Research Article

Efficacy of Platelet-Rich Plasma in the Treatment of Fractures: A Meta-Analysis

Zhu Xu, Han Hu, Bin Wu, Chenglong Huang, Qin Liu, and Bin Chen

Department of Orthopaedics, The Second Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang 314000, China

Correspondence should be addressed to Bin Chen; chenbin.jx@qq.com

Received 24 March 2022; Revised 6 May 2022; Accepted 9 May 2022; Published 2 June 2022

Academic Editor: Ahmed Faeq Hussein

Copyright © 2022 Zhu Xu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Although numerous studies have reported the effectiveness of platelet-rich plasma (PRP) in promoting and enhancing bone healing, many orthopedic physicians remain skeptical of platelet-rich plasma in the treatment of fractures. The objective of this meta-analysis was to assess the efficacy of PRP in the treatment of fractures.

Methods. We search for research on PRP treatment of fractures in Pubmed, Embase, Medline, and Cochrane libraries. Two independent reviewers assessed included studies and met to develop a consensus on included studies. We also assessed the risk of bias using Review Manager 5.3 software.

Results. The present meta-analysis included 10 randomized controlled trials (RCT) containing 652 patients. In the fixed-effect meta-analysis of 10 RCTs, 8 RCTs found that fracture patients benefited from PRP treatment. The use of PRP reduced the time of fracture healing in 4 RCTs. Three RCTs found that PRP adjuvant therapy enhanced bone mineral density in the fracture trace and reduced the time of bone regeneration in mandibular fractures patients (standardized mean difference (SMD) = −1.99, 95% confidence interval (CI) = −2.64 − −1.35). And 3 RCTs found that PRP adjuvant therapy decreased the risk of revision surgery in fracture patients (SMD = 1.83, 95%CI = 1.10 − 3.04). Conclusion. PRP adjuvant therapy is beneficial for the treatment of fracture patients, particularly those with mandibular fractures, and decreased the risk of revision surgery in fracture patients.

1. Introduction

Every year, millions of individuals in China suffer from fractures, and the incidence of fractures is increasing year by year as the population ages [1, 2]. Although most fracture patients can be cured, about 10% of fracture patients particularly the elderly experience difficulty healing [3, 4]. Furthermore, reducing the fracture healing time not only improves the quality of life of patients and reduces pain but also reduces the economic burden of fracture patients [1]. Fracture healing is an extremely complex biological repair process that is influenced by many factors. In the field of orthopedics and traumatology, how to promote early fracture healing has always been a hot topic.

Platelet-rich plasma (PRP) is a super-physiological platelet concentrate, which can provide a microenvironment rich in growth factors and other cytokines to enhance cell proliferation and migration and bone healing [5]. PRP has been utilized to promote the healing of bones and soft tissues since the early 1990s. PRP has been shown in previous studies to activate and release platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), vascular endothelial growth factor, insulin-like growth factor, and epidermal growth factor, among other cytokines, all of which are important in the repair of soft tissue and bone diseases [6, 7]. PRP’s ability to repair tendons, ligaments, muscles, and cartilage has been studied in several randomized clinical trials [8]. PRP has also been found to promote histological healing after fracture and the biomechanical strength of fracture healing [9]. Some studies, however, have found that PRP has no significant effect on fracture healing, such Griffin et al. found that there is no evidence of a difference in the risk of revision surgery within 1 year in participants treated with PRP therapy compared with those not treated [10]. According to Singh et al., PRP had no effect on femoral shaft fracture healing treated with closed intramedullary nailing [11]. The difference in the effect of PRP in the treatment of fractures is thought to be related to the preparation
and activation method, concentration, site of action, and fracture fixation of PRP according to researchers, and separate studies have limitations in research methods, follow-up, and research design [12, 13].

Some randomized controlled trials (RCTs) about the efficacy of PRP on fractures have recently been reported, but the conclusion is still unclear. And there are still few studies on the efficacy of PRP on fractures. In the present study, we investigated the efficacy of PRP on fractures using a meta-analysis.

2. Methods

2.1. Search Strategy. We searched for studies related to the effect of PRP on the treatment of fractures from January to March 2021. The period span was from January 2010 to December 2020, and the language was confined to English. Two reviewers independently selected trials and extracted data according to predetermined selection criteria. Any inconsistencies would eventually be resolved through mutual discussion.

Keywords for literature search were as follows: "platelet-rich plasma," "fractures," "hollow screws," "femoral neck fractures," "hip joint fractures," "mandibular fractures," "long bone nonunion."

2.2. Selection Criteria. (1) Fracture patients; (2) use PRP as the main or auxiliary treatment; (3) RCTs on humans; (4) follow-up time is at least 3 months.

2.3. Data Extraction. By reading the entire text, two reviewers independently extracted the following key data: author, publication date, methods of randomization, description of randomization, methods of blinding, participant characteristics (gender, disease, and region), sample size, intervention plan, evaluation method, follow-up time, and treatment outcome.

2.4. Statistical Analysis and Heterogeneity. The meta-analysis was carried out using Review Manager 5.3 software. To calculate such differences, we used standardized mean difference (SMD) as the primary effect size. The point estimate and 95% confidence interval (CI) for each effect size were provided. If there was no statistical heterogeneity ($P > 0.1$), fixed-effects model analysis was used; if there was heterogeneity ($P < 0.1$), the source of heterogeneity first was analyzed first. If there was no obvious clinical heterogeneity and no definite source of statistical heterogeneity could be found, random-effects model analysis could be used; if there was obvious clinical heterogeneity or methodological heterogeneity or inadequate data provided, then descriptive analysis was performed. Low-quality studies could be removed for sensitivity analysis if there was significant statistical heterogeneity due to the different methodological quality of the included studies.

3. Results

3.1. Selection of Trials. After searching 4 databases, 266 studies have been found (Figure 1). After removing duplicated

| Study (author, year) | Random sequence generation | Randomized hiding | Blinding | Exit and follow-up | Total score |
|---------------------|---------------------------|------------------|----------|-------------------|-------------|
| Wei et al., 2012 [19] | 2 | 1 | 1 | 1 | 5 |
| Daif, 2013 [16] | 2 | 1 | 1 | 0 | 4 |
| Griffin et al., 2013 [10] | 2 | 1 | 1 | 1 | 5 |
| Al-Khawalani et al., 2014 [20] | 2 | 1 | 2 | 1 | 6 |
| Samy, 2015 [17] | 2 | 1 | 1 | 0 | 4 |
| Rodriguez and Urso, 2015 [15] | 1 | 1 | 1 | 0 | 3 |
| Ghaffarpasand et al., 2016 [21] | 2 | 1 | 2 | 1 | 6 |
| Namazi and Mehbudi, 2016 [18] | 2 | 1 | 1 | 0 | 4 |
| Singh et al., 2017 [11] | 2 | 1 | 2 | 1 | 6 |
| Castillo et al., 2018 [22] | 2 | 1 | 2 | 1 | 6 |

Finally, after reviewing the complete text of 35 studies, we excluded 25 studies and totally included 10 studies in the final analysis according to selection criteria.
3.2. Quality Evaluation. We used a modified Jadad scale to assess the methodological quality of these studies in the present meta-analysis from 4 dimensions, including random sequence generation, randomized hiding, blinding, and exit and follow-up [14]. As shown in Table 1, the study of Rodriguez and Urso [15] was scored 3, which was assessed as a low-quality clinical trial. RCTs with a literature score greater than 3 are considered high-quality clinical trials (Daif [16], Samy [17], and Namazi and Mehbudi [18]), 2 (Wei et al. [19] and Griffin et al. [10]), and 4 (Al-Khawlani et al. [20], Ghaffarpasand et al. [21], Singh et al. [11], and Castillo et al. [22]) clinical trials, respectively. In addition, Review Manager 5.3 software was used to assess the quality of the trials, including the risk of bias graph (Figure 2) and risk of bias summary (Figure 3).

3.3. General Review of the Effect of PRP on Fractures. As shown in Table 2, a total of 652 fracture patients were enrolled in 10 clinical trials, with 175 cases of intra-articular calcaneal fractures patients, 60 cases of mandibular fracture patients, 160 cases of hip fracture patients, 60 cases of fracture neck femur patients, 20 cases of bimalleolar fractures patients, 75 cases of long bone nonunion patients, 30 cases of distal radius fracture patients, and 72 cases of acute diaphyseal femur fractures patients. Other studies, except for those by Griffin et al. [10] and Singh et al. [11], had all found that PRP treatment benefited fracture patients. Griffin et al. [10] showed no evidence of a difference in the risk of revision surgery within 1 year in participants treated with PRP therapy compared with those not treated; Singh et al. [11] found that PRP had no effect on femoral shaft fracture healing treated with closed intramedullary nailing. Four studies found that the use of PRP shorted the time of fracture healing, namely, the studies by Al-Khawlani et al. [20], Samy [17], Rodriguez and Urso [15], and Ghaffarpasand et al. [21].

3.4. Effect of PRP on Bone Mineral Density during the Treatment of Mandibular Fractures. The effect of PRP on bone mineral density during the treatment of mandibular fractures has been studied in three clinical experiments: Al-Khawlani et al. [20], Castillo et al. [22], and Daif [16]. As shown in Figure 4, there was no heterogeneity between these three studies ($I^2 = 0\%$, $P = 0.20$), and the PRP increased bone mineral density in the fracture trace and shorted the time of bone regeneration in mandibular fractures patients ($SMD = -1.99, 95\% CI = -2.64 - -1.35$).

3.5. Effect of PRP on the Risk of Revision Surgery for Fracture. Ghaffarpasand et al. [21], Griffin et al. [10], and Samy [17] are three clinical trials that investigated the effect of PRP on
| Study            | Year | Disease                  | Design | Participants (n) | Treatment                                                                 | Male/female | Age (years) | Follow-up (months) | Main finding                                                                                                                                                                                                 |
|------------------|------|--------------------------|--------|------------------|-----------------------------------------------------------------------------|-------------|-------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wei              | 2012 | Intra-articular calcaneal fractures | RCT    | 90 85            | Allograft or autograft, Allograft combined + PRP                           | —           | 18–60 (mean: 46) | 72                | PRP augmented the favorable outcome of allografts in the management of displaced calcaneal fractures                                                                                                           |
| Daif             | 2013 | Mandibular fractures     | RCT    | 12 12            | Bone plates + screws, Bone plates + screws + PRP                           | 16/8        | 17–22 (mean: 32) | 6                 | Direct application of the PRP along the fracture lines may enhance the bone regeneration in mandibular fractures                                                                                               |
| Griffin          | 2013 | Hip fracture             | RCT    | 78 82            | Closed fracture reduction, Closed fracture reduction + PRP                 | 26/73       | 83 ± 7.8    | 12                | No evidence of a difference in the risk of revision surgery within 1 year in participants treated with PRP therapy compared with those not treated PRP seems to aid the acceleration of bone healing in mandibular fractures. |
| Al-Khawlani      | 2014 | Mandibular fracture      | RCT    | 8 8              | Open reduction + direct osteosynthesis + PRF, Open reduction + direct osteosynthesis + PRP | —           | 20–42       | 6                 | PRP shortens the clinical and radiation healing time of fracture neck femur                                                                                                                                |
| Samy             | 2015 | Fracture neck femur      | RCT    | 30 30            | Cannulated screws, Cannulated screws + PRP                                 | 39/21       | 30 ± 7.8    | 12–48             | PRP expedites fracture healing of the distal tibia and fibula in patients with significant comorbidities.                                                                                                 |
| Rodriguez        | 2015 | Bimalleolar fractures    | RCT    | 10 10            | Ilizarov fixator + concentrated bone marrow, Ilizarov fixator + concentrated bone marrow + PRP | —           | 52.9        | Mean: 18          | Application of PRP along with autologous bone graft in the site of nonunion of long bone after intramedullary nailing results in a higher cure rate, shorter healing duration, lower limb shortening, and less postoperative pain. |
| Ghafrasand       | 2016 | Long bone nonunion       | RCT    | 38 37            | Placebo, PRP                                                              | 33/5        | 26.3 ± 6.2   | 9                 |                                                                                                              |
| Study  | Year | Disease                  | Design | Participants (n) | Treatment                              | Male/female | Age (years) | Follow-up (months) | Main finding                                                                 |
|--------|------|--------------------------|--------|------------------|----------------------------------------|-------------|--------------|-------------------|-----------------------------------------------------------------------------|
| Namazi | 2016 | Distal radius fracture   | RCT    | 15               | Closed reduction + percutaneous         | 13/2        | 33.4         | 6                 | PRP may have a significant effect on the reduction of pain and amount of difficulty in functions, including specific and usual activities after intra-articular distal radius fractures. |
| Singh  | 2017 | Acute diaphyseal femur fractures | RCT   | 39               | Intramedullary nailing + PRP           | 37/2        | 32.9         | 6                 | PRP has no effect on femoral shaft fracture healing treated with closed intramedullary nailing. |
| Castillo | 2018 | Mandibular fracture      | RCT    | 10               | Internal fracture reduction + PRP      | 9/1         | 31.2 ± 8.5   | 3                 | PRP increased the bone intensity and density in the fracture trace allowing bone regeneration and recovery in a shorter time than in patients in which it was not used. |

Note: RCT: randomized controlled trial; PRP: platelet-rich plasma.
All studies conclude that PRP benefits fracture healing time, pain, bone density, and bone strength, all of which are important factors in fracture treatment. PRP treatment was found to shorten the healing time of fractures in 4 RCTs [15, 17, 20, 21]. PRP promotes fracture healing by releasing its contents to stimulate mitosis and mesenchymal cell development and differentiation. It has no obvious effect on the synthesis of alkaline phosphatase and the synthesis of osteoblast collagen, but it can accelerate angiogenesis and increase the activity of macrophages to promote trauma repair [29, 30]. TGF-β stimulates the chemotaxis and mitosis of osteoblast precursor cells and osteoblasts, induces the production of factors such as PDGF and TGF-α, promotes the synthesis of the extracellular matrix such as collagen and fibrin, inhibits the activity of metalloproteinases, and contributes to the formation of extracellular matrix deposition and fibrosis while inhibiting the formation of osteoclasts and bone resorption [31, 32].

The principle of PRP preparation is to separate them by centrifugation according to the different sedimentation coefficients of the various components in the blood [23, 24]. There is currently no defined and standardized method for extracting PRP. The preparation procedure can be divided into primary centrifugation, secondary centrifugation, and tertiary centrifugation. And data showed the second centrifugation method had the highest PRP extraction rate and the most extensive clinical application [25, 26]. In the present study, there is great heterogeneity in the preparation of PRP between various studies, and the composition, concentration, and activation mode of PRP are independent between different studies. As a result, it is impossible to determine the true effect of PRP on fractures because different studies’ study methodologies differ, and it is also difficult to determine whether the substance that is working is PRP or other active substances.

Because of the aforementioned reasons, we cannot know the true effect of PRP, and our study can evaluate whether patients with fractures benefit from PRP treatment. Shortening the healing time, enhancing bone density and bone strength, reducing pain, reducing pain, and decreasing the risk of reoperation are only a few of the advantages. PRP treatment was found to shorten the healing time of fractures in 4 RCTs [15, 17, 20, 21]. PRP promotes fracture healing by releasing its contents from platelets. Platelets contain growth factors, fibrin, cathespin A, and other proteins, the most important of which are PDGF and TGF-β [27, 28]. The main function of PDGF is to stimulate mitosis and mesenchymal cell development and differentiation. It has no obvious effect on the synthesis of alkaline phosphatase and the synthesis of osteoblast collagen, but it can accelerate angiogenesis and increase the activity of macrophages to promote trauma repair [29, 30]. TGF-β stimulates the chemotaxis and mitosis of osteoblast precursor cells and osteoblasts, induces the production of factors such as PDGF and TGF-α, promotes the synthesis of the extracellular matrix such as collagen and fibrin, inhibits the activity of metalloproteinases, and contributes to the formation of extracellular matrix deposition and fibrosis while inhibiting the formation of osteoclasts and bone resorption [31, 32].
Mandibular fractures are among the most common fractures, and the goal of mandibular fracture treatment is to restore the occlusal function before the fracture, improve bone stability, and restore anatomical structure [33, 34]. PRP did not appear to provide any statistically significant benefit to healing in an osteotomized defect of the rabbit mandible in the rabbit osteotomy model [35]. In the present study, 3 RCTs found that PRP treatment enhanced bone mineral density in the fracture trace and reduced the bone regeneration time in patients with mandibular fractures [16, 20, 22]. As a result, the effect of PRP treatment on mandibular fractures has not yet reached a clear conclusion, and further research is required.

PRP adjuvant therapy, according to our meta-analysis, is beneficial for the treatment of fracture patients, especially for mandibular fractures patients, and decreased the risk of revision surgery in fracture patients. However, our meta-analysis has limitations: there are only 652 participants, the sample size is small, and some studies are partially added. Nonetheless, according to our study, PRP is beneficial for fractures healing.

Data Availability

The data used to support the findings of this study are included within the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare that they have no competing interest.

Acknowledgments

This work was supported by Jiaxing public welfare science and technology projects, no. 2021AD30059.

References

[1] F. Song, Y. Zeng, J. Tian, Y. Lv, and X. Ni, "Epidemiology and the economic burden of pediatric fractures in China: a retrospective study of 14,141 fractures," Bone, vol. 144, article 115498, 2021.

[2] H. Lv, W. Chen, T. Zhang et al., “Traumatic fractures in China from 2012 to 2014: a National Survey of 512, 187 individuals,” Osteoporosis International, vol. 31, no. 11, pp. 2167–2178, 2020.

[3] A. Tw, B. Aj, B. Cb, B. Sg, C. Mc, and C. Jab, “Does a fracture liaison service program minimize recurrent fragility fractures in the elderly with osteoporotic vertebral compression fractures?,” The American Journal of Surgery, vol. 217, no. 3, pp. 557–560, 2019.

[4] Y. Dikmen, P. B. Delis, and A. M. Esquinas, “Threshold of number of rib fractures in elderly blunt trauma: a simple or complex matter of numbers?,” Surgery, vol. 162, no. 6, p. 1343, 2017.

[5] T. E. Foster, B. L. Puskas, B. R. Mandelbaum, M. B. Gerhardt, and S. A. Rodeo, "Platelet-rich plasma," American Journal of Sports Medicine, vol. 37, no. 11, pp. 2259–2272, 2009.

[6] K. Oku Da, T. Kawase, M. Momose, M. Murata, and H. Yoshie, "Platelet-rich plasma contains high levels of platelet-derived growth factor and transforming growth factor-β and modulates the proliferation of periodontally related cells in vitro," Journal of Periodontology, vol. 74, no. 6, pp. 849–857, 2003.

[7] S. Harrison, P. Vavken, S. Keyv, M. Jacobson, D. Zurakowski, and M. M. Murray, "Platelet activation by collagen provides sustained release of anabolic cytokines," The American Journal of Sports Medicine, vol. 39, no. 4, pp. 729–734, 2011.

[8] A. Martínez-Martínez, F. Ruiz-Santiago, and J. García-Espinoza, “Plasma rico en plaquetas: ¿mito o realidad?,” Radiología, vol. 60, no. 6, pp. 465–475, 2018.

[9] E. M. Van Lieshout and D. Den Hartog, "Effect of platelet-rich plasma on fracture healing," Injury, vol. 52, pp. S58–S66, 2021.

[10] X. L. Griffin, J. Achten, N. Parsons, and M. L. Costa, “Platelet-rich therapy in the treatment of patients with hip fractures: a single centre, parallel group, participant-blinded, randomised controlled trial,” BMJ Open, vol. 3, no. 6, p. e002583, 2013.

[11] R. Singh, R. Rohilla, J. Gawande, and P. K. Sehgal, “To evaluate the role of platelet-rich plasma in healing of acute diaphyseal fractures of the femur,” Chinese Journal of Traumatology, vol. 20, no. 1, pp. 39–44, 2017.

[12] A. Oryan, S. Alidadi, and A. Moshiri, “Platelet-rich plasma for bone healing and regeneration,” Expert Opinion on Biological Therapy, vol. 16, no. 2, pp. 213–232, 2016.

[13] "Platelet-rich plasma for bone healing," Dental Abstracts, vol. 58, no. 1, pp. 17-18, 2013.

[14] J. Sarris and G. J. Byrne, “A systematic review of insomnia and complementary medicine,” Sleep Medicine Reviews, vol. 15, no. 2, pp. 99–106, 2011.

[15] E. R. Rodriguez-Collazo and M. L. Urso, “Combined use of the Ilizarov method, concentrated bone marrow aspirate (cBMA), and platelet-rich plasma (PRP) to expedite healing of bimalleolar fractures,” Strategies in Trauma and Limb Reconstruction, vol. 10, no. 3, pp. 161–166, 2015.

[16] E. T. Daif, “Effect of autologous platelet-rich plasma on bone regeneration in mandibular fractures,” Dental Traumatology, vol. 29, no. 5, pp. 399–403, 2013.

[17] M. A. Samy, “The role of platelet rich plasma in management of fracture neck femur: new insights,” International Orthopaedics, vol. 40, no. 5, pp. 1019–1024, 2016.

[18] H. Namazi and A. Mehbudi, “Investigating the effect of intra-articular PRP injection on pain and function improvement in patients with distal radius fracture,” Orthopaedics & Trauma, Surgery & Research, vol. 102, no. 1, pp. 47–52, 2016.

[19] L. C. Wei, G. H. Lei, P. Y. Sheng et al., “The role of platelet rich plasma in management of fracture neck femur: new insights,” Journal of Orthopaedic Research, vol. 30, no. 10, pp. 1570–1576, 2012.

[20] E. Al-Khawlani, O. A. Adly, A. S. Ahmed, E. D. El-Desouky, A. H. Abass, and A. A. Abdelmaboob, “Evaluation of platelet-rich fibrin versus platelet-rich plasma on the outcome of mandibular fracture,” Egyptian Journal of Oral and Maxillofacial Surgery, vol. 5, no. 3, pp. 96–102, 2014.

[21] F. Ghaffarpasand, M. Shahrezaei, and M. Dehghankhalili, “Effects of platelet rich plasma on healing rate of long bone non-union fractures: a randomized double-blind placebo controlled clinical trial,” Bulletin of Emergency & Trauma, vol. 4, no. 3, pp. 134–140, 2016.

[22] G. Castillo-Cardiel, V. M. Medina-Quintana, M. Lomeli-Enríquez, F. Medrano-Muoz, and A. Gonzalez-Ojeda, “Platelet-rich plasma and its effect in bone regeneration in...
mandibular fractures. Controlled clinical trial,” *Gaceta Médica de México*, vol. 153, no. 4, 2019.

[23] J. Chahla, M. E. Cinque, N. S. Piuzzi et al., “A call for standardization in platelet-rich plasma preparation protocols and composition reporting,” *JBJS*, vol. 99, no. 20, pp. 1769–1779, 2017.

[24] M. Ahmad, “Platelet-rich plasma: a review,” *Current Medicinal Chemistry*, vol. 6, no. 1, pp. 41–45, 2017.

[25] S. Lhee, J. Kim, J. Jeon, and D. Lee, “Comparison of laboratory data among the six different prp separation systems using 144 samples,” *British Journal of Sports Medicine*, vol. 50, no. 22, p. e4.9-e4, 2016.

[26] L. A. Rossi, I. R. Murray, C. R. Chu, G. F. Muschler, and N. S. Piuzzi, “Classification systems for platelet-rich plasma,” *The Bone & Joint Journal*, vol. 101-B, no. 8, pp. 891–896, 2019.

[27] K. Baba, Y. Yamazaki, Y. Sone et al., “An in vitro long-term study of cryopreserved umbilical cord blood-derived platelet-rich plasma containing growth factors–PDGF-BB, TGF-β, and VEGF,” *Journal of Cranio-Maxillofacial Surgery*, vol. 47, no. 4, pp. 668–675, 2019.

[28] C. G. Ziegler, R. V. Sloun, S. Gonzalez, K. E. Whitney, and R. F. Laprade, “Characterization of growth factors, cytokines, and chemokines in bone marrow concentrate and platelet-rich plasma: a prospective analysis,” *The American Journal of Sports Medicine*, vol. 47, no. 9, pp. 2174–2187, 2019.

[29] J. G. Andrew, J. A. Hoyland, A. J. Freemont, and D. R. Marsh, “Platelet-derived growth factor expression in normally healing human fractures,” *Bone*, vol. 16, no. 4, pp. 455–460, 1995.

[30] J. O. Hollinger, A. O. Onikepe, J. Mackrell, T. Einhorn, and C. E. Hart, “Accelerated fracture healing in the geriatric, osteoporotic rat with recombinant human platelet-derived growth factor-bb and an injectable beta-tricalcium phosphate/collagen matrix,” *Journal of Orthopaedic Research*, vol. 26, no. 1, pp. 83–90, 2008.

[31] I. Grafe, Y. Tao, S. Alexander et al., “Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta,” *Nature Medicine*, vol. 20, no. 6, pp. 670–675, 2014.

[32] E. Haghighizadeh, M. Shahrezae, S. R. Sharifzadeh, and M. Momeni, “Transforming growth factor-β3 relation with osteoporosis and osteoporotic fractures,” *Journal of Research in Medical Sciences*, vol. 24, no. 1, p. 46, 2019.

[33] V. A. Pereira-Filho, L. Oliveira, J. M. S. N. Reis, M. A. C. Gabrielli, R. S. Neto, and M. S. Monnazzi, “Evaluation of three different osteosynthesis methods for mandibular angle fractures,” *The Journal of Craniofacial Surgery*, vol. 27, no. 7, pp. 1770–1773, 2016.

[34] J. Snäll, E. Kormi, C. Lindqvist et al., “Impairment of wound healing after operative treatment of mandibular fractures, and the influence of dexamethasone,” *British Journal of Oral & Maxillofacial Surgery*, vol. 51, no. 8, pp. 808–812, 2013.

[35] M. Miloro, D. J. Haralson, and V. Desa, “Bone healing in a rabbit mandibular defect using platelet-rich plasma,” *Journal of Oral and Maxillofacial Surgery*, vol. 68, no. 6, pp. 1225–1230, 2010.