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

Yudy Ardilla Utomo, Lilies Dwi Sulistyani

Department of Oral Maxillofacial Surgery, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia

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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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 “Mandible” 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 (perform-
TABLE 2. Excluded studies with reasons

<table>
<thead>
<tr>
<th>Author, year [Ref.]</th>
<th>Reason for exclusion</th>
</tr>
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<tbody>
<tr>
<td>Agarwal, 2019 [21]</td>
<td>Wrong intervention (PRF alone) and comparison (DFDBA)</td>
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<tr>
<td>Tatullo, 2012 [22]</td>
<td>Wrong intervention and comparison (xenograft)</td>
</tr>
<tr>
<td>Hartlev, 2021 [23]</td>
<td>Wrong measured outcome (no bony regeneration outcome)</td>
</tr>
<tr>
<td>Trimmel, 2021 [24]</td>
<td>Wrong intervention (allograft) and comparison (healing time)</td>
</tr>
<tr>
<td>Rosenfeld, 2020 [25]</td>
<td>Wrong study type (case study)</td>
</tr>
<tr>
<td>Choukroun, 2006 [18]</td>
<td>Wrong outcome measure (histologic)</td>
</tr>
<tr>
<td>Thakkar, 2016 [26]</td>
<td>Wrong intervention (PRF + DFDBA) and comparison (DFDBA)</td>
</tr>
<tr>
<td>Agarwal, 2016 [27]</td>
<td>Wrong intervention (PRF + DFDBA) and comparison (DFDBA)</td>
</tr>
<tr>
<td>Chadwick, 2016 [28]</td>
<td>Wrong intervention (PRF) and comparison (DFDBA)</td>
</tr>
<tr>
<td>Abdel-Rahman, 2021 [29]</td>
<td>Wrong study type (case letter)</td>
</tr>
<tr>
<td>Dayashankara Rao, 2021 [31]</td>
<td>Wrong outcome measure (bone loss)</td>
</tr>
<tr>
<td>Tabrizi, 2020 [32]</td>
<td>Wrong outcome measure (stability)</td>
</tr>
<tr>
<td>Wang, 2021 [33]</td>
<td>Wrong outcome measure (implant survival)</td>
</tr>
<tr>
<td>Mendez Caramés, 2022 [34]</td>
<td>Wrong intervention (xenograft + PRF)</td>
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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.
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Preparation and application of platelet-rich fibrin

Preparation of PRF varied among all four studies. Moussa et al. [35] used the proposed procedure of 3,500 rpm for 12.15 minutes. Hartle et al. [36] prepared PRF at 3,000 rpm for 10 minutes. Serroni et al. [37] and Shawky et al. [38] used PRF as a filling in all studies. However, the surgical site or covering the bone graft was not described in detail in all studies. The overall risk of bias was low in 50% of the studies, and the other 50% revealed some concerns in the other 50% (Figure 2). The overall risk of bias was low in 50% of the studies, and the other 50% revealed some concerns in the other 50% (Figure 2).

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 the other 50% revealed some concerns in the other 50% (Figure 2).

TABLE 3. Included studies’ characteristics and outcomes

<table>
<thead>
<tr>
<th>Author, year [Ref.]</th>
<th>Study type</th>
<th>No. of study participants</th>
<th>Disease and treatment</th>
<th>Population characteristics</th>
<th>Intervention (test)</th>
<th>Follow-up</th>
<th>Bony parameters evaluated</th>
<th>Outcomes (test vs. control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moussa, 2016 [35]</td>
<td>Randomized controlled trial</td>
<td>12 patients</td>
<td>Anterior maxilla horizontal alveolar defect and augmentation</td>
<td>Test: Age = 27.0 ± 15.0 years Sex (F : M) = 4 : 3 Control: Age = 25.7 ± 15.0 years Sex (F : M) = 4 : 3</td>
<td>PRF preparation: autogenous, 3,500 rpm 12-15 minutes; Bone graft source: palatal anterior region</td>
<td>4 months</td>
<td>Clinical and CBCT</td>
<td>Gained width (mm) 2.7 ± 0.9 vs. 2.2 ± 0.8 (p = 0.138)</td>
</tr>
<tr>
<td>Hartle, 2019 [36]</td>
<td>Randomized controlled trial</td>
<td>27 patients</td>
<td>Alveolar process atrophy and lateral ridge augmentation</td>
<td>Test: Age = 42.9 ± 12.4 years Sex (F : M) = 6 : 8 Control: Age = 52.3 ± 13.6 years Sex (F : M) = 6 : 7</td>
<td>PRF preparation: autogenous, 1,300 rpm 14 minutes; Bone graft source: lateral mandible</td>
<td>6 months</td>
<td>CBCT volumetric change</td>
<td>Bone volume (mm³): 426 ± 144 vs. 465 ± 232 (p = 0.61)</td>
</tr>
<tr>
<td>Serroni, 2021 [37]</td>
<td>Randomized controlled trial</td>
<td>54 patients</td>
<td>Periodontitis furcation defect, open flap debridement, and autogenous bone graft</td>
<td>Age = 54 ± 14 years Test: Sex (F : M) = 1 : 1 Control: Sex (F : M) = 1 : 1</td>
<td>PRF preparation: autogenous, 3,000 rpm 10 minutes; Bone graft source: close to experimental teeth</td>
<td>6 months</td>
<td>Periapical radiographic vertical bone level change</td>
<td>Vertical bone level change (mm): 1.738 ± 0.254 vs. 1.724 ± 0.257 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Shawky, 2016 [38]</td>
<td>Randomized controlled trial</td>
<td>24 patients</td>
<td>Unilateral alveolar cleft and reconstruction</td>
<td>Test: Age = 10.92 ± 1.56 years Sex (F : M) = 1 : 3 Control: Age = 10.92 ± 1.88 years Sex (F : M) = 5 : 4</td>
<td>PRF preparation: autogenous, 3,000 rpm 10 minutes; Bone graft source: anterior iliac crest</td>
<td>6 months</td>
<td>Newly formed bone</td>
<td>Newly formed bone: 82.6% ± 3.9% vs. 68.38% ± 6.67% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Thanasut, 2021 [39]</td>
<td>Randomized controlled trial</td>
<td>13 patients</td>
<td>Alveolar cleft and reconstruction</td>
<td>Test: Age = 9.8 ± 1.6 years Sex (F : M) = all males Control: Age = 10.3 ± 1.9 years Sex (F : M) = 4 : 3</td>
<td>PRF preparation: autogenous, 3,000 rpm 10 minutes; Bone graft source: iliac crest</td>
<td>6 months</td>
<td>Regenerated bone volume</td>
<td>Regenerated bone volume: 64.9% ± 19.6% and 67.0% ± 8.7% (p &lt; 0.05)</td>
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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.
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Involvement. The addition of L-PRF and autogenous substantial improvement in periodontitis with furcation involvement treated with basic open flap debridement, autogenous bone graft, and PRF.

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 $82.6\% \pm 3.9\%$ in PRF and autogenous NVBG-treated group, and as $68.38\% \pm 6.67\%$ 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 $64.9\% \pm 19.6\%$ and $67.0\% \pm 8.7\%$ ($p > 0.05$).

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.

References


