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Clinical Study on the Treatment of Delayed Union After Long Bone Fracture Surgery with Platelet-Rich Plasma and Intramedullary Nail Dynamization

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Abstracts: *Background*: The purpose of this study was to investigate the clinical effect of platelet-rich plasma (PRP) combined with intramedullary nailing in the treatment of delayed union after long bone fracture surgery. *Methods*: To retrospectively analyze the clinical data of 60 patients with delayed healing of long bone fractures treated in the Department of Orthopaedics of the Fourth Affiliated Hospital of Guangzhou Medical University in 2023 from January 2021 to December 2021, patients were randomly divided into a combined treatment group (30 cases) and a control group (30 cases). PRP combined with intramedullary nail dynamic therapy was used for combined treatment, while only intramedullary nail dynamic therapy was used for the control group. *Results*: Bone healing was achieved in 28 patients in the combination group (93.3%), and the mean bone healing time was 4.2 ± 1.1 months. The former group was significantly better than the control group (76.7%, 6.5 ± 1.4 months) ($p < 0.05$). At the last follow-up, the recovery rate of limb function was 90.0% in the combined treatment group and 70.0% in the control group, and the former had an advantage in this aspect ($p < 0.05$). No disability or death occurred during follow-up in either group. *Conclusion*: PRP combined with intramedullary nailing has a significant clinical effect on delayed union after long bone fracture surgery, which can effectively promote fracture healing and improve patient prognosis.

Keywords: Platelet-rich plasma; Intramedullary nail dynamization; Long bone fracture; Delayed union; Clinical study

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1. Introduction

Bone healing is a complex biological process in the human body related to fracture repair, encompassing various stages such as hematoma organization, primary callus formation, and callus remodeling. It involves the participation of multiple cell types, including osteoblasts, osteoclasts, and vascular endothelial cells, as well as numerous biomolecules like bone morphogenetic proteins and insulin-like growth factors [1]. However, when patients are affected by factors such as poor local blood circulation, infection, and malnutrition, the injured site is prone to delayed healing or non-union [2,3]. Long bone fractures are one of the common traumatic diseases in clinical practice, and issues of delayed healing or non-union after surgery severely impact patients' prognosis and quality of life. According to the "Guidelines for Perioperative Management of Accelerated Rehabilitation After Major Orthopedic Surgery in China," the incidence of delayed healing after long bone fracture surgery ranges from approximately 5% to 15%. This statistic not only signifies that a large number of patients endure long-term pain and suffering but also bear a heavy economic burden. For example, in the case of femoral shaft fractures, patients with delayed healing experience an extended hospital stay of 2–3 months and additional medical expenses of 30,000 to 50,000 yuan [4,5]. Therefore, addressing the issue of delayed healing in long bone fractures has become a focal point of research.

PRP is an autologous plasma preparation derived from human blood. Due to its unique origin, PRP often poses no risk of disease transmission or immune rejection, exhibiting high safety and tolerability in clinical applications. Furthermore, PRP is rich in various growth factors, including platelet-derived growth factor, transforming growth factor-β, and vascular endothelial growth factor. These growth factors work synergistically to accelerate the healing process of fractures [6]. In recent years, PRP has gained widespread application and research in the field of orthopedics, covering not only fracture non-union but also osteoarthritis, tendon injury repair, and other aspects [7].

Dynamic intramedullary nailing is one of the commonly used methods to treat delayed fracture healing [8,9]. Its principle is to remove the locking screw at one end of the intramedullary nail, breaking the original stable mechanical environment of the fracture end and increasing the micro-movement of the fracture end. Moderate micro-movement can simulate physiological stress stimulation, activate osteoblast activity at the fracture site, promote callus formation and remodeling, and thus promote fracture healing [10]. From a biomechanical perspective, after dynamic intramedullary nailing, the stress distribution at the fracture end is closer to the natural state, and the stress stimulation intensity increases by 15% - 20%. This change in the mechanical environment can effectively promote the mineralization and shaping of the callus [11]. However, there is currently no consensus in the academic community on the effect of using dynamic intramedullary nailing alone or combined with PRP to treat delayed healing of long bone fractures [12].

This study aims to deeply explore the clinical effect of PRP combined with dynamic intramedullary nailing in the treatment of delayed healing of long bone fractures. By comparing the efficacy of combined therapy with dynamic intramedullary nailing alone, the specific role of PRP in promoting fracture healing will be clarified. This study provides a scientific basis for clinically optimizing treatment plans, thereby improving the treatment effect of patients with delayed healing after long bone fracture surgery and filling some gaps in current research on combined therapy.

2. Research objects and methods

2.1. Research objects

From January 2021 to December 2023, a total of 71 patients with delayed healing of long bone fractures were treated at the Fourth Affiliated Hospital of Guangzhou Medical University. Sixty patients who met the inclusion and exclusion criteria were randomly selected, with 30 patients in the combined treatment group and 30 patients in the control group. The combined treatment group received PRP combined with dynamic intramedullary nailing, while the control group only received dynamic intramedullary nailing. The grouping process strictly followed the principle of randomization to ensure that the two groups of patients were comparable in baseline data such as age, gender, fracture site, and fracture type.

This study is a Guangzhou Science and Technology Plan Project (No. 20220101064). The clinical data of patients was approved for use by the Ethics Committee of the Fourth Affiliated Hospital of Guangzhou Medical University (Approval No. 2021-D-037), and all patients were exempted from informed consent. This study does not involve any conflicts of interest.

2.2. Inclusion criteria

(1) No signs of fracture healing after more than 6 months;

(2) Reliable internal fixation at the fracture end, without breakage or loosening of the internal fixation;

(3) Bone defect at the fracture end $\leq$ 5mm;

(4) Follow-up time exceeding 12 months with complete follow-up treatment.

2.3. Exclusion criteria

(1) Infectious nonunion of bones;

(2) Combined with severe metabolic diseases, such as diabetes, etc.;

(3) Heavy smoking and drinking history that cannot be quit during treatment;

(4) Pathological fractures.

2.4. Preparation of PRP

Autologous PRP was prepared using a two-step centrifugation method, as described below: 10 mL of blood was drawn from the patient's antecubital vein using a 10mL disposable syringe pre-filled with 1 mL of sodium citrate anticoagulant and an 18G needle, and this was repeated for a total of 2 tubes; under sterile conditions, the blood was centrifuged at a radius of 15 cm and a speed of 1500 r/min for 10 minutes, resulting in three layers of separation; the lower layer of red blood cells was slowly discharged; the remaining portion was centrifuged again at a radius of 15 cm and a speed of 2000 r/min for 10 minutes; subsequently, the lower layer of red blood cells was slowly discharged, and 2.0–2.5 mL of the middle layer from each tube was retained for injection, yielding PRP. Routine quality control was performed on the obtained PRP product, and the platelet concentration in the PRP prepared by the above method was 3–6 times that of whole blood.

2.5. Experimental methods

In the control group, the locking screws at one end of the intramedullary nail were removed under local or lumbar anesthesia to perform intramedullary nail dynamization. Strict aseptic techniques were followed during the surgical procedure to ensure the safety and effectiveness of the operation. The experimental group received an injection of PRP at the fracture site under local or lumbar anesthesia and C-arm monitoring, along with intramedullary nail dynamization. The specific steps were as follows: After completing the intramedullary nail dynamization, the fracture site was located through C-arm fluoroscopy, and the prepared PRP was slowly injected around the fracture end to ensure uniform distribution of PRP in the fracture area.

2.6. Evaluation of therapeutic effect

Detailed records were kept of patients' bone healing time, bone healing rate, and limb function recovery. X-ray films were used to evaluate fracture healing, and the Johner-Wruhs scoring system was employed to assess limb function recovery.

The recovery of limb function was evaluated using the Johner-Wruhs scoring system. This scoring system assesses the patient's limb function from multiple aspects such as pain, function, appearance, range of movement, etc., and is divided into four grades: excellent, good, medium, and poor.

2.7. Statistical analysis

SPSS 22.0 software was used for statistical analysis. The Shapiro-Wilk test was performed to determine whether the measurement data followed a normal distribution. Normally distributed measurement data were expressed as mean ± standard deviation (SD), and comparisons between the two groups were made using the two-sample *t*-test. Comparisons of count data between the two groups were conducted using the χ^2 test, and the results were expressed as *n*(%). A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of general information between the two groups

The general information of 60 patients is shown in **Table 1**. The combined treatment group included 30 patients, with 18 males (60%) and 12 females (40%). The age range was 25 to 58 years old, with an average age of 42.5 ± 8.3 years old. In this group, there were 15 cases (50%) of femoral fractures and 15 cases (50%) of tibial fractures. 22 patients (73.3%) had closed fractures, and 8 patients (26.7%) had open fractures. In the control group, there were 19 males (63.3%) and 11 females (36.7%). The age range was 23 to 59 years old, with an average age of 41.8 ± 7.9 years old. 16 patients (53.3%) had femoral fractures, and 14 patients (46.7%) had tibial fractures. 21 patients (70%) had closed fractures, and the remaining patients had open fractures. There were no statistically significant differences in general information such as age, gender, fracture site, and fracture type between the two groups (*P* > 0.05), indicating comparability between the groups.

Table 1. Comparison of general information between the two groups

Item	Combination therapy group (*n* = 30)	Control group (*n* = 30)	t/χ^2 value	*P*-value
Age (years)	42.5 ± 8.3	41.8 ± 7.9	0.335	0.739
Gender (Male/Female)	18/12	19/11	0.070	0.791
Fracture Site (Femur/Tibia)	15/15	16/14	0.067	0.796
Fracture Type (Closed/Open)	22/8	21/9	0.082	0.775

3.2. Comparison of clinical data between the two groups

As shown in **Table 2**, the average fracture healing time in the combination therapy group was 4.2 ± 1.1 months, which was significantly shorter than the 6.5 ± 1.4 months in the control group, and the difference was statistically significant (*P* < 0.05).

Table 2. Comparison of fracture healing time between the two groups

Item	Combination therapy group (*n* = 30)	Control group (*n* = 30)	*t*-value	*P*-value
Mean fracture healing time (months)	4.2 ± 1.1	6.5 ± 1.4	6.97	< 0.001

3.3. Comparison of clinical healing rates between the two groups

At 12 months post-operation, the clinical healing rate in the combined treatment group was 93.3% (28/30), which was significantly higher than the 76.7% (23/30) in the control group. The difference was statistically significant (P <0.05) (**Table 3**).

Table 3. Comparison of clinical healing rates between the two groups

Item	Combination therapy group (n=30)	Control group (n=30)	χ^2 Value	*P* Value
Number of clinical healings	28	23	4.320	0.037
Clinical healing rate	93.3%	76.7%		

3.4. Comparison of functional recovery between the two groups

In terms of functional recovery, the excellent and good rate of the Johner-Wruhs score in the combined treatment group was 90.0% (27/30), which was significantly higher than the 70.0% (21/30) in the control group. The difference was statistically significant ($\chi^2 = 4.800$, $P < 0.05$). The specific scoring results are shown in **Table 4**.

Table 4. Comparison of functional recovery between the two groups

Rating grade	Combination therapy group (*n* = 30)	Control group (*n* = 30)
Excellent	15	10
Good	12	11
Fair	2	7
Poor	1	2

3.5. Comparison of complications between the two groups

No severe complications occurred in both groups. In the combined treatment group, 2 patients experienced mild local pain and 1 patient had a short-term fever, all of which resolved spontaneously. In the control group, 1 patient developed a superficial infection that was successfully treated with antibiotics (**Table 5**). Overall, both treatment methods demonstrated good safety profiles.

Table 5. Comparison of postoperative complications between the two groups

Complication	Combination therapy group (*n* = 30)	Control group (*n* = 30)
Pain	2	0
Fever	1	0
Infection	0	1

4. Discussion

The core pathological feature of delayed fracture healing is the inhibition of osteogenesis caused by stress shielding at the fracture site [13]. Dynamization of intramedullary nails changes the mechanical environment at the fracture site and increases micro-movement by removing the locking screw at one end of the nail. Longitudinal stress stimulation at the fracture site can promote callus formation and mineral deposition, which is beneficial for fracture healing. Moderate micro-movement can stimulate callus formation and remodeling, activate osteoblast activity at the fracture site, and promote the repair and regeneration of bone tissue. Furthermore, the various growth factors abundant in PRP play key roles in the treatment of delayed healing of long bone fractures: (1) Platelet-derived growth factor can chemoattract osteoblasts and mesenchymal stem cells, promote their proliferation and differentiation, and provide an adequate cell source for fracture healing; (2) Transforming growth factor-β can regulate the synthesis and deposition of extracellular matrix, promoting the formation and mineralization of bone matrix; (3) Vascular endothelial growth factor can stimulate angiogenesis, improve blood supply to the fracture site, and create a favorable nutritional environment for fracture healing [14]. Throughout the treatment process, PRP provides a rich source of bioactive substances, while dynamization of intramedullary nails creates favorable mechanical stimulation. The combined application of these two treatment modalities further improves the therapeutic effect and accelerates the process of fracture healing. This study, through a prospective controlled design, verified the clinical efficacy of PRP injection combined with dynamization of interlocking intramedullary nails for the treatment of delayed healing of long bone diaphyseal fractures. The results fully demonstrate that PRP combined with dynamization of intramedullary nails has a significant clinical effect in the treatment of delayed healing after long bone fracture surgery. Compared with the dynamization of intramedullary nails alone, the combined treatment approach has clear advantages regarding bone healing time, bone healing rate, and limb function recovery ($P < 0.05$). These results suggest that early biomechanical intervention combined with PRP treatment can optimize the microenvironment for fracture healing and promote fracture healing.

The results of this study are consistent with most literature reports [15,16]. However, the conclusion is not entirely consistent, and further research may be needed on the clinical efficacy of PRP. In some scholars' studies, the clinical efficacy of PRP is uncertain [17]. This phenomenon may be closely related to factors such as PRP preparation methods, injection doses, and timing. Different preparation methods may lead to differences in the concentration and activity of growth factors in PRP, and insufficient injection doses or improper timing may not fully exert the role of PRP in promoting fracture healing. This study adopted standardized PRP preparation and injection methods, strictly controlling each link in the preparation process to ensure the quality and activity of PRP, while reasonably selecting the injection timing, which may be an important factors that help improve the treatment effect.

This study has certain limitations. Firstly, the sample size of this study is relatively small, with only 60 patients included. The small sample size may lead to certain sampling errors in the research results, affecting the universality and reliability of the results. Secondly, the follow-up time is relatively short, only 12 months, and the long-term effects and long-term complications of fracture healing have not been fully observed. Additionally, this study is a single-center study, and the research results may be influenced by factors such as patient sources, treatment levels, and research conditions of a single hospital.

Based on the limitations of this study, larger-scale, multi-center, long-term follow-up randomized controlled studies are needed to further verify the effectiveness and safety of PRP combined with intramedullary nail dynamization for the treatment of delayed union after long bone fracture surgery. During the research process, research variables should be strictly controlled to ensure the scientificity and reliability of the research results. Furthermore, the optimal preparation method of PRP should be further explored to optimize indicators such as platelet concentration and growth factor activity; determine the optimal injection dose and timing of PRP to fully exert its role in promoting fracture healing. At the same time, actively explore the combined application of PRP with other biological agents or physical therapies, expand the selection of treatment methods, and provide better and more effective treatment options for patients with delayed union after long bone fracture surgery.

5. Conclusion

The combined therapy of PRP and dynamization of intramedullary nails for delayed union after long bone fracture surgery has significant clinical effects, effectively reducing fracture healing time and improving clinical healing rates and excellent functional recovery rates. This combined therapy is safe and feasible, providing a new option for the treatment of delayed union after long bone fracture surgery. However, further research is still needed to optimize the treatment regimen and explore its long-term efficacy and mechanism. In clinical practice, doctors can comprehensively consider and select appropriate treatment methods based on the specific conditions of patients to improve treatment effectiveness and patient prognosis.

Disclosure statement

The authors declare no conflict of interest.

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