REVIEW PAPER

PLATELET-RICH FIBRIN IN COMBINATION WITH MANDIBULAR OR MAXILLARY NON-VASCULARIZED BONE GRAFT: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Autogenous non-vascularized bone graft (NVBG) is the gold standard for treating defects smaller than 6 cm. In the maxillofacial region, NVBG is useful to treat periodontal defects, congenital defects, ridge atrophy, sinus augmentation, etc. The addition of autogenous platelet-rich fibrin (PRF) was reported to improve clinical outcomes. However, no high-quality evidence was ever made regarding this treatment combination.

Objectives: To assess the evidence of adding PRF to autogenous NVBG in the mandibular and maxillary regions.

Material and methods: Literature searches were conducted in PubMed, EMBASE, ProQuest, Scopus, EBSCOhost, and Science Direct to identify randomized controlled trials comparing PRF combined with autogenous NVBG and autogenous NVBG alone. The main outcomes were quantitative bone regeneration measured as height, length, volume, percentage, or other possible quantitative outcomes.

Results: Five studies were included in this systematic review comparing PRF and autogenous NVBG to ANVBG alone, with a total of 130 patients with ridge resorption, periodontitis with furcation involvement, or alveolar cleft. Measurements of outcomes were displayed as gained width, vertical bone changes, and volumetric changes. Two studies presented significant differences in the tested group.

Conclusions: PRF may improve bone regeneration in combination with autogenous NVBG. Future studies need to investigate with a larger population, size of defects, and better outcome measurements.

Key words: autogenous non-vascularized bone graft, bone regeneration, mandibular reconstruction, maxillary reconstruction, platelet-rich fibrin.

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INTRODUCTION

Bone regeneration is one of the essential aspects in restoring stomatognathic functions in defective jawbones [1, 2]. Because of the central location of maxillary and mandibular bones, bony defects can result in changes in physiological processes, such as breathing and mastication, and psycho-social functions, including speech and self-confidence, affected by esthetics of the face. Bone regeneration is required to treat these defects, provide support for dental implants, jaw reconstruction after cystic lesion removal, cleft repair, etc. [3, 4].

Several methods are widely used to treat bony defects, from filling it with bone matrices to grafting bones to induce or help skeletal defects to regenerate [5]. Bone grafts are proven to be the most effective method of restoring bony jaw defects caused by a disease or invasive treatment. Autogenous bone grafts are bone transplantation using bone with a donor site from the same individual, with or without vascularization [6, 7]. Vascularized

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bone-graft are generally used to treat defects bigger than 6 cm because of their perceived benefit of lower resorption rate and higher success rate [8]. However, it requires a more demanding technique than non-vascularized technique [8, 9]. Therefore, the development of methods to improve the regenerative potential of non-vascularized bone graft (NVBG) are currently on the rise [6].

Platelet-rich fibrin is a second-generation platelet concentrate, showing a substantial regenerative property with minimal to no inflammatory reactions upon application in defects [10]. Platelets are cells derived from the bone marrow containing or producing several biomolecules, such as platelet-derived growth factors (PDGF), interleukin 1, platelet-derived endothelial growth factors, basic fibroblast growth factor, transforming growth factors (TGF-1 and TGF-2), and vascular endothelial growth factors. It's currently used in regenerative medicine for soft and hard tissues.

The effect of adjunct PRF in bone grafting is currently being studied to understand its' potential. Case reports have shown significant results of adding platelet-rich fibrin to bone grafting procedures for bone regeneration in sinus augmentation, cleft reconstruction, and fistula management [11, 12]. However, the known effect of addition of PRF to autogenous NVBG is limited. Therefore, the current study aimed to assess the evidence of adding PRF to autogenous NVBG in the mandibular and maxillary regions.

MATERIAL AND METHODS

PROTOCOL AND REGISTRATION

This study was conducted following Cochrane handbook for systematic reviews of interventions guidelines, and reports were made in accordance with preferred reporting project guidelines for systematic review and meta-analysis (PRISMA). This study was registered in PROSPERO under the protocol number of CRD42022333022.

ELIGIBILITY CRITERIA

Studies were screened based on inclusion criteria of PICOS strategy. Patients under 70 years of age with good health or controlled systemic disease treated with non-vascularized autologous bone graft for regenerative or repair purposes were included. The intervention investigated in this study was PRF and non-vascularized bone graft compared with non-vascularized bone grafting without PRF. Quantitative bone regeneration measured as height, length, volume, percentage, or other possible quantitative outcomes was recorded as the primary outcome. Randomized clinical trials with or without blinding were included in this study, with no restriction of publication year.

SEARCH STRATEGY

Literature searches were conducted on six electronic databases, including PubMed, EMBASE, ProQuest, Scopus, EBSCOhost, and Science Direct, without language and publication year restrictions. Keywords used to identify eligible studies were "Bone Graft" OR "Bone Regeneration" AND "Platelet Rich Fibrin" AND "Mandibula" OR "Maxilla". No publication year restriction were applied in this study. Strategies and keyword arrangements were made according to each database's advance search guidelines (Table 1).

DATA EXTRACTION

Data were extracted after a full paper review by both the authors. The extracted data were: (1) first author name and publication year; (2) study type; (3) number of study participants; (4) included disease and treatment; (5) population characteristics, including age and sex ratio; (6) intervention of tested group, PRF preparation, and bone-graft donor site; (7) follow-up period; (8) bony parameters evaluated and outcomes.

RISK OF BIAS ASSESSMENT

Risk of bias was assessed using the revised Cochrane risk of bias tool for randomized controlled trials (RoB v. 2.0) [13]. Domains included for assessment were bias arising from randomization process (selection bias), bias due to deviations from intended interventions (perfor-

TABLE 1. Key words and search strategy for each database, without any restriction

Database	Key words and search strategy
PubMed	(((Non-vascularized Bone Graft) OR (Non-vascularised Bone Graft) OR (Bone regeneration)) AND (Platelet-Rich Fibrin)) AND ((Mandibula) OR (Maxilla))
ProQuest	(Non-vascularized Bone Graft OR Non-vascularised Bone Graft OR Bone Regeneration) AND (Platelet-Rich Fibrin) AND (Maxilla OR Mandibula)
EMBASE	(Non-vascularized Bone Graft OR Non-vascularised Bone Graft OR Bone Regeneration) AND (Platelet-Rich Fibrin) AND (Maxilla OR Mandibula)
Scopus	(Non-vascularized Bone Graft OR Non-vascularised Bone Graft OR Bone Regeneration) AND (Platelet-Rich Fibrin) AND (Maxilla OR Mandibula)
EBSCOhost	(Non-vascularized Bone Graft OR Non-vascularised Bone Graft OR Bone Regeneration) AND (Platelet-Rich Fibrin) AND (Maxilla OR Mandibula)
Science Direct	(Non-vascularized Bone Graft OR Non-vascularised Bone Graft OR Bone Regeneration) AND (Platelet-Rich Fibrin) AND (Maxilla OR Mandibula)

TABLE 2. Excluded studies with reasons

Author, year [Ref.]	Reason for exclusion
Agarwal, 2019 [21]	Wrong intervention (PRF alone) and comparison (DFDBA)
Tatullo, 2012 [22]	Wrong intervention and comparison (xenograft)
Hartlev, 2021 [23]	Wrong measured outcome (no bony regeneration outcome)
Trimmel, 2021 [24]	Wrong intervention (allograft) and comparison (healing time)
Rosenfeld, 2020 [25]	Wrong study type (case study)
Choukroun, 2006 [18]	Wrong outcome measure (histologic)
Thakkar, 2016 [26]	Wrong intervention (PRF + DFDBA) and comparison (DFDBA)
Agarwal, 2016 [27]	Wrong intervention (PRF + DFDBA) and comparison (DFDBA)
Chadwick, 2016 [28]	Wrong intervention (PRF) and comparison (DFDBA)
Abdel-Rahman, 2021 [29]	Wrong study type (case letter)
Attar, 2017 [30]	Wrong intervention (allogeneic and autogenous bone combination + PRF)
Dayashankara Rao, 2021 [31]	Wrong outcome measure (bone loss)
Tabrizi, 2020 [32]	Wrong outcome measure (stability)
Wang, 2021 [33]	Wrong outcome measure (implant survival)
Mendez Caramês, 2022 [34]	Wrong intervention (xenograft + PRF)

mance bias), bias due to missing outcome data (attrition bias), bias in measurements of the outcome (detection bias), and bias in selection of the reported result (reporting bias). Two authors (YU and LDS) assessed the included studies independently; then, each study was rated as low-risk, with some concerns or high-risk of bias based on the guidelines. If all domains were rated as low-risk, the study's overall assessment was rated as low-risk. Moreover, studies with at least one domain rated with some concerns of bias would be rated to have some concerns of bias, and studies with at least one domain with a high-risk of bias would be rated as high-risk of bias.

RESULTS

STUDY SELECTION

A total of 1,194 records were identified from all three electronic databases. Then, 312 duplicates were removed, and 770 articles were excluded based on the title and abstract screening. After screening 112 records, 20 full-text articles were retrieved and assessed for eligibility, of which fifteen articles did not meet the eligibility criteria, and the reasons are presented in Table 2. Five studies were included for qualitative analysis.

Study selection process is presented as PRISMA diagram flow in Figure 1.

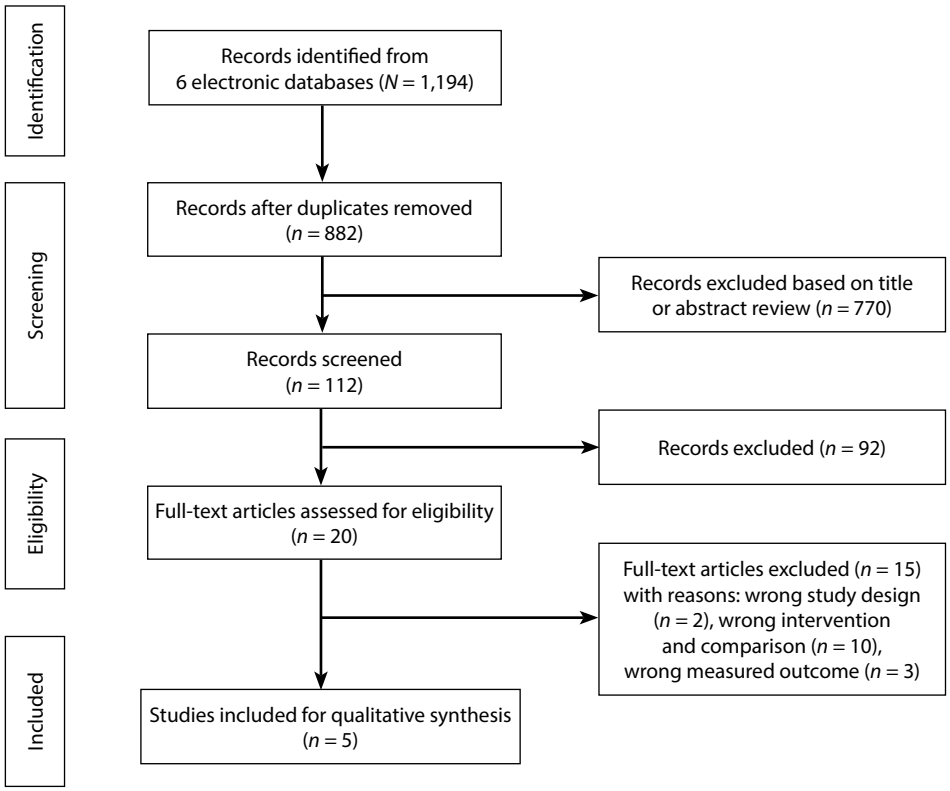

FIGURE 1. Prisma flow diagram. Records were screened and assessed using PRISMA flow. 1,194 records were identified from six databases. Then, duplicates were removed and 112 records were screened based on title and abstract review. Finally, 20 articles were assessed for eligibility, and 5 were included for qualitative analysis

STUDY CHARACTERISTICS

Five randomized controlled trials were included, and their characteristics are presented in Table 3. All studies included patients with bony defects in the maxillary and mandibular regions, diagnosed as anterior maxilla horizontal defect, alveolar process atrophy, periodontitis furcation defect, and unilateral alveolar cleft. All trials used autogenous blood as the source of PRF, and preparations varied across studies with bone grafts harvested from different donor sites. Follow-up periods were 4 months in one research, and 6 months in the rest of the research. Outcomes were measured clinically and radiographically in all studies.

RISK OF BIAS ASSESSMENT

All studies were assessed as having low-risk or some concerns of bias. The overall risk of bias was low in 50% of the studies, and some concerns in the other 50% (Figure 2). Randomization method was not clearly in one paper, and the others used either block randomization, computer-generated, or asking the participant to take an envelope. Interventions were clearly stated in all studies, but one did not display the exact procedure used to prepare PRF. All studies reported almost all their participants' data, and the risk for measurement of outcome and selective reporting was low in four studies.

PREPARATION AND APPLICATION OF PLATELET-RICH FIBRIN

Platelet-rich fibrin preparation varied among all four studies. Mousa *et al.* [35] used the proposed procedure of 3,500 rpm for 12-15 minutes. Hartlev *et al.* [36] prepared autogenous samples by centrifugation at 1,300 rpm for 14 minutes (PRF made using this method is called 'advanced platelet-rich fibrin' (A-PRF)). The other two studies by Serroni *et al.* [37] and Shawky *et al.* [38] used PRF prepared at 3,000 rpm for 10 minutes, resulting in a leucocyte- and platelet-rich fibrin (L-PRF) concentrate. L-PRF was also applied by Thanasut *et al.* [39] in their study. All studies used PRF as membranes, either by sealing the surgical site or covering the bone graft. However, Shawky *et al.* [38] used PRF as fillings and harvested cancellous bone.

TABLE 3. Included studies' characteristics and outcomes

Author, year [Ref.]	Study type	No. of study participants	Disease and treatment	Population characteristics	Intervention (test)	Follow-up	Bony parameters evaluated	Outcomes (test vs. control)
Moussa, 2016 [35]	Randomized controlled trial	12 patients	Anterior maxilla horizontal alveolar defect and augmentation	Test: Age = 27.0 ± 15.0 years Sex (F : M) = 4 : 3 Control: Age = 25.7 ± 15.2 years Sex (F : M) = 4 : 3	PRF preparation: autogenous, 3,500 rpm 12-15 minutes; Bone graft source: palatal anterior region	4 months	Clinical and CBCT bucco-palatal width change	Gained width (mm) 2.7 ± 0.9 vs. 2.2 ± 0.8 ($p = 0.138$)
Hartlev, 2019 [36]	Randomized controlled trial	27 patients	Alveolar process atrophy and lateral ridge augmentation	Test: Age = 47.9 ± 12.4 years Sex (F : M) = 6 : 8 Control: Age = 52.3 ± 13.6 years Sex (F : M) = 6 : 7	PRF preparation: autogenous, 1,300 rpm 14 minutes Bone graft source: lateral mandible	6 months	CBCT volumetric change	Bone volume (mm^3): 426 ± 144 vs. 465 ± 232 ($p = 0.61$)
Serroni, 2021 [37]	Randomized controlled trial	54 patients	Periodontitis furcation defect, open flap debridement, and autogenous bone graft	Age = 54 ± 14 years Test: Sex (F : M) = 1 : 1 Control: Sex (F : M) = 1 : 1	PRF preparation: autogenous, 3,000 rpm 10 minutes Bone graft source: close to experimental teeth	6 months	Periapical radiographic vertical bone level change	Vertical bone level change (mm): 1.758 ± 0.254 vs. 1.724 ± 0.257 ($p < 0.05$)
Shawky, 2016 [38]	Randomized controlled trial	24 patients	Unilateral alveolar cleft and reconstruction	Test: Age = 10.92 ± 1.56 years Sex (F : M) = 1 : 3 Control: Age = 10.92 ± 1.88 years Sex (F : M) = 5 : 4	PRF preparation: autogenous, 3,000 rpm 10 minutes Bone graft source: anterior iliac crest	6 months	Newly formed bone	Newly formed bone: 82.6% ± 3.9% vs. 68.38% ± 6.67% ($p < 0.05$)
Thanasut, 2021 [39]	Randomized controlled trial	13 patients	Alveolar cleft and reconstruction	Test: Age = 9.8 ± 1.6 years Sex (F : M) = all males Control: Age = 10.3 ± 1.9 years Sex (F : M) = 4 : 3	PRF preparation: autogenous, 3,000 rpm 10 minutes Bone graft source: iliac crest	6 months	Regenerated bone volume	Regenerated bone volume: 64.9% ± 19.6% and 67.0% ± 8.7% ($p > 0.05$)

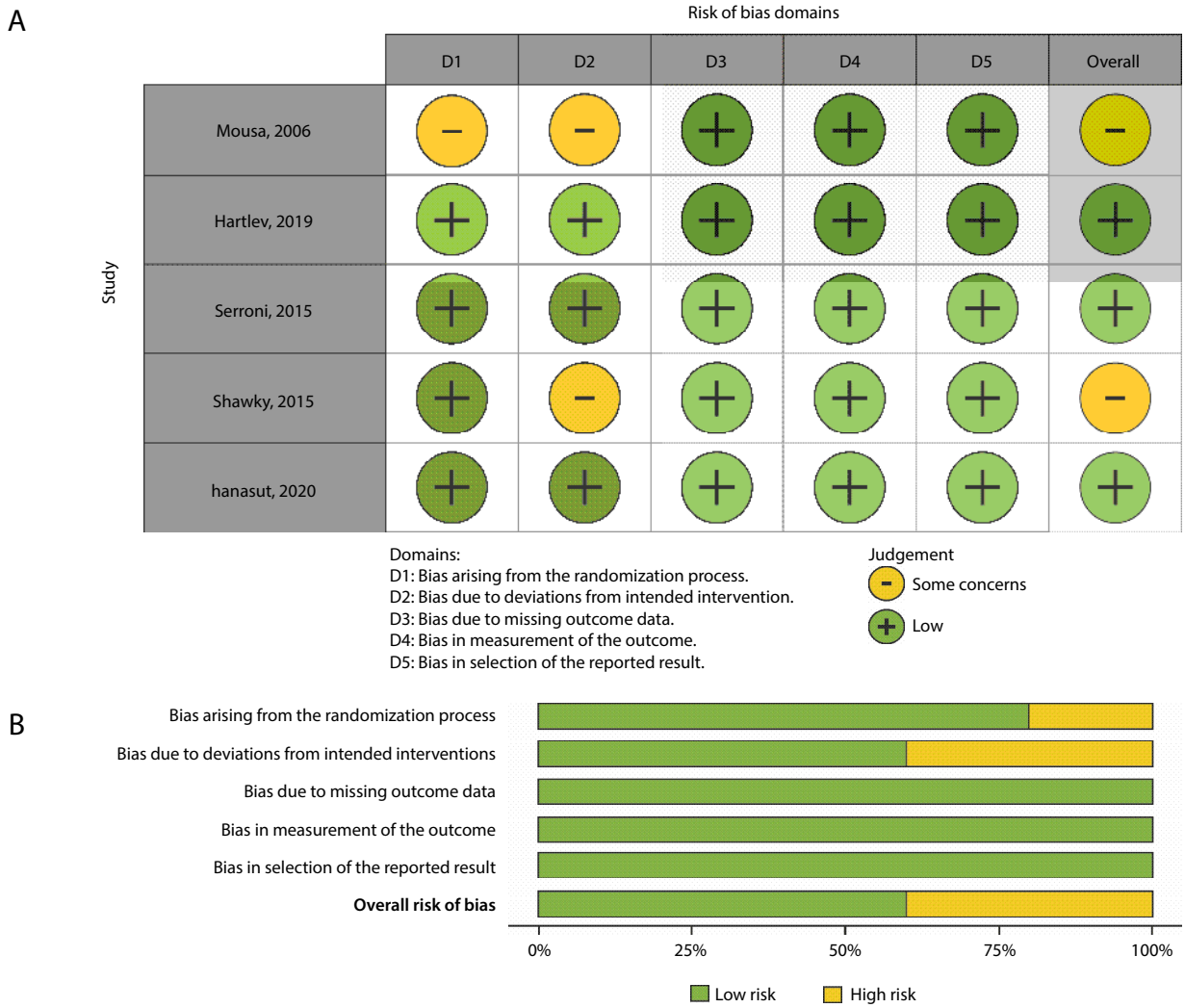

FIGURE 2. Risk of bias plot. Risk of bias of included studies was assessed using revised Cochrane risk of bias tool for randomized controlled trials (RoB v. 2.0). Two studies showed some concerns in the overall results, while the other three included studies presented low-risk of bias

BONE GRAFT DONOR SITE

Four donor sites were recorded in the studies, including the anterior palatal region, lateral mandible, around experimental teeth, and anterior iliac crest.

BONE REGENERATION

The parameter of bone regeneration was not uniform in all included studies. Clinical and radiographical evaluations were mainly used to assess the regeneration occurring. Moussa *et al.* [35] evaluated bone gain buccopalatally using CBCT 4 months after grafting, with a higher gain than control (2.7 ± 0.9 mm vs. 2.2 ± 0.8 mm), but no statistical significance was observed (p = 0.138). The amount of augmented bone volume was observed using CBCT by Hartlev *et al.* [36], with lower volume in the tested group (426 ± 144 mm^3 vs. 465 ± 232 mm^3), but not statistically significant (p = 0.61). Serroni *et al.* [37] reported bone regeneration by measuring the vertical height of the treated area based on the periapical radiograph. The tested group showed a slightly greater improvement in the vertical bone level (1.758 ± 0.254 mm vs. 1.724 ± 0.257 mm), and was statistically significant ($p < 0.05$). Shawky *et al.* [38] measured CBCT volumetric change in patients. They displayed the data as newly formed bone with a higher percentage observed in the tested group (82.6% ± 3.9% vs. 68.38% ± 6.67%), which was statistically significant ($p < 0.05$). Lastly, Thanasut *et al.* [39] showed volumetric change percentage with median value for the tested and control groups of 64.9% ± 19.6% and 67.0% ± 8.7%, without statistical significance ($p > 0.05$).

DISCUSSION

Autogenous NVBG is currently the gold standard for grafting defects in the maxilla and mandible regions, with adequate regenerative properties and success

rate [9, 14]. Nonetheless, a commonly accepted model is to use a vascularized bone graft (VBG) in larger defects (> 6 cm) to improve outcomes in the transplanted site [8]. Although evidence suggests an increased risk of donor site morbidity, additional hospital stay, and additional procedure length due to the need of using more demanding techniques, VBG achieved better clinical success rates [8, 14, 15]. This is mainly due to nutrition provided by better vascularization of the bone. However, the compared regeneration level between NVBG and VBG varies, with some authors observing a higher effect in VBG compared with NVBG [8].

The use of PRF in clinical settings is relatively novel. This formulation of platelet concentrate contains growth factors that theoretically can promote growth and regenerative processes, and have been proven by several trials to be clinically effective [16, 17]. PRF also have angiogenesis properties, which with the addition of bone graft, help the new bone to form better vascularization [18].

The current study investigated the effect of adding PRF to autogenous NVBG, and whether it promotes bone regeneration and formation effectively. The study results were mixed, and the measurement of outcomes also varied.

Ridge augmentation using PRF and autogenous NVBG combination for implant placement has no significant improvement compared with control groups. Moussa *et al.* [35] and Hartlev *et al.* [36] added PRF to bone grafting procedure for ridge augmentation. The first study examined linear changes, and the second one compared volumetric changes. However, both the studies showed slight and statistically insignificant differences between the tested and control groups. Moreover, both the studies also reviewed bone loss after the procedure, in which the tested group showed higher retention in the study by Moussa *et al.* [35] and no overall difference in volumetric change.

Residual ridge resorption and atrophy are caused by several local and systemic factors, including those, which affect jaw posteriorly or anteriorly, the presence of systemic diseases, and patients' age [19]. Moussa *et al.* [35] studied the intervention in the anterior maxilla, while Hartlev *et al.* [36] included all segments of the maxilla. However, both the studies demonstrated contradictory results. The first one showed lower bone resorption in the tested group (anterior maxilla). The second paper revealed higher bone resorption in any group of anterior regions than the posterior part. Nevertheless, these differences could result from different PRF preparation between these two studies, and different methods of measurement of outcomes.

In Serroni *et al.* [37] study, periodontal furcation defects were treated with autogenous bone graft and L-PRF. Bone grafting with no membrane showed a substantial improvement in periodontitis with furcation involvement. The addition of L-PRF and autogenous NVBG showed greater bone regeneration compared with the control group, measured as vertical bone level change, with statistical significance ($p < 0.05$). Improvements were also observed in other clinical parameters of periodontal health. This study suggests a significant and clinically relevant improvement in periodontitis with furcation involvement treated with basic open flap debridement, autogenous bone graft, and PRF.

Shawky *et al.* [38] demonstrated a significant difference in the tested group compared with the control group in alveolar cleft patients. Newly formed bones were measured as 82.6% ± 3.9% in PRF and autogenous NVBG-treated group, and as 68.38% ± 6.67% in the control group (NVBG only), with statistically significant difference ($p < 0.05$). The changes were observed using a CT scan, and data were displayed as volumetric changes in percentage. On the other hand, no difference in the same population group were observed in a study by Thanasut *et al.* [39], with results between the tested and control groups as 64.9% ± 19.6% and 67.0% ± 8.7% ($p > 0.05$).

However, all of the pathologies presented are different in nature, with different pathogenesis and prognosis. Ridge resorptions are atrophy in the edentulous area and are mainly a result of functional loss after a tooth loss [19, 20]. Therefore, removing the etiology of the disease by placing implants or dentures needs to be done to stop the phenomenon. Even after restorations with a dental prosthesis, bone resorption does not stop altogether, but is only reduced in rate. Periodontitis is, on the other hand, an inflammatory, plaque-induced disease, and its' progressivity can be reduced by maintenance practices, with a relatively good prognosis following a regenerative treatment [17]. Cleft reconstruction, which showed substantial improvement after regeneration, does not have prolonged inflammation or ongoing disease process, providing better prognosis and outcomes.

In this study, the authors found that research on adding PRF to autogenous NVBG was still minimal. Most excluded studies either used only PRF as the tested treatment, combined PRF with allogenic bone graft (harvested from other people), or used xenografts as the bone graft material. These studies, however, provide a rationale that clinicians must treat patients minimally invasive. Harvesting bone and blood altogether for jaw reconstruction or regeneration is arguably more invasive than using other sources for bone filling material, and research to find a substitute is also essential.

Variable methods to measure outcomes need to be addressed in future trials. CBCT is relatively better and provides a clear volumetric parameters of the treated site.

All studies included in the present review have a relatively small defect (< 6 cm) with various pathology, with the study conducted by Shawky et al. having the largest defect. No post-resection reconstruction, patients treated with enucleation, or palatal cleft were recorded in this review, and no RCT has ever been conducted for those treatments. The author of this review argues that

the bone regeneration effect of adding PRF and autogenous NVBG needs to be studied in populations with larger defects, justifying the more invasive nature of this combination. Different measurement of bone regeneration also needs to be developed in the near future to provide better evidence.

CONCLUSIONS

PRF provides some effects on autogenous NVBG in the mandibular and maxillary regions. However, due to minimal evidence retrieved from the available studies, further clinical trials need to be conducted. The issues to be addressed in next studies include larger sample size, larger defects (> 6 cm), and measurements of outcomes.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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