

## Efficacy of Platelet-rich Plasma on Promoting Bone Healing in Maxillofacial Defects: A Systematic Review

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### Abstract

Platelet-rich plasma (PRP) has been significantly important in oral and maxillofacial surgery as it is rich in growth factors and can promote bone healing. However, its clinical efficacy remains controversial as some studies reported no significant improvement in new bone formation after treatment with PRP. The current study aimed to evaluate scientific evidence about the efficacy of PRP incorporation on enhancing bone healing in maxillofacial defects.

English scientific articles were retrieved from ScienceDirect and MEDLINE (via PubMed). Keywords including "platelet-rich plasma," "bone healing," and "maxillofacial" were obtained from Medical Subject Headings. Only studies comparing a group who underwent surgery using bone graft and who received PRP and a control group without PRP were included in the analysis. This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.

In total, 19 articles were retrieved. Of 19 articles, only 9 reported significant improvement in bone regeneration after treatment with PRP for maxillofacial defects.

Although PRP is popular, previous studies in the literature have not confirmed the efficacy of PRP on enhancing bone regeneration in the maxillofacial region. Therefore, further randomized controlled studies should be conducted to validate the effects of PRP.

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### Introduction

Reconstruction of large bony defects in the maxillofacial region remains a major surgical challenge.<sup>1</sup> The use of surgical reconstruction with artificial alternatives for defective maxillofacial hard and soft tissues has been recorded throughout history. In previous decades, the number of studies about tissue engineering and regenerative medicine using biomaterials and stem cells has been increasing. To regenerate new tissue formation, different strategies have been used in clinical studies, and some in animal and *in vitro* experiments.<sup>2,3</sup>

In oral and maxillofacial surgery, autologous bone grafts remain the gold standard for bone reconstruction.<sup>4</sup> To enhance the regenerative process of new tissue regeneration, autologous growth factors, including platelet-rich plasma (PRP), have been utilized. PRP is an autologous platelet concentration with a high growth factor content. The local application of PRP in bone augmentation surgery aims to release growth factors, including bone morphogenetic proteins (BMP), platelet-derived growth factor, transforming growth factor-h, and insulin growth factor-I, which mediate osteogenesis processes.<sup>6</sup> These growth factors, particularly BMP, induce mesenchymal stem cell differentiation into osteoblasts, referred to as osteoinduction, which leads to the production of new bone tissue.<sup>7</sup> Therefore, PRP is an important adjunct for promoting faster healing after different oral and maxillofacial surgery procedures, such as sinus lift operation, alveolar ridge augmentation, and reconstruction of bony defects caused by trauma, cleft defects,

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infections, cysts, and neoplasms.<sup>8</sup>

Several studies reported that PRP incorporation to various bone scaffolds and autogenous bone grafts can successfully induce bone healing in critical-sized maxillofacial defects.<sup>5,9,10</sup> Cerruti et al. and Plachova et al. as cited in Messora et al. mentioned that the regenerative capacity of PRP and its benefits in bone grafts remains controversial.<sup>11</sup> Therefore, this study aimed to evaluate studies that assessed the efficacy of PRP on enhancing bone healing in maxillofacial defects.

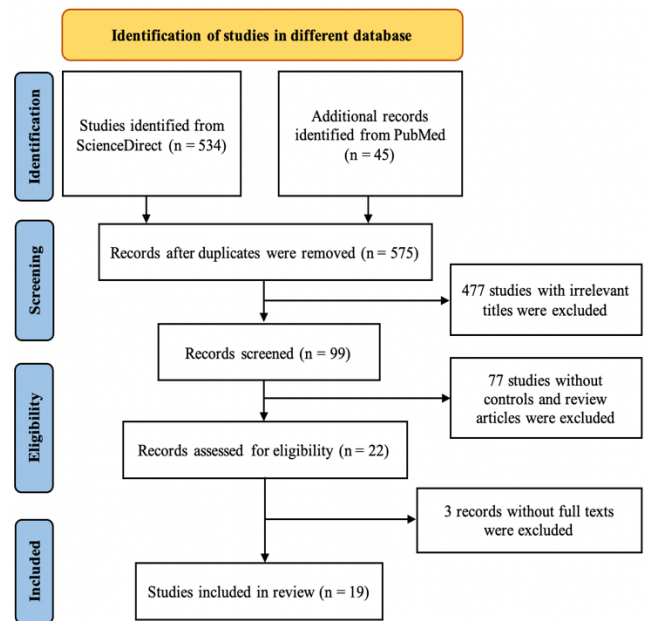
### Materials and methods

A systematic database search was performed on July 4–10, 2021, by one author. The keywords were entered to electronic databases including MEDLINE via PubMed and ScienceDirect, and articles published between 2001 and 2021 were searched. The keywords and string used were “platelet-rich plasma” AND “bone healing” AND “maxillofacial.” Only articles written in the English language were included in the analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart was used. Studies unrelated to PRP for bone regeneration in the oral and maxillofacial region, those without a control group, and those without full texts and review articles were excluded.

### Results

The search strategy was established based on the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines, as shown in Figure 1. The initial search used the following keywords: “platelet-rich plasma” AND “bone healing” AND “maxillofacial,” and it was performed between 2001 and 2021. In total, 579 articles were searched. Of 579 articles, 2 were duplicates; hence, they were excluded. Moreover, 477 studies with irrelevant titles were not included. The remaining 99 articles were assessed, and only 22 articles were found to meet the inclusion criteria. However, only 19 full-text articles could be downloaded.

In total, 9 of 19 articles showed that PRP is effective in increasing bone density after bone grafting procedures at the maxillofacial region.<sup>5,8,11–17</sup> Meanwhile, the other 10 articles reported no significant differences (Table 1).<sup>18–27</sup>



**Figure 1.** Preferred Reporting Items for Systematic Review and Meta-Analysis flow chart diagram for the 19 articles included in this review.

### Discussion

Healing via scar tissue formation rather than native bone regeneration after injury has been commonly observed.<sup>9</sup> To prevent this phenomenon, the use of different regenerative approaches has been recommended. The application of both natural and synthetic biomaterials as bone graft materials have been suggested.<sup>2,28</sup> As an adjunct for improving tissue regeneration, growth factors, such as the well-known BMPs, in oral and maxillofacial surgery have been comprehensively assessed. Although BMP is a promising strategy, their use in clinical settings is extremely limited due to its high cost and low throughput.<sup>29</sup> Therefore, autologous materials remain the mainstay of bone tissue regeneration attempts.<sup>30</sup> PRP, an autologous platelet concentrate, promotes bone healing after oral and maxillofacial surgery arena.<sup>14,31,32</sup>

PRP is the term used to describe autologous platelets created via centrifugation and suspended in autologous plasma at a concentration greater than that normally found in the peripheral blood with approximately 1 million platelets/mL.<sup>33</sup> Platelets play important roles not only on hemostatic physiology but also on wound healing due to its high growth factor content. Interestingly, the addition of a platelet concentrate to surgical wound could enhance the

body's natural wound healing processes.<sup>34</sup>

Osseointegration and remodeling are biological processes in which the bone graft material is resorbed by osteoclasts and replaced by new vascularized osteoids.<sup>8,35,36</sup> Growth factors released by platelets stimulate osteoblast differentiation and function as well as the division and differentiation of osteoclast precursor cells.<sup>37</sup> The stimulation of osteoclasts can facilitate the faster removal of bone graft materials and their substitution by newly formed bones. *In vitro* and *in vivo* studies have shown that PRP may modulate the expression of some bone matrix proteins (e.g., osteopontin and osteocalcin), which are directly related to the maturation of osteoblasts and subsequent mineralization.<sup>38,39</sup>

Vascularization allows the migration of nutrients and gases for cell survival and growth. Hence, it is another essential strategy for a successful bone regeneration.<sup>40</sup> In the early stage of healing, the vascularization of granulation tissues may lead to a better wound healing in the PRP-treated group than in the control group. Therefore, the risk of excavation in the bone defect area is reduced.<sup>41</sup> Platelet-derived growth factor released by PRP could stimulate early inflammatory reactions as well as the migration and proliferation of fibroblasts, thereby inducing the formation of fibrin, which leads to wound healing.<sup>42</sup>

Several studies about PRP incorporation to bone graft materials, such as alveolar bone augmentation and sinus lift, have shown that the PRP-treated groups had a better bone regeneration than the control group.<sup>34,35</sup> However, the results have been inconsistent (Table 1). Yamada et al. 2004 revealed that particulate cancellous bone and marrow combined with PRP were highly effective for mandibular reconstruction.<sup>43</sup>

Roldan et al. 2004 used a rat model to evaluate the effect of PRP and BMP on

autografts and allografts in critical-size mandibular defects. However, this study did not show improved bone formation after treatment with PRP.<sup>18</sup>

PRP incorporation to bone grafts did not significantly enhance bone healing as evidenced by the absence of early vascular ingrowth and osteoid deposition on methylene blue staining and basic fuchsin color assays.<sup>44</sup> This finding could also be explained by the fact that the PRP preparation procedures varied, thereby affecting bone healing success. Further, PRP and the release of growth factors could have occurred at the subperiosteum, which affected the outcomes in the experimental and control sites.<sup>45</sup> In clinical trials, patients admitted for surgery may have underlying systemic conditions, such as osteoporosis and diabetes mellitus. As autologous bone grafts must be harvested, patients who undergo this procedure are at risk of poor bone quality. This can then compromise the bone quality at the augmented site and skew the comparison between the PRP-treated and control groups.<sup>42</sup>

## Conclusions

The results of experimental and clinical studies about the efficacy of PRP on improving bone healing in maxillofacial defects were inconsistent. Therefore, future randomized controlled trials should be conducted to validate whether PRP is effective on enhancing bone tissue regeneration in maxillofacial defects.

## Declaration of Interest

The authors declare that is no conflict of interest.

No.	Authors	Year	Type of Sample	Number Of Patients	Evaluation of the Efficacy of Platelet-rich Plasma (PRP) on Bone Healing
1	Mall BB, Singh P, Sharma N, Reddy P <sup>5</sup>	2017	40 patients underwent surgical enucleation of the cystic lesion or resection of the impacted mandibular teeth. The surgical defect worsened with PRP and hydroxyapatite	40 patients	The PRP treatment had a high success rate and extremely low rate of complications, such as pain, inflammation, and infection. Ultrasonographic evaluation was found to be advantageous for evaluating bone formation and mineralization. Color Doppler evaluation could predict the vascularization in the affected area, which is indicative of wound healing.
2	Roldan JC, Jepsen S, Miller J, Freitag S, Rueger DC, Terheyden H <sup>18</sup>	2003	Mandible of Wistar rats	28 Wistar rats	Histomorphometry evaluation indicated that the addition of PRP did not significantly enhance bone formation in the inorganic bovine bone and the autologous bone grafts.
3	Choi BH, Choi CJ, Im JY, Huh JJ, Suh JJ, Lee SH <sup>19</sup>	2003	8 mongrel dogs, each weighing more than 15 kg	8 mongrel dogs	PRP incorporation to autogenous bone grafts did not enhance new bone formation in the mandibular defects.
4	Desai AP, Sahoo N, Pal AK, Chowdury SKR <sup>8</sup>	2021	50 patients aged 8–50 years who required bone grafts for alveolar cleft defects and surgical defects after the resection of osteolytic jaw lesions were selected randomly	50 patients	PRP enhanced bone graft healing in the maxillofacial region as evidenced by a higher bone density in Hounsfield unit.
5	Dolder JVD, Mooren R, Vloon APG, Stoeltinga PJW, Jansen JA <sup>20</sup>	2006	Rat bone marrow cells, goat, and humans	6 male Wistar rats and goat and human PRP (1 patient)	PRP contains osteoinductive growth factors, which are likely species related. However, the results cannot be generalized due to large intraspecies variations.
6	Ramanathan A, Cariappa KM <sup>21</sup>	2014	5 patients were included in the control group. However, PRP gel was not used	5 patients	The study and control groups did not significantly differ. Both groups had significant healing changes at the 24-week follow-up. All surgical sites exhibited significant healing changes over 6 months.
7	Messoro MR, Nagata MJH, Fucini SE, Pola NM, Campos N, Oliveira GCV, Bosco AF, Garcia VG, Furlaneto FAC <sup>11</sup>	2014	10 male adult dogs	10 male adult dogs	At 90 days after surgery, the non-PRP grafts were significantly less dense than the PRP grafts. PRP enhanced the healing of Fresh Frozen Bone Allograft in resection defects in the mandibles.

8	Fennis JPM, Stoelinga PJW, Jansen JA <sup>12</sup>	2004	12 goats underwent continuity resection at the mandibular angle	12 goats	All goats had an uneven healing. Based on the histological and histomorphometric evaluation, PRP significantly enhanced bone healing at the 6- and 12-week groups.
9	Gerard D, Carlson ER, Gotcher JE, Jacobs M <sup>22</sup>	2007	12 adult dogs underwent resection for bilateral inferior mandibular border defects measuring 2 x 1 cm. Meanwhile, 1 dog was included in the control group	12 dogs	PRP enhanced early autologous graft healing. However, after two months, the effect was no longer significant. PRP did not change the rate at which the new bone was formed, and there was no increase in trabecular density in these grafts.
10	Huang Y, Li Z, Dessel JV, Salmon B, Huang B, Lambrichts I, Politis C, Jacobs R <sup>13</sup>	2019	72 dental implants were placed in the healed mandible sites of 9 beagle dogs	72 dental implants, 9 beagle dogs	PRP and PPP with conventional implant placement led to similar primary and secondary implant stability. However, the peri-implant bone volume and structural integration improved.
11	Ozdemir B, Kurtis B, Tuter G, Senguven B, Tokman B, Pinar-Ozdemir S, Demirel Ilkim, Ozcan G <sup>23</sup>	2012	28 rabbits calvarial bones	28 rabbits calvarial	Although new bone formation was histomorphologically remarkable in the double application PRP groups, the histomorphometric data did not significantly differ.
12	Mooren RE, Merckx MA, Bronkhorst EM, Jansen JA, Stoelinga PJ <sup>24</sup>	2007	20 goats	20 goats	Histologic and histomorphometric examination showed that early and late bone healing was not enhanced in the PRP-treated group.
13	Niimi K, Yoshizawa M, Koyama T, Funayama A <sup>14</sup>	2017	3 upper molars of Fischer rats	3 upper molars of Fischer rats	The presence of a rich fibrin network and early inflammatory reactions in the experimental group may lead to thick, vessel-rich granulation tissues. PRP may stimulate wound healing after tooth extraction for bone defects and may have some beneficial effects on the outcomes.
14	Plachokova AS, van den Dolder J, van den Beucken JJ, Jansen JA <sup>25</sup>	2009	Rats, goats, and humans	72 implants	Rat and goat PRP had no effect on new bone formation. Human PRP improved the initial osteogenic response to human bone graft. Compared with human PRP combined with synthetic bone substitute, human PRP combined with human autologous bone graft was associated with a greater osteogenesis.



15	Thor AL, Hong J, Kieller G, Sennerby L, Rasmusson L <sup>26</sup>	2012	6 dogs	6 dogs	PRP failed to induce greater new bone regeneration in a peri-implant defect model compared with whole blood. Implants treated with hydrofluoric acid had higher percentages of new bone formation in the defect.
16	Yamada Y, Ueda M, Hibi H, Nagasaka T <sup>15</sup>	2004	Dog mandible	Dog mandible	Combined dog mesenchymal stem cells and PRP had stable and predictable outcomes after implant treatment compared with autogenous particulate cancellous bone and marrow.
17	Yoshimi R, Yamada Y, Ito K, Nakamura S, Abe A, Nagasaka T, Okabe K, Kohgo T, Baba S, Ueda M <sup>16</sup>	2009	Dog mandible	Dog mandible	Mesenchymal stem cells and/or PRP might have their own potential and promote new bone regeneration in the three-dimensional structure using PuraMatrix scaffolds.
18	Kazakos K, Lyras ND, Thomaidis V, Agrogiannis V, Botaitis S, Drosos G, Kokka A, Verettas D <sup>27</sup>	2011	30 New Zealand white rabbits	30 New Zealand white rabbits	The application of PRP gel alone or in combination with GBR did not enhance bone healing process.
19	Kim TH, Kim SH, Sándor GK, Kim YD <sup>17</sup>	2014	12 rabbits	12 rabbits	The addition of PRP, platelet-rich fibrin, and concentrated growth factor significantly improved bone formation after 6 weeks. The effect of PRP, platelet-rich fibrin, and concentrated growth factor was similar, and their application may be effective in increasing the success rate of bone engineering.

**Table 1.** Summary of the 19 retrieved articles.

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