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Review Article

A Review of the Role of Platelet-Rich Plasma in Fracture Healing

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Abstract

Fractures are a global health concern affecting millions of people annually, with the elderly being more susceptible. Although the majority of patients with fractures recover, approximately 10% of them, particularly the elderly, encounter difficulties in the healing process. Platelet-rich plasma (PRP) is a concentrated solution of platelets that contain numerous growth factors and other bioactive molecules, which make it effective in promoting tissue repair and regeneration. Additionally, PRP injections can enhance local blood flow and stimulate angiogenesis, which can contribute to better healing outcomes in the treated area. Recent literature reviews suggest that PRP has clinical efficacy in accelerating the fracture healing process, treating delayed unions and non-unions, and serving as an adjuvant method when used alone or in combination with surgical procedures. However, the clinical heterogeneity of the available studies warrants the need for further research with high-quality randomized controlled trials involving a large number of participants to provide appropriate guidelines for PRP use. The present narrative review aims to present the recent data in relation to the effectiveness of the use of the PRP injection technique in the process of bone fracture healing.

Keywords: Bone healing, Fracture, Platelet – rich plasma

Introduction

Globally, millions of people suffer from fractures each year, and with an aging population, the incidence of fractures is on the rise[1]. Although the majority of patients with fractures recover, approximately 10% of them, particularly the elderly, encounter difficulties in the healing process[2]. The most recent epidemiological data are characteristic: An estimated 178 million new cases of fractures were recorded globally in 2019, an increase of more than 33% compared to the corresponding figures for 1990; the total incidence of acute and/or chronic symptomatology due to fractures amounted to 455 million (70% increase compared to 1990), and finally, years lived with disability (YLDs) due to any type of fracture were estimated at 25.8 million (a big increase of 65.3% in comparison to 1990)[3].

Accelerating the healing time of fractures not only improves patients' quality of life but also reduces the economic burden of fractures on individuals and countries. Fracture healing is a complex biological process influenced by multiple factors. Facilitating early fracture healing has always been a significant topic of discussion in the fields of orthopedics and traumatology. Among the options that have been proposed and used in recent years in the effort to enhance and accelerate the healing process of fractures in various sites of the human body is the technique of injection platelet – rich plasma (PRP) directly on the fracture site[4]. PRP is a plasma that contains a higher concentration of platelets than normal plasma, and it is rich in growth factors

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and other bioactive molecules. These components give PRP important biological properties that can aid in tissue repair and regeneration, and improve local microcirculation in the area where it is injected[5]. As a minimally invasive method, in recent years it has found important therapeutic applications in various pathological conditions that involve multiple medical specialties, such as orthopaedics[6], rheumatology[7], plastic surgery[8] and dermatology[9].

The aim of this narrative review is to present recent research findings regarding the effectiveness of the PRP injection technique in promoting fracture healing in various bones of the human body.

Platelet – rich plasma and fracture healing

Platelet-rich plasma (PRP) is a blood-derived product that contains a higher concentration of platelets than whole blood in its physiological state. This provides a microenvironment rich in growth factors and cytokines that can enhance cell proliferation, migration, and bone healing[10]. The concept of PRP was first introduced by CS Kingley, who reported the first evidence of a blood coagulation factor VI antagonist in a PRP solution[11]. In a typical PRP solution, the concentration of platelets is 3 to 8 times higher than that in normal blood, with smaller concentrations of various other active biological factors such as fibrins and white blood cells[12]. When activated, platelets can release a large number of active biological factors associated with the regeneration and healing processes of injured tissues in the human body, including bone tissue, interstitial connective tissue, and collagen[13].

The most important of these active biological agents are the following[4]:

- Hepatocyte growth factor – HGF: Stimulates the growth of hepatocytes, epithelial and endothelial cells.
- Vascular endothelial growth factor – VEGF: Stimulates the migration and proliferation of vascular endothelial cells, which is a prerequisite for the start of the angiogenesis process.
- Insulin growth factor – IGF: Very important factor in the processes of regeneration of bone tissue, promoting the formation of bone matrix and cartilage, stimulating the differentiation and proliferation of the embryonic stem cells (ESCs).
- Transforming growth factor-β – TGF-β: Another important biologic factor in the process of fracture healing, with an important role in inflammation, deposition of bone matrix, bone absorption and inhibition of the formation of the osteoclasts.
- Fibroblast growth factor – FGF: Promotes wound healing, along with the mitotic stimulation of the articular chondrocytes.
- Epidermal growth factor – EGF: Has an active role in angiogenesis and re- epithelization and finally.
- Platelet – derived growth factor – PDGF: Activates the macrophages, stimulates angiogenesis along with the activity and proliferation of fibroblasts, Schwann cells and vascular smooth muscle cells.

Healthy bone tissue possesses the intrinsic ability to heal and remodel fractures caused by injuries. However, this process can be hindered or delayed due to various complications, leading to delayed bone union or non-union[14]. To address these complications, the classical treatment of orthopedic surgeons has been open reduction and rigid internal fixation (ORIF) with or without the use of bone grafts (homologous or heterologous)[15]. Despite the satisfactory results of these methods, they are often accompanied by complications and adverse effects such as increased surgical time, blood loss, prolonged hospitalization, and donor site complications from bone grafts[16]. For these reasons, the international scientific community has explored alternative methods and techniques to accelerate the process of fracture healing when it has been disrupted.

In 1998, Marx et al.[17] published one of the earliest research papers on the effectiveness of PRP in promoting bone healing. They reported a successful treatment of 88 mandibular defects (>5 cm) caused by benign or malignant tumors. The treatment involved the combination of autologous bone graft and topical application of PRP solution. The authors' main finding was that the application of PRP significantly accelerated the formation of new bone tissue around the autologous bone graft for at least the first six months following the procedure. These positive results gave the impetus to further investigation into the effects of PRP on the healing of fractures that do not progress as expected.

Delayed healing is defined as the cases where the fracture healing is prolonged for more than 3 months, while pseudoarthroses or non-unions are characterized by a delay that exceeds 6-9 months. Excessive fibrocartilage production is the most common pathophysiological cause for these complications, occurring in approximately 5-10% of fractures[18]. However, precise monitoring of fracture healing is challenging, as no more accurate methods than the patient's clinical symptoms and radiological images of the fracture are used. Therefore, it is often difficult to determine the initiation period of the processes that lead to these complications. A number of causes have been implicated in the occurrence of delayed union and pseudarthrosis of fractures; these include smoking, increased age of the patient, the presence of chronic conditions, and active infection[19]. However, the combination of mechanical instability in the fracture site and vascularization disorder in the affected area is likely the most significant reason[20]. Biological growth factors, which play a crucial role in the process of fracture healing, come into play at this point. These factors, including platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), transforming growth factors (TGF-β1, -β2, -β3), insulin-like growth factor (IGF), fibroblast growth factor (FGF), and bone morphogenetic proteins (BMPs), are present in PRP solution

Author / Country	Type of study	Studies Included	Method of treatment	Results
Roffi et al., (2016)[21], Italy	Systematic review	64 clinical studies (45 pre-clinical and 19 clinical)	PRP in bone defects	Positive pre-clinical results: 84,4% histological, 75% radiological and 72.7% biomechanical; the clinical results, however were inconclusive
Marcazzan et al., (2018)[22], Italy	Systematic review	35 animal studies (rats and rabbits)	PRP in bone healing	Inconclusive results, which cannot confirm the positive experimental and preclinical results in this field.
Van Lieshout and Hartog, (2021)[23], The Netherlands	Systematic review	9 clinical studies (8 randomized- controlled studies and one cohort study)	PRP in bone healing across different sites in the human body	Controversial results; the routine use of the method cannot be supported.
Zhang et al., (2021)[24], China	Systematic review	44 studies (9 clinical, 9 preclinical *in vivo* animal and 26 preclinical *in vitro* studies)	PRP in bone fracture treatment	The positive results of the preclinical studies were not translated into similar results on the clinical studies.
Andersen et al., (2012)[25], UK	Systematic review	18 clinical studies	PRP in the treatment of non-union fractures	Although the majority of the studies showed positive results, the level of the corresponding evidence was low (Level VI); further research is needed in this area.
Li et al., (2022)[26], China	Systematic review and meta-analysis	13 clinical Studies (549 patients)	PRP in the treatment of delayed unions and non-union of long bone fractures	PRP can be a useful method for promoting bone healing in patients with delayed union and non-union of long bone fractures, and can definitely be recommended as an adjuvant method, either alone, or in combination with surgical intervention.
Xu et al., (2022)[27], China	Systematic review and meta-analysis	10 randomized- controlled studies (652 patients)	PRP in the treatment of bone fractures	PRP can be beneficial as an adjuvant therapy for the treatment of various fractures of the human body, especially those of the mandible; it reduces the time of bone healing, enhances bone mineral density on the fracture site and, decreases the risk for a subsequent revision surgical procedure.
Jamal et al., (2022)[28], UK	Systematic review	27 clinical studies (1.631 patients)	PRP in the treatment of diverse bone pathologies	18 studies showed positive results, 8 showed no clinically significant results and only one showed unfavorable results.

Table 1. Summary of literature key findings regarding PRP in fracture healing.

in sufficient quantities. These biological growth factors have various interrelated mechanisms, and they seem to have the potential to promote fracture healing, especially in cases where it is interrupted and disturbed[14].

Malhotra et al. (2013)[14] published an initial literature review on the effectiveness of PRP in bone healing. Their analysis led to the following conclusions:

1) Studies to date have not demonstrated any synergistic effect of combining PRP with autologous or allogeneic bone grafts.
2) The use of PRP can be justified when combined with synthetic osteoconductive scaffolds.
3) In some cases, PRP may provide added benefits when used in conjunction with synthetic bone graft substitutes.
4) The use of PRP alone, without other methods to enhance bone healing, is not recommended due to lack of efficacy.

The field has seen continued research since then, with several original clinical studies, systematic reviews, and meta-analyses published in subsequent years. The next section will focus on presenting the most recent of these

studies, with a particular emphasis on relevant systematic reviews and meta-analyses of the literature. Table 1 will provide a summary of the findings from these studies.

Current understanding of PRP's effectiveness in bone healing

In 2016, Roffi et al.[21] conducted a systematic review to evaluate the effectiveness of PRP in bone defect healing, which covered a period of 20 years from 1996 to 2016. The review included a total of 64 original studies, among which 19 were clinical and 45 were pre-clinical *in vivo* studies. The authors reported that the preclinical studies showed positive histological, radiological, and biomechanical results in 84.4%, 75%, and 72.7% of cases, respectively. However, the clinical effectiveness of the method was less clear, and no definite conclusions could be drawn. According to the authors' final conclusion, the low-quality methodology and high heterogeneity of the clinical studies conducted so far made it impossible to confirm the fairly good efficacy results observed in pre-clinical studies in a clinical setting.

Two years later, Marcazzan et al.[22] conducted a systematic literature review to evaluate the effectiveness of PRP in bone healing in animal studies. The review included 35 studies conducted on rabbits and rats. Similar to the previous review, the results were inconclusive. The authors noted a significant variability in the species studied, type of fractures and bone defects, protocols used, leukocyte and platelet baseline values, growth factors, biomaterials used, and follow-up time. As a result, the authors concluded that solid scientific conclusions could not be drawn regarding the effectiveness of PRP even at the experimental level of animal models.

Van Van Lieshout and Hartog (2021)[23] conducted a systematic literature review on the efficacy of PRP in fracture healing, which included 9 clinical studies (8 randomized-controlled studies and one cohort study) that examined the effectiveness of the method on various areas of the human body, including femoral neck, scaphoid bone, distal radius, combined tibia and fibula, and calcaneal fractures. The results of the review were once again controversial, as the authors found a high degree of heterogeneity in the clinical studies, specifically in terms of the method technique, the number of patients, and the platelet count. While the technique was found to be completely safe, the authors concluded that routine use of PRP to accelerate fracture healing cannot be supported based on these findings.

In the same year, Zhang et al.[24] conducted a systematic literature review on clinical and preclinical studies regarding the effectiveness of PRP on bone fracture treatment. They analyzed 44 studies (9 clinical, 9 preclinical *in vivo* animal, and 26 preclinical *in vitro* studies). The results of the review were consistent with those of Roffi et al.[21]: Although the preclinical studies showed promising positive results, they were not translated into positive results in the clinical studies, and there was no solid evidence that PRP injection accelerates the course of fracture healing. Furthermore, there were large discrepancies between the protocols for the application of the method.

Andersen et al.[25] also conducted a systematic literature review to evaluate the effectiveness of PRP on the management of fracture non-union. Although they included 18 relevant studies, the heterogeneity of the method's protocols, along with the different outcome measures, prevented the authors from conducting a meta-analysis of the studies. Their final conclusion was that, although the majority of the studies showed positive results, the level of corresponding evidence was low (Level VI). The authors suggested further research by conducting randomized-controlled studies with follow-up periods longer than 11 months and using larger amounts of PRP (e.g., 5–20 ml).

Li et al. (2022)[26] conducted a systematic review and meta-analysis on the clinical effectiveness of PRP in treating delayed union or non-union of long bone fractures. The study included 13 articles with a total of 549 participants, comprising three randomized-controlled trials, nine retrospective studies, and one prospective study. The primary outcome measures were healing rate and duration, functional result, pain relief, and complications. The meta-analysis found that bone healing was achieved in 94.19% of patients treated with PRP combined with operation for open reduction and internal fixation, and in 78.69% of patients treated with PRP alone. The healing rate in the PRP group was 85.8%, compared to 60.76% in the control group. The mean bony union time was 4.64 months in the PRP group, compared to 5.15 months in the control group. Four studies reported satisfactory reduction of patients' pain. The authors concluded that PRP can be a useful adjuvant method for promoting bone healing in patients with delayed union and non-union of long bone fractures, whether used alone or in combination with surgical intervention.

In the same year, Xu et al.[27] conducted a systematic review and meta-analysis, analyzing 10 randomized-controlled studies with 652 patients to investigate the effectiveness of PRP on fracture healing. They concluded that PRP is a beneficial adjuvant therapy for treating various types of fractures, particularly those of the mandible. PRP can reduce the time needed for bone healing, enhance bone mineral density at the fracture site, and decrease the risk of subsequent revision surgical procedures.

Jamal et al. (2022)[28] conducted a systematic review on the efficacy of PRP in fracture management and bone healing. The review included 27 clinical studies with a total of 1.631 participants, covering various conditions such as acute fractures, delayed unions, non-unions, lumbar spine pathologies, and tibial lengthening procedures. Of the 27 studies, 18 reported positive results, while 8 showed no clinically significant results. Only one study reported unfavorable results. The authors concluded that there is considerable evidence of substantial clinical effectiveness of PRP as a treatment method. However, further high-

quality randomized-controlled studies are required to confirm these findings.

Discussion

Although the characteristics of PRP have been described since 1954 [11], its use in clinical practice for the treatment of fractures, particularly in cases of delayed union and non-union, took many decades to become established[29]. PRP solution contains a concentration of platelets 3 to 8 times higher than that of normal blood, which provides several theoretical advantages for tissue regeneration during various pathological conditions[30]. Recent clinical studies have demonstrated the efficacy of PRP infusion in treating chronic diabetic ulcers[31], osteoarthritis of the knee joint[32], plantar fasciitis[33], and even military drill injuries[4]. Moreover, since PRP solution also contains white blood cells in sufficient quantity, it is believed to enhance the body's defense against local inflammation and its attempt to eliminate local pathogenic microorganisms[34].

Yang et al., (2022)[39] in a network meta-analysis of randomized-controlled studies regarding the efficacy of the various available adjuvant therapies for the treatment of delayed unions and non-unions of fractures concluded that: 1) Bone marrow aspirate in combination with PRP and autologous cancellous bone have the potential to improve the healing rate, 2) Low intensity pulsed ultrasonography intervention shorten the healing time significantly and, 3) Electromagnetic field and extracorporeal shock wave therapy are associated with high risk of adverse effects.

PRP has been extensively investigated in multiple randomized clinical trials for its efficacy in repairing cartilage, tendons, muscles, and ligaments, and has also shown promising results in enhancing histological healing and biomechanical strength in fracture cases. However, some studies have suggested that PRP may not significantly impact fracture healing. For instance, Griffin et al. (2013)[36] found no evidence of a difference in the risk of revision surgery within one year between participants treated with PRP therapy and those who were not treated. Similarly, Singh et al. (2017)[37] reported no effect of PRP on femoral shaft fracture healing with closed intramedullary nailing. Researchers suggest that the inconsistent effects of PRP on fracture healing may be due to various factors, including the preparation and activation method, concentration, site of administration, and type of fracture fixation[38]. In a recent network meta-analysis of randomized-controlled studies regarding the efficacy of the various available adjuvant therapies for the treatment of delayed unions and non-unions of fractures, Yang et al. (2022)[39] concluded that bone marrow aspirate in combination with PRP and autologous cancellous bone have the potential to improve the healing rate, while low intensity pulsed ultrasonography intervention can shorten the healing time significantly. On the other hand, electromagnetic field and extracorporeal shock wave therapy are associated with high risks of adverse effects.

Regarding the most recent original clinical trials, two studies reported positive outcomes of autologous PRP treatment for bone fractures: Ranjan et al. (2022)[40] suggested that PRP injection is likely an effective and safe method for treating delayed unions of long bone fractures, while Rani et al. (2022)[41] found that PRP was effective in treating mechanically stable non-unions of long bone fractures.

This narrative review presents data on the effectiveness of PRP in the fracture healing process, focusing on systematic reviews and meta-analyses published in recent years. The review found the following main results:

1. Several literature reviews showed inconclusive results regarding the effectiveness of PRP, with pre-clinical studies showing positive results but not corresponding with clinical studies[21-24].
2. Positive results were based on low-quality (level IV) research data[25].
3. However, two recent meta-analyses have shown that PRP is effective in the fracture healing process, particularly for mandibular fractures[27], and in the treatment of delayed unions and non-unions of long bone fractures[26].

Conclusion

PRP holds significant promise as a therapeutic approach for the treatment of bone fractures and their complications. Due to the diverse range of clinical studies with varying use protocols and therapeutic indications, the findings on its efficacy have been inconclusive. Nonetheless, it has shown promising clinical results as an adjuvant method, either alone or in conjunction with surgical procedures, in expediting the fracture healing process and treating delayed unions and non-unions of long bones. However, to establish concrete scientific conclusions and formulate appropriate guidelines, further high-quality randomized-controlled studies with a substantial number of participants are essential.

References

1. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 2012;23(9):2239–56.
2. Wasfie T, Jackson A, Brock C, Galovska S, McCullough JR, Burgess JA. Does a fracture liaison service program minimize recurrent fragility fractures in the elderly with osteoporotic vertebral compression fractures? Am J Surg 2019;217(3):557–60.
3. GBD 2019 Fracture Collaborators. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Healthy Longev 2021;2(9):e580–92.
4. Xu PC, Xuan M, Cheng B. Effects and mechanism of platelet-rich plasma on military drill injury: a review. Mil Med Res 2020;7:56.
5. Acebes-Huerta A, Arias-Fernández T, Bernardo Á, Muñoz-Turrillas MC, Fernández-Fuertes J, Seghatchian J, et al. Platelet-derived bio-products: Classification update, applications, concerns and new perspectives. Transfus Apher Sci 2020;59(1):102716.
6. Li S, Xing F, Yan T, Zhang S, Chen F. Multiple Injections of Platelet-Rich

Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta- Analysis of Current Evidence in Randomized Controlled Trials. J Pers Med 2023;13(3):429.
7. Jacobs A, Elghawy O, Lugo Baruqui D, Aly Elghawy A. Current State of Platelet-rich Plasma in the Treatment of Rheumatic Disease: A Retrospective Review of the Literature. Curr Rheumatol Rev 2023; doi: 10.2174/1573397119666230420112017.
8. Hesseler MJ, Shyam N. Platelet-rich plasma and its utility in medical dermatology: A systematic review. J Am Acad Dermatol 2019; 81(3):834–46.
9. Han X, Ji D, Liu Y, Hu S. Efficacy and Safety of Transplantation of Autologous Fat, Platelet-Rich Plasma (PRP) and Stromal Vascular Fraction (SVF) in the Treatment of Acne Scar: Systematic Review and Meta-analysis. Aesthetic Plast Surg 2023; Mar 7;
10. Le ADK, Enweze L, DeBaun MR, Dragoo JL. Platelet-Rich Plasma. Clinics in Sports Medicine. 2019;38(1):17–44.
11. Kingsley CS. Blood coagulation; evidence of an antagonist to factor VI in platelet-rich human plasma. Nature 1954;173(4407):723–4.
12. Lana JF, Macedo A, Ingrao ILG, Huber SC, Santos GS, Santana MHA. Leukocyte- rich PRP for knee osteoarthritis: Current concepts. J Clin Orthop Trauma 2019;10(Suppl 1):S179–82.
13. Anitua E, Alkhraisat MH, Orive G. Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J Control Release 2012;157(1):29–38.
14. Malhotra A, Pelletier MH, Yu Y, Walsh WR. Can platelet-rich plasma (PRP) improve bone healing? A comparison between the theory and experimental outcomes. Arch Orthop Trauma Surg 2013; 133(2):153–65.
15. Novicoff WM, Manaswi A, Hogan MV, Brubaker SM, Mihalko WM, Saleh KJ. Critical analysis of the evidence for current technologies in bone-healing and repair. J Bone Joint Surg Am 2008;90 Suppl 1:85–91.
16. Pape HC, Evans A, Kobbe P. Autologous bone graft: properties and techniques. J Orthop Trauma 2010;24 Suppl 1:S36-40.
17. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 85(6):638–46.
18. Marsell R, Einhorn TA. Emerging bone healing therapies. J Orthop Trauma 2010;24 Suppl 1:S4-8.
19. Hak DJ, Fitzpatrick D, Bishop JA, Marsh JL, Tilp S, Schnettler R, et al. Delayed union and nonunions: epidemiology, clinical issues, and financial aspects. Injury 2014;45:S3–7.
20. Gaston MS, Simpson AHRW. Inhibition of fracture healing. J Bone Joint Surg Br 2007;89(12):1553–60.
21. Roffi A, Di Matteo B, Krishnakumar GS, Kon E, Filardo G. Platelet-rich plasma for the treatment of bone defects: from pre-clinical rational to evidence in the clinical practice. A systematic review. Int Orthop 2017;41(2):221–37.
22. Marcazzan S, Weinstein RL, Del Fabbro M. Efficacy of platelets in bone healing: A systematic review on animal studies. Platelets 2018; 29(4):326–37.
23. Van Lieshout EMM, Den Hartog D. Effect of platelet-rich plasma on fracture healing. Injury 2021;52:S58–66.
24. Zhang Y, Xing F, Luo R, Duan X. Platelet-Rich Plasma for Bone Fracture Treatment: A Systematic Review of Current Evidence in Preclinical and Clinical Studies. Front Med (Lausanne) 2021;8:676033.
25. Andersen C, Wragg NM, Shariatzadeh M, Wilson SL. The Use of Platelet-Rich Plasma (PRP) for the Management of Non-union Fractures. Curr Osteoporos Rep 2021;19(1):1–14.
26. Li S, Xing F, Luo R, Liu M. Clinical Effectiveness of Platelet-Rich Plasma for Long- Bone Delayed Union and Nonunion: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2021;8:771252.
27. Xu Z, Hu H, Wu B, Huang C, Liu Q, Chen B. Efficacy of Platelet-Rich Plasma in the Treatment of Fractures: A Meta-Analysis. Hussein AF, editor. Computational and Mathematical Methods in Medicine 2022; 2022:1–8.
28. Jamal MS, Hurley ET, Asad H, Asad A, Taneja T. The role of Platelet Rich Plasma and other orthobiologics in bone healing and fracture management: A systematic review. J Clin Orthop Trauma 2022; 25:101759.
29. Chahla J, Cinque ME, Piuzzi NS, Mannava S, Geeslin AG, Murray IR, et al. A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting. Journal of Bone and Joint Surgery 2017;99(20):1769–79.
30. Anitua E, Alkhraisat MH, Orive G. Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J Control Release 2012;157(1):29–38.
31. Yammine K, Ghanimeh J, Jil Agopian S, Assi C, Hayek F. PRP Versus Standard of Care for Venous leg Ulcers: A Systematic Review and Meta-Analysis of Prospective Comparative Studies. Int J Low Extrem Wounds 2022;153473462210944 24.
32. Li S, Xing F, Yan T, Zhang S, Chen F. Multiple Injections of Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta- Analysis of Current Evidence in Randomized Controlled Trials. J Pers Med 2023;13(3):429.
33. Gupta A, Ortiz-Babilonia C, Xu AL, Rogers D, Vulcano E, Aiyer AA. The Statistical Fragility of Platelet-Rich Plasma as Treatment for Plantar Fasciitis: A Systematic Review and Simulated Fragility Analysis. Foot Ankle Orthop 2022;7(4):24730114221144050.
34. Li H, Hamza T, Tidwell JE, Clovis N, Li B. Unique antimicrobial effects of platelet- rich plasma and its efficacy as a prophylaxis to prevent implant-associated spinal infection. Adv Healthc Mater 2013; 2(9):1277–84.
35. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-Rich Plasma as a Treatment for Patellar Tendinopathy. The American Journal of Sports Medicine 2014;42(3):610–8.
36. Griffin XL, Achten J, Parsons N, Costa ML. Platelet-rich therapy in the treatment of patients with hip fractures: a single centre, parallel group, participant-blinded, randomised controlled trial. BMJ Open 2013;3(6):e002583.
37. Singh R, Rohilla R, Gawande J, Kumar Sehgal P. To evaluate the role of platelet-rich plasma in healing of acute diaphyseal fractures of the femur. Chinese Journal of Traumatology 2017;20(1):39–44.
38. Oryan A, Alidadi S, Moshiri A. Platelet-rich plasma for bone healing and regeneration. Expert Opinion on Biological Therapy 2016; 16(2):213–32.
39. Yang J, Zhang X, Liang W, Chen G, Ma Y, Zhou Y, et al. Efficacy of adjuvant treatment for fracture nonunion/delayed union: a network meta-analysis of randomized controlled trials. BMC Musculoskelet Disord 2022;23(1):481.
40. Ranjan R, Kumar R, Jeyaraman M, Arora A, Kumar S, Nallakumarasamy A. Autologous platelet-rich plasma in the delayed union of long bone fractures - A quasi experimental study. J Orthop 2023;36:76–81.
41. Rani N, Perut F, Granchi D, Sante GD, Pennello E, Mazzotta A, et al. Ultrasound- guided injection of platelet-rich plasma or cord blood platelet-rich plasma in nonunion: a randomized controlled trial. Regen Med 2022;17(5):271–81.