (25,26). Despite these statements, there is still not enough evidence of their beneficial effects during immediate implant placement (26,27) and the reports on their efficacy for hard tissue healing (28–31) and osseointegration (32–35) remain controversial.

The concentration of 1 million platelets/µL in 5 mL plasma was stated to improve hard and soft tissue healing. This effect was not observed when smaller concentrations were used, neither did greater concentrations further accelerate healing (36).

Platelet-rich plasma (PRP) is an increased concentration of autologous platelets in a small volume of plasma after centrifugation. It is an efficient source of GFs (37). Their amount in PRP is stated to be 6–8 times more than in whole blood (38). Platelet-rich plasma is applied as a barrier membrane for RP; in conjunction with bone graft materials for GBR; and treatment of osseous defects (39).

Platelet-rich plasma facilitates graft handling and placement, improves its stability, enhances revascularization, soft tissue healing, and bone formation (36). Platelet-rich plasma also contains inflammatory cells, proteins, growth factors, and adhesion molecules, which facilitate cell recruitment, proliferation, and angiogenesis (40–42).

AIM
This review aims to summarize the current knowledge of the use of PRP for ridge preservation (RP) and evaluate its efficacy. The high study heterogeneity required an in-depth and comprehensive analysis of the methodology, patient recruitment, treatment and examination protocols, and all additional factors, that could have possibly led to misleading results. We identified the research gaps and uncertainties in the existing literature and gave recommendations for further research.

MATERIALS AND METHODS
The present review is based on the scientific electronic database and includes 222 studies on the application of PRP for ARP. The results were compared and summarized to define the success rate and reliability of this technique. The study heterogeneity was carefully analyzed to determine the cause and give guidelines for future assessment.

RESULTS
According to the majority of articles, the history of this technique dates back to 1998 and the work of Marx et al. However, much earlier (in 1970) Matras et al. (43) used fibrin glues for soft tissue healing in rats (44). Rosenthal (45) described the use of platelet-fibrinogen-thrombin mixture for sealing corneal wounds. In the last decades, several authors—Dohan Ehrenfest et al. (46-49), Everts et al. (50, 51), Cieslik-Bielecka et al. (52, 53), have shed light on the features and terminology of platelet concentrates (44).

The term PRP was introduced by Kingsley in 1954 (54) and its regenerative properties were then described by Ross et al. (55). Dohan Ehrenfest et al. had a major contribution to the research of PRP (46, 56–58). The material gained popularity due to its capacity to participate in hemostasis and facilitate tissue healing (12, 59–67).
It turned out that growth factors in platelets enhanced bone formation and therefore PRP was found beneficial for jaw reconstructions (43). Whitman et al. (68) were the first to use autologous platelet gel in maxillofacial surgery with the placement of titanium implants. The authors found it beneficial for the consolidation of the osseous fragments and the adherence of the soft-tissue flap.

In the 1990s the application of PRP was regarded as a promising treatment protocol (12,69,70). It was introduced in dentistry in 1998 when Marx et al. used it in combination with autologous bone for mandibular reconstruction following resection. The authors observed promising results regarding new bone formation (13). Since then numerous studies validated its application in dentoalveolar and reconstructive surgeries, implantology, and periodontal treatment (14,21,22,46,71–90). The combination of PRP with bone grafts has been introduced in implant dentistry as a method that accelerates soft-tissue healing and regeneration (63,65,66).

In 1999 Anitua introduced the first 100% autologous PRP replacing the previously used xenogenic thrombin with calcium ions. The outcomes demonstrated that this combination led to improved epithelialization after 4 days and increased bone maturation after 10–16 weeks compared to the cases with only autogenous bone (70).

It has been suggested that PRP improves soft tissue healing, facilitates reepithelialization and revascularization (39), and has positive effects on bone preservation and augmentation. It enriches bone graft materials with GFs that accelerate bone regeneration; the volume and quality of newly formed tissues are improved (8,91–94).

There is high heterogeneity in the electronic database regarding hard and soft tissue healing, bone density, bone regeneration, and patient morbidity following the application of leukocyte PRP (L-PRP) (21,95–99). On the other hand, there is more consistent evidence regarding the use of pure PRP (P-PRP). Five randomized controlled trials (RCTs) reported better healing and less discomfort when P-PRP had been used (20,22,23,100,101). A recent split-mouth RCT showed higher bone density in the P-PRP sites (102). It was proven by histomorphometric analysis that P-PRP had led to higher bone regeneration compared to spontaneous healing in the third molar region (23). On the contrary, another non-randomized CT found no statistically significant difference regarding bone volume in 1-month and 2-month follow-up (30).

In 2020 Anitua et al. published a review article on the application of PRP in oral and maxillofacial surgery based on the existing literature by that time. They noticed that P-PRP was more beneficial in RP, GBR, and management of postoperative complications. The authors also suggested that the key point for the efficacy of PRP was the method of its preparation (103).

Del Fabbro et al. (104) performed a systematic review and a meta-analysis with CCT and RCT to assess the effect of APCs on RP. They reported that APCs promoted soft-tissue healing, improve bone density and reduce postoperative symptoms.

Annunziata et al. (105) also published a systematic review on the utilization of APCs for RP. Their article included controlled CT with a total of 320 extractions. Autologous platelet concentrates were reported to have improved soft tissue healing and patient morbidity following the extractions. Their potential for bone regeneration, however, was not convincing enough. The authors suggested further methodologically standardized research to clarify the efficacy of APCs.

Several reviews have suggested that the use of PRP was beneficial for bone density and soft tissue regeneration, but the outcomes regarding bone preservation remained unclear (106,107).

Alissa et al. conducted an RCT to evaluate the effect of PRP for hard and soft tissue preservation following tooth removal. They reported that PRP led to improved soft tissue healing, better volumetric preservation, and formation of denser, longer and wider trabeculae. However, the sample size was not big enough to detect a statistically significant enhancement of bone healing (21).

Edrev et al. evaluated the effect of the application of PRP after the removal of impacted teeth and odontogenic cysts. After the surgical intervention, the wounds were filled with either PRP alone or in conjunction with collagen or autologous bone graft. The efficacy of PRP was assessed by the following criteria: pain and swelling (a subjective assessment)
and bone density, evaluated by CBCT (an objective assessment). The authors reported that the best results, regarding bone density, were achieved when PRP was used in conjunction with autogenous bone, followed by the application of PRP, combined with collagen, and then PRP alone. They concluded that the utilization of PRP could improve bone healing successfully (108).

Celio-Mariano (109) demonstrated an improved bone regeneration in postextraction sockets following third mandibular molar removal and PRP application.

In contrast, after radiographic and histomorphometric assessments Aghaloo et al. (110) reported that the use of PRP for cranial defects in rabbits did not improve bone formation.

Yamamoto et al. (111) conducted a study in rats to evaluate the efficacy of PRP for RP. After histological and histomorphometric analyses, the authors reported that PRP led to more collagen deposition than bone formation during the first month. On the 30th day, there was no statistically significant difference between the experimental group and the control one. Platelet-rich plasms did not enhance wound healing and even showed less bone formation during the intermediate periods of healing. Similar results were reported when PRP was used for the treatment of bone defects in dog, goat, and rabbit models (Gerard et al. (112), Mooren et al. (113), Oliveira Filho et al. (114)). Likewise, DeNicolo et al. (115) demonstrated that the utilization of PRP alone or in conjunction with xenografts (bovine bone) did not improve bone regeneration. Plachkova et al. (116) even suggested that many of the positive reports on PRP efficacy did not meet the standards for study quality.

Several studies have suggested that PRP has positive antibacterial properties against Gr(+ oral bacteria, and thus has a beneficial role in soft tissue healing (Menzes et al. (117), Drago et al. (118)).

Garcia-Martinez et al. (119) carried out an in vitro study, which demonstrated that PRP treatment enhanced cell proliferation for 15 days. However, they did not have a long-term effect (for 1 month), which the authors explained by cell exhaustion.

YS Kim et al. evaluated clinically and radiologically whether absorbable gelatin sponge and sponge soaked with PRP could prevent bone resorption and facilitate its regeneration after tooth removal. Eighty patients participated in the study and were divided into three groups—extraction sites, filled with a gelatin sponge (group A), with a sponge and PRP (gr. B), and a control group. In a 12-week follow-up, the authors observed accelerated wound healing and better gingival height preservation in both experimental groups, compared to the control one. There was no statistically significant difference in terms of horizontal width preservation. The radiographic assessment confirmed the clinical results and showed less bone height resorption and higher bone density in the experimental groups. The difference between group A and group B was insignificant (120).

According to Dutta et al., the application of PRP and platelet-rich fibrin (PRF) in postextraction alveoli led to reduced pain and swelling and accelerated wound healing compared to the use of hydroxyapatite at 3rd, 7th, and 14th day (121).

Taschieri et al. (122) compared the clinical and radiographic results of immediate implant placement with and without the application of PRP. They analyzed retrospectively the soft tissue healing, the level of the marginal bone, the survival rates of implants and prosthetic constructions, and the postsurgical complications. The study presented 126 implants with a 5-6-year follow-up after their loading. No significant difference in terms of survival was registered between both groups (97.4% in the test group versus 97.8% in the control group). The difference in the marginal bone was insignificant, too. The soft tissue healing score, however, showed better results in the test group on the 3rd and 7th days postoperatively. The clinical and radiographic assessment did not prove the superiority of PRP utilization during immediate implant placement. The long-term follow-up (4–5 years) showed similar results regarding implant and prosthesis survival, bone preservation, and functional success. The only sufficient difference was that the PRP group demonstrated improved soft tissue healing one week after the surgery.

Schlegel et al. (123) used PRP in animals and reported that it had a beneficial effect on osseointegration of dental implants after 2 and 4 weeks. However, it did not have such effect after 8 weeks.

Zechner et al. (124) performed a histomorphometric evaluation of the osseointegration process
with and without PRP application. The authors observed better results in the PRP group after 3 and 6 weeks, but not after 12 weeks.

Mancuso et al. (125) conducted a study to evaluate the effect of plasma rich in growth factors (PRGF) following tooth removal. The authors reported a decrease in the incidence of alveolar osteitis when PRGF was used. In addition, better hemostasis and faster soft tissue healing were observed in the experimental group. Furthermore, the application of PRGF in postextraction osseous defects was reported to have led to an increased bone width, greater bone density, and improved tissue closure (70).

Mozzati et al. reported satisfactory results after PRGF application in postextraction alveoli in diabetic insulin-dependent patients with reduced pain and improved wound healing in the first 2 weeks (20). Anitua et al. reported that PRGF had beneficial effects regarding bone regeneration (volume and density), soft tissue healing, patient morbidity, the thickness of keratinized tissues, and the amount of newly formed bone (23).

On the contrary, Farina et al. found no difference regarding bone density and mineralization (30).

The combination autogenous bone-PRP has been reported to accelerate osteogenesis and improve the quality of the newly formed bone (13). It has been suggested that PRP led to early consolidation and accelerated mineralization of the bone grafting material for twice the time needed with an autograft alone (15). Furthermore, PRP has been stated to increase the trabecular bone density by about 15–30% (13).

Some studies suggest that PRP promotes bone formation not only when autogenous bone is used, but also with bone grafting materials. It reduces the healing time and the donor site morbidity; accelerates tissue healing and improves the quality of the newly formed bone (126–131).

Orabee et al. conducted a study to evaluate the osteoinductive properties of the combination of calcium sulfate and PRP (CS-PRP). They investigated 52 extraction sites. Ridge preservation with CS-PRP was performed in half of the sockets. The other half served as a control group and were left on spontaneous healing. After 9 months the authors measured the bone density and height in the grafted sites and the control group and concluded that the CS-PRP combination could be used as a successful, cost-effective method for RP (36).

After histological and radiographic observations, Cheah et al. reported that PRP combined with calcium sulfate hemihydrate (PRP-CSH) showed positive results on preservation and augmentation in horizontal and vertical aspects of the ridge, and enhanced new bone formation, as well (132).

In 2012 Kutkut et al. compared the results of PRP with a collagen material (control group) with those with calcium sulfate and PRP. The histomorphometric evaluation demonstrated a significant difference in the amount of newly formed bone (66% versus 38% in the control group) (133).

Yerke et al. reported that the combinations PRP-CSH and PRF-CSH did not show significant improvement regarding soft tissue healing. The authors recommend further research with histologic assessment, longer follow-up periods, and the inclusion of more cases (134).

In split-mouth research, Sammartino et al. performed a histological evaluation of PRP incorporation onto collagen barriers after third molar removal (99). They reported accelerated bone maturation but without an increase in regeneration.

Nisar et al. (135) conducted a comparative study in a split-mouth manner to assess the dimensional changes after RP with a collagen plug and PRP (test side) and spontaneous healing (control). The follow-up examination on the 3rd and 6th months after the surgery showed a statistically significant difference regarding bone height preservation, which was better on the grafted side. In terms of bone width—a statistically significant difference was not observed between the groups. The authors were the first to describe the application of PRP and a collagen plug for RP to combine their regenerative properties. This combination serves as a scaffold for periodontal cells and can be used for tissue engineering (136, 137).

In 2004 Suba et al. published the results of socket grafting in dogs with β-tricalcium phosphate alone and in combination with PRP (test side). They observed high-density new bone in the test side (after 6 weeks). After 12 weeks the difference between the groups was moderate. After 24 weeks the bone density at the test and control sides was equal (138).
Torres et al. reported that PRP could prevent titanium mesh exposure. The test group showed no exposure, while the control one—27%. In addition, there was an increase in bone formation when PRP was used (139).

Tonito T. et al. (140) conducted a clinical trial to evaluate the effect of PRP in conjunction with anorganic bovine bone on alveolar ridge preservation. They filled the postextraction sockets with a mixture of xenograft particles and PRP gel and covered them with a PRP clot membrane. Biopsies were obtained 4 months after the extraction and histomorphometric evaluation was performed. The results showed 26.5% new bone, 45.6% bone marrow spaces, and 24.5% residual graft material. There was no statistically significant difference regarding these ratios compared to previous reports (by Vance) (141). However, the bone regeneration index (2.12 ± 0.1) and structural density index (2.7 ± 0.11) showed a significant difference (1.89 ± 0.10 and 2.3 ± 0.12 reported by Vance, respectively) (140).

Yilmaz et al. (142) utilized PRP and bovine xenograft in deep intrabony defects and observed a significant improvement one year following the procedure.

Mahdi et al. observed the effects of PRP and platelet-poor plasma (PPP) on postextraction alveoli with buccal dehiscence. The authors performed clinical and histomorphometric analyses and found that PRP enhanced bone formation in the first month but did not have a prolonged effect after 2 months. They reported significant horizontal bone resorption in a 1- and 2-month period (143). These results correspond to the findings of Araujo and Lindhe, (144) who reported a significant volumetric alternation in the first two months after the removal of mandibular premolars in dogs, and to the findings of Fickl et al. (145) who found that horizontal bone loss occurred after RP procedures in dogs. Mahdi et al. also observed that all sockets were filled with newly formed bone one month following the extractions. These results corresponded to the findings of Cardaropoli et al. (146) in dog models, who reported that most of the alveoli were filled with new bone after 1 month.

Hatakeyama et al. (147) conducted a study in dogs to determine the efficacy of PPP, PRP, and PRF for ridge augmentation of postextraction alveoli with artificially created buccal dehiscence. The extraction sites were grafted with one of the materials (PPP, PRP, PRF) or were left on spontaneous healing (a control group). The specimens were evaluated histologically and by microcomputed tomography. The PPP group showed the highest results regarding the median area of newly formed bone and the bone width. However, PRP- and PRF-treated sites showed better maturation. By scanning electron microscope, they found that the fibrin network was more condensed in the PRF group. The authors reported that under severe circumstances the GFs from platelets could interfere with bone formation and recommended the application of PPP in cases with buccal dehiscence. After a careful assessment, they concluded that bone regeneration depended on the selected material, the size of the postextraction socket, and the condition of its walls.

Similar to Mahdi et al., Gawai and Sobhana (148) demonstrated an improved osteogenic response in the first month after PRP use but with no long-term effects. Thorwarth et al. (149) also observed only short-term results after PRP use.

Several studies demonstrated that the combination of PRP with allografts for the treatment of intrabony defects demonstrated promising results (150–155).

Shanaman et al. (93) published a case series aiming to evaluate the efficacy of the combination PRP-allograft material for bone regeneration in osseous defects with vertical and horizontal deficiencies. The authors observed 3 cases in which the combination decalcified freeze-dried bone allograft (DFDBA)-PRP was used for regeneration of osseous defects before implant insertion. The graft mixture was easy to handle and facilitated its placement and initial stability. They reported gains in width and height, observed clinically and radiographically, which promoted the following implant placement. The histologic assessment showed newly formed bone and residual graft, surrounded by connective tissue. However, the addition of PRP did not show better results compared to those reported in similar studies where only bone grafts were used. It is difficult to determine the efficacy of PRP when combined with different bone grafts and substitutes. There are numerous clinical variables, which can ultimately change the
treatment results, independent of the application of PRP. The fact that all of the cases required additional grafting subsequently suggested that PRP did not show good osteoinductive capacity. Moreover, the histologic evaluation suggested that its addition did not improve the quality of the new bone. On the contrary, some other studies suggested that PRP accelerated the consolidation and mineralization, thus improving the quality and quantity of the newly formed bone (13,15,70). These reports, however, observed the application of PRP only in conjunction with autologous bone.

The opinions in the literature regarding the regenerative potential of platelets remain controversial (156–159). Even though an increased platelet count (1 to 3 times) shows good regenerative potential (156,160,161), some authors have demonstrated that too high concentrations (3–8 times) do not have the same impact (162–165). It has even been suggested that such concentrations inhibit osteoblasts (157) and the excessive amount of GFs has a cytotoxic effect (158).

Some studies have suggested that PRP accelerates bone formation when applied in conjunction with autogenous bone (13,166,167), xenografts (168), and allografts (169). In contrast, there are reports, suggesting that the combination PRP-autogenous bone (110,113,170) or PRP-xenograft (166) did not show statistically significant improvement in terms of bone regeneration.

Moraschini and Barboza (107) published a review on the effect of APCs on RP. They found high heterogeneity concerning the study design and methodology, surgical approaches, the length of follow-up periods, and the protocol of APC preparation. Most of the studies confirmed that APCs accelerated soft-tissue healing and epithelization (21,70,98,171–174). Regarding hard tissue regeneration and preservation, some studies reported better results in the alveoli treated with APCs, compared to the control groups (21,175), while other studies found no statistically significant difference (30,171).

The reported efficacy of APCs for bone preservation is heterogeneous, which might be due to various reasons. One of them is the different techniques for the measurement of bone changes. For qualitative assessment, the authors use periapical radiographs, histomorphometry, micro-computed tomography, nanoindentation test, cone-beam computer tomography (CBCT) (105). Several authors reported no qualitative difference between sockets treated with APCs and those left on natural healing (21,23,30,175). Two studies (23,176) evaluated by CBCT the horizontal alveolar resorption and the bone filling rate and demonstrated significantly greater bone filling and less bone resorption in the test group.

In line with some previous reviews (29,104,107,177), Annunziata et al. concluded that a quantitative analysis of the efficacy of APCs could not be performed due to the heterogeneity of the existing data (105). These previous studies suggested that APCs might be beneficial in reducing postoperative morbidity (pain, swelling, trismus, inflammation) (104,107,177) and enhancing soft-tissue healing (29,107). They reported only limited evidence for the efficacy of APCs for bone regeneration (29,107,177).

The lack of specific standards for the preparation of APCs sufficiently limits the consistency of the existing data. The authors suggested better standardization of the experimental designs, further research on the correlation between platelet count and concentration of GFs, and their biological behavior and effects (105).

**DISCUSSION**

Platelets play a key role in repair mechanisms. Their alpha granules contain vital GFs that participate in cell migration, differentiation, and proliferation (178–181). Most of the studies demonstrate that platelet products facilitate cell proliferation (specifically those, sensitive to their GFs—osteoblasts (182–187), chondrocytes (188), fibroblasts (189,190), endothelial and periodontal cells (191–193), while others suggest that PRP does not influence the proliferation of fibroblasts and osteoblasts (194,195) and even has a negative effect on macrophage-like cells (196). Platelet viability and activity depend on the centrifugation method (speed and time), the volume of the collected blood, the types of cell separators, anticoagulants, platelet activators, etc. (197,198).

Several systematic reviews and meta-analyses (104,199–203) were performed aiming to summarize the current knowledge. However, the data on the effects of PRP in tissue preservation, healing, and regeneration remains controversial (204). Some authors...
(205–211) have reported that PRP is a suitable material for bone regeneration, while others (175,209,212–217) have disclaimed its efficacy.

It remains controversial whether PRP accelerates and improves bone formation (218). However, its adhesive properties are undisputed (219,220). Recently, PRP utilization in oral surgery has been researched thoroughly and several types of the product have been used in clinical practice (103).

After careful analysis of the above-mentioned studies, we found some possible reasons for the heterogeneity. First of all, there is a lack of standards for the preparation of APCs. We detected some methodological mistakes, such as testing of inactivated suspensions and testing APCs from one species to another without considering an immune response (221,222). Second, we suggest further evaluation when PRP should be used alone and when in conjunction with other grafting materials. Third, there are gaps in the study designs and methods, which could lead to invalid results and a lack of statistical significance. For instance, there are different lengths of follow-up periods, small sample sizes, lack of randomization, etc. Moreover, patient comorbidity should also be considered as there are various health conditions, causing problems with bleeding, wound healing, and tissue regeneration. We also suggest further research to investigate the effects of PRP in medically compromised patients. RCTs carried in a split-mouth manner are also a valuable source of information.

CONCLUSION

Autologous platelet concentrate application aims to accelerate tissue healing and facilitate implant placement.

However, the scientific data about APC efficacy for soft tissue healing and volumetric preservation of the alveolar ridge are not univocal.

The heterogeneity among studies might be due to the different treatment protocols. Some authors used APCs in conjunction with bone substitutes, while others applied APCs alone (21,30). Moreover, the methods of preparation were not the same.

Due to the high heterogeneity in the existing literature and the controversial results among studies, it is difficult to give a strong opinion and specific recommendations on the application of PRP. For more reliable and comparable results, standardization of study methods and treatment protocols is needed.

Longitudinal studies, RCTs, and meta-analyses are required to evaluate its efficacy and validate its positive impact on newly formed tissues. We carefully studied, compared, and analyzed the electronic database and not only summarized the current knowledge but also gave guidelines for further research.

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