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Clinical Study on the Treatment of Long Bone Fracture Non-union with Extracorporeal Shock Wave Therapy Combined with Platelet-rich Plasma

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Abstract

Objective: The objective of the study was to evaluate of the therapeutic efficacy of extracorporeal shock wave therapy (ESWT) combined with platelet-rich plasma (PRP) injection in patients with long bone fracture non-union.

Material and Methods: A total of 36 patients identified with long bone fracture non-union treated from September 2020 to September 2023 were enrolled into this study. Employing a random number table method, they were randomly divided into three groups, with 12 cases in each group. Based on the treatment modality, the groups were categorized as the ESWT group, PRP group, and combination ESWT + PRP group. Routine radiographs and musculoskeletal ultrasound were obtained before treatment and at 3-, 6-, and 9-month post-treatment intervals to observe for bone callus formation and assess fracture line imaging scores with the aim to evaluate the treatment efficacy of each group.

Results: With the extension of treatment time, the bone callus and fracture line imaging scores of the three groups gradually increased ($P < 0.05$). At 3-, 6-, and 9-month post-treatment, the scores of the ESWT combined with the PRP group were significantly better than those of the singular ESWT group and PRP group, and the differences were statistically significant ($P < 0.05$).

Conclusion: Therapy with singular ESWT, singular PRP, and combination ESWT + PRP has demonstrated effective improvement in fracture healing for patients with long bone fracture non-union. The synergistic effects of combination therapy were more significant, surpassing the efficacy of singular ESWT or PRP applications. The combined use of ESWT and PRP represents a safe and promising alternative treatment for long-bone fracture non-union, making it a compelling choice in the context of fracture healing.

Keywords: Extracorporeal shock wave therapy, Platelet-rich plasma, Non-union of fracture.

Introduction

The definition of non-union of fracture remains somewhat controversial and the American Academy of Orthopedic Surgeons defines non-union as a fracture that has not healed for at least 9 months, with no apparent signs of healing observed for more than 3 consecutive months [1]. While the majority of fracture patients can heal after treatment, approximately 5–10% of non-union patients cannot achieve healing due to specific patient complications (such as diabetes and osteoporosis), local post-operative wound infections, high-energy injuries, the patient's age, and poor blood supply to specific fracture sites [2-4]. At present clinical treatment methods for non-union include bone grafting, dynamic intramedullary

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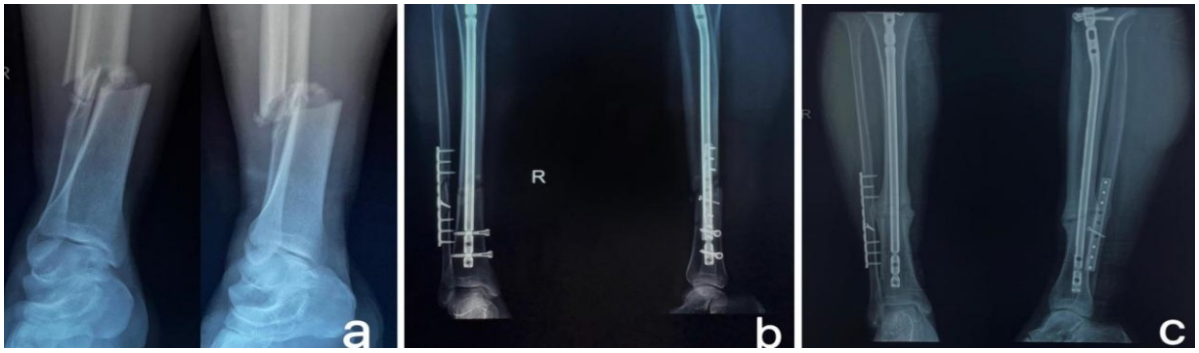

Figure 1: (a) X-ray anteroposterior and lateral views on the day of the fracture; (b) X-ray anteroposterior and lateral views after internal fixation surgery; and (c) X-ray anteroposterior and lateral views at the first visit to our hospital.

nailing, and reinforced plate fixation. Repeat surgery with bone grafting is often considered the "gold standard," but these treatment methods typically require a second operation, leading to increased treatment costs, prolonged treatment times, and an elevated risk of post-operative complications, thereby becoming a significant economic burden on society [5, 6]. Extracorporeal shock wave therapy (ESWT) is a treatment involving special sound waves that reach their peak in an extremely short time, exerting beneficial therapeutic effects on human tissues through various mechanisms. Platelet-rich plasma (PRP) is a plasma component obtained by centrifuging whole blood to achieve a platelet concentration 3–5 times higher than that of whole blood, containing a high proportion of various growth factors and cytokines involved in tissue repair and regeneration processes. Both treatment modalities are characterized by their safety, effectiveness, simplicity, and minimal tissue damage. Under the guidance of musculoskeletal ultrasound, precise positioning of the fracture ends is achievable, contributing to an enhanced therapeutic outcome in non-union cases. This study aims to explore the clinical efficacy of combining ESWT with PRP for the treatment of non-union under musculoskeletal ultrasound guidance, providing valuable insights for the clinical management of non-union.

Clinical Data and Methods

General Information

A retrospective study was conducted on non-union of fracture patients admitted to the Orthopedics Department at Central Hospital Affiliated to Shenyang Medical College from September 2020 to September 2023. Inclusion criteria for patients were as follows: (1) Age ≥18 years; (2) meeting the diagnostic criteria for non-union of bones; (3) non-healing gap at the fracture end ≤5 mm; (4) X-rays showing a clear fracture gap, hardened bone quality at the fracture end, and no formation of bone trabeculae between bone calluses; and (5) patients willing to participate in the study and signed an informed consent form.

Exclusion criteria were: (1) Bleeding disorders or currently receiving anticoagulant therapy; (2) suffering from or having a history of cancer or tumors; (3) previous use of any autologous blood products or stem cell preparations; (4) unstable fixation at the non-union site; (5) plasma total cholesterol >5.18 mmol/L or triglycerides >1.7 mmol/L; (6) implanted cardiac pacemaker; (7) local thrombus formation; (8) severe atrophic non-union or infectious non-union; (9) platelet count ≥150,000/uL; and (10) patients with severe cognitive impairment. According to the above inclusion and exclusion criteria, a total of 36 patients meeting the selection criteria were enrolled in the study. This included six cases of humerus fractures, eight cases of radius-ulna fractures, 12 cases of femur fractures, and 10 cases of tibia-fibula fractures. The patients with non-union were randomly divided into three groups, with 12 cases in each group, defined as the ESWT group, PRP group, and ESWT + PRP group, using a random number table. The comparison of age, gender composition, and disease duration among the three groups showed no statistically significant differences ($P > 0.05$), as shown in Table 1.

Therapeutic Methods

ESWT group: Before treatment, musculoskeletal ultrasound is used to locate the fracture ends, avoiding important vascular and neural pathways, as well as avoiding internal fixation devices. Measurement of the skin-to-fracture distance through musculoskeletal ultrasound is conducted to

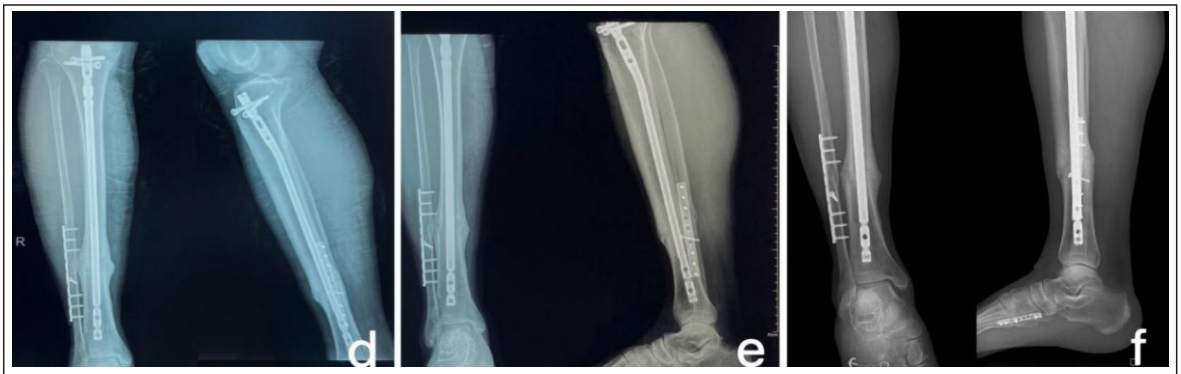

Figure 2: (a) X-ray anteroposterior and lateral views after 3 months of combined treatment; (b) X-ray anteroposterior and lateral views after 6 months of combined treatment; and (c) X-ray anteroposterior and lateral views after 9 months of combined treatment.

Figure 3: (a) illustrates the use of musculoskeletal ultrasound for positioning the fracture ends before extracorporeal shock wave treatment, avoiding important vascular and nerve pathways, as well as steering clear of internal fixation devices and (b) depicts the treatment of the fracture ends using radial shock waves.

determine the depth of the focused shock wave focus. For the treatment of superficial fractures (such as radius and ulna, tibia, and fibula), a radial pressure wave treatment machine is used. During treatment, the deep head (D15) is used with a frequency of 2Hz, and the standard head (R15) is used with a frequency of 10Hz alternately. The pressure is gradually increased based on the patient's tolerance (1.5 bar–4.9 bar). Approximately 500 shocks are delivered per treatment point, and the number of shocks is controlled at around 2000–4000 pulses. For deeper fractures that do not heal, a combination of a radial pressure wave treatment device and a focused shock wave treatment machine is used. The focused shock wave treatment machine delivers approximately 2000 shocks per session (selecting 1–2 treatment points, evenly distributed). The energy density is 0.2–0.3 mJ/mm2, and the frequency is 1–2 Hz. The radial pressure wave treatment machine uses a deep treatment head (D15) with a frequency of 2Hz. The pressure is gradually increased based on the patient's tolerance (1.5 bar–4.9 bar), and approximately 500 shocks are delivered per treatment point. The number of shocks is controlled at around 2000–4000 pulses. Each treatment is spaced 3–4 days apart, and each course consists of a total of 12 treatments. After each course, there is a 1-month rest period.

PRP Group: The WG-YLJ-I centrifuge from WEGO Company was utilized for the preparation of PRP. 5 mL of sodium citrate was drawn into a 50 mL syringe, ensuring thorough lubrication of the syringe walls. Within 5 min, 45 mL of blood was drawn from the patient's median cubital vein, allowing for complete mixing with the sodium citrate. The blood was then injected into the centrifuge tube, and the first centrifugation was carried out with the addition of 52–54 mL of physiological saline in the balancing tube. After 14 min of centrifugation, the plasma layer was extracted to a depth of 1 mm from the cone. Following rebalancing, the second centrifugation was performed. In post-second centrifugation, the supernatant was drawn into the tube, leaving 5–6 mL. Gentle clockwise agitation was applied to obtain PRP. Following preparation, PRP was injected into the fracture site under musculoskeletal ultrasound guidance. Injections were administered every 3 months, totaling three injections.

ESWT+PRP Group: Each treatment cycle begins with PRP injection under musculoskeletal ultrasound guidance. After a 2-week rest period to allow for optimal wound healing at the incision site, ESWT is administered. This protocol is repeated for a total of three treatment cycles. The treatment plans for ESWT and PRP follow the procedures outlined in the ESWT and PRP groups mentioned earlier. Patients from all three groups underwent follow-up musculoskeletal ultrasound and X-ray examinations in the 3rd, 6th, and 9th months post-treatment to assess the status of the musculoskeletal tissues and the alignment of the fracture site in both anteroposterior and lateral views.

Efficacy Assessment Criteria

Before treatment and at the 3rd, 6th, and 9th months post-treatment, evaluations were

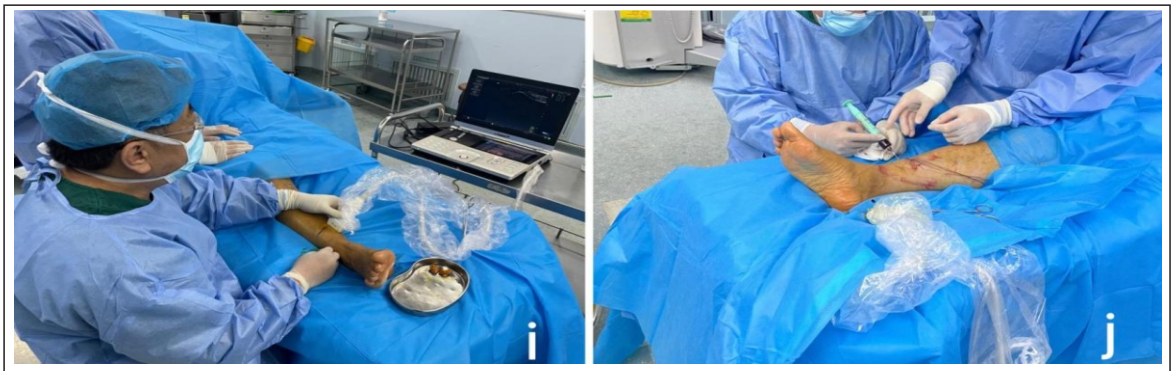

Figure 4: (a) Use of musculoskeletal ultrasound for positioning the fracture ends during platelet-rich plasma (PRP) injection, avoiding important vascular and nerve pathways, and ensuring that PRP is injected at the fracture ends and (b) demonstrates the injection of prepared PRP into the fracture ends.

Table 1: Baseline characteristics of patients with non-union in the three groups

Group	Sample size(case)	Gender (case)		Age ($\bar{X} \pm S$, year)	Course of disease ($\bar{X} \pm S$, month)
		Male	Female		
ESWT group	n=12	7	5	36.92±13.9	13.88±12.36
PRP group	n=12	6	6	39.92±13.58	20.42±13.88
ESWT+PRP group	n=12	8	4	38.25±10.7	17.5±14.64
Test value		χ^2=0.686		F=0.165	F=0.691
P-value		0.71		0.848	0.508

ESWT: Extracorporeal shock wave therapy, PRP: Platelet-rich Plasma

conducted through follow-up X-rays in anteroposterior and lateral views of the fracture site to observe bone callus, assess the radiographic scores related to the fracture line, and examine musculoskeletal ultrasound images. In addition, musculoskeletal ultrasound was utilized to measure the distance between fracture ends and assesses the blood flow in the vicinity of the fracture site for patients in all three treatment groups.

Radiographic scoring of bone callus

The Fernandez-Esteve bone callus grading criteria are as follows [7]: Grade 1: 0 points, no bone callus at the fracture site; Grade 2: 1 point, faint bone callus formation at the fracture site; Grade 3: 2 points, bone callus formation on one side of the fracture site; Grade 4: 3 points, bone callus formation on both sides of the fracture site; Grade 5: 4 points, structural bone callus formation; Grade 6: 5 points, moderate absorption of external bone callus; Grade 7: 6 points, complete absorption of external bone callus.

Fracture line radiographic scoring

The radiographic scoring criteria for fracture lines are as follows: Grade 1: 0 points, the fracture line is clear with no changes; Grade 2: 1 point, the fracture line begins to blur; Grade 3: 2 points, the fracture line is blurred but not disappeared, and there is a relatively firm connection; Grade 4: 3 points, the fracture line disappears, and high-density bone callus is formed; Grade 5: 4 points, the density of the medullary cavity begins to decrease; Grade 6: 5 points, a significant decrease in medullary cavity density.

Statistical Analysis

Data analysis was conducted using SPSS 27.0 statistical software. Descriptive statistics for continuous variables were expressed as mean ± standard deviation. For within-group comparisons before and after treatment, repeated measures analysis of variance (ANOVA) was employed. Group-wise post hoc comparisons were performed using the LSD-t test. Categorical variables such as gender were presented as frequencies and group-wise comparisons were conducted using the Chi-square test. Age, duration of illness, and other inter-group comparisons were carried out using one-way ANOVA. In all analyses, $P < 0.05$ was considered statistically significant.

Results

Bone Callus Radiographic Scoring Results

After treatment, the radiographic scores of bone callus at different time points were higher than those before treatment in all three groups, and the differences were statistically significant ($F = 20.455$, $F = 18.44$, $F = 40.069$, $P < 0.05$). In intergroup comparisons, the ESWT + PRP group exhibited significantly higher scores at the 3rd, 6th, and 9th months after treatment compared to the ESWT group and PRP group, and the differences were statistically significant ($F = 3.667$, $F = 4.695$, $F = 5.981$, $P < 0.05$), as shown in Table 2.

Fracture Line Radiographic Scoring Results

After treatment, the radiographic scores of the fracture lines at different time points were higher than those before treatment in all three groups, and the differences were statistically significant ($F = 30.24$, $F = 29.062$, $F = 89.786$, $P < 0.05$). In intergroup comparisons, the ESWT + PRP group showed significantly higher scores at the 3rd, 6th, and 9th months after treatment compared to the ESWT group and PRP group, and the differences were statistically significant ($F = 4.294$, $F = 5.478$, $F = 26.802$, $P < 0.05$), as shown in Table 3.

Using repeated measures ANOVA, we

Table 2: Radiographic scores of bone callus at different time points before and after treatment in three patient groups. ($\bar{X} \pm S$, score)

Group	Sample size(case)	Before treatment	Three months of treatment	Six months of treatment	Nine months of treatment	F-value	P-value
ESWT group	n=12	0.58±0.67	1.45±0.79	2.51±1.08	3.87±1.02	20.455	<0.001
PRP group	n=12	0.67±0.78	1.71±0.89	2.42±1.17	3.42±1.14	18.44	<0.001
ESWT+PRP group	n=12	0.64±0.49	2.03±0.49	3.17±0.72	4.67±0.89	40.069	<0.001
F-value		0.064	3.667	4.695	5.981		
P-value		0.938	0.036	0.023	0.006		

ESWT: Extracorporeal shock wave therapy, PRP: Platelet-rich plasma

Table 3: Radiographic scores of fracture lines at different time points before and after treatment in three patient groups. ($\bar{X} \pm S$, score)

Group	Sample size(case)	Before Treatment	Three months of treatment	Six months of treatment	Nine months of treatment	F-value	*P*-value
ESWT group	n=12	0.67±0.49	1.42±0.79	1.92±1.04	2.58±0.79	30.24	<0.001
PRP group	n=12	0.83±0.58	1.5±0.81	2.08±0.79	2.67±0.49	29.062	<0.001
ESWT+PRP group	n=12	0.75±0.62	2.17±0.39	2.92±0.52	4.08±0.29	89.786	<0.001
F-value		0.26	4.294	5.478	26.802		
P-value		0.773	0.022	0.009	<0.001		

ESWT: Extracorporeal shock wave therapy, PRP: Platelet-rich Plasma

employed a pairwise comparison approach to assess the impact of different intervention measures on the healing of fractures in patients over time. Compared to pre-intervention, all pairwise comparisons resulted in $P < 0.05$. Before treatment, there were no statistically significant differences in the bone callus and fracture line radiographic scores among the three groups ($P > 0.05$). However, after 3, 6, and 9 months of treatment, the differences in the bone callus and fracture line radiographic scores were statistically significant compared to pre-treatment ($P < 0.05$). As the treatment duration increased, the bone callus and fracture line radiographic scores gradually increased in all three groups ($P < 0.05$). At 3, 6, and 9 months after treatment, the ESWT combined with the PRP group demonstrated significantly higher scores in all three assessments compared to the single ESWT group and PRP group, and these differences were statistically significant ($P < 0.05$).

As an example, we present a patient that suffered a right tibia and fibula fracture due to a traffic accident. After 10 months, the patient presented to our hospital with a diagnosis of non-union of the right tibia. During this period, the patient underwent radial pressure waves and PRP combined treatment (Figs. 1 to 4).

Discussion

There are currently various treatment methods available for the treatment of non-union fractures. However, existing treatment approaches often come with a range of side effects, such as increased treatment costs and an elevated risk of post-operative complications. Therefore, this study adopts a combined application of ESWT and PRP to investigate the therapeutic effects of their joint application in patients with non-union fractures.

ESWT, as a non-invasive treatment modality, delivers a series of focused shockwave or radial pressure pulses to specific target areas through an appropriate generator, inducing biological and physiological effects in the tissues and cells of the target region. Possible mechanisms of action for ESWT include pressure effects generated by the propagation through tissues of varying densities; tension generated leading to the formation and rapid expansion and rupture of microbubbles in local body tissues, creating cavitation effects; effects of high-density tissue disruption; activation of metabolic processes within the body; induction of microfractures to stimulate the release of bone growth factors, among others [8, 9, 10]. Research by Willems et al. [11] demonstrated a healing rate of 73% in patients with non-union fractures treated with ESWT, similar to the observed healing rate in patients undergoing surgical treatment. These favorable characteristics establish shockwave therapy as a frontline treatment for delayed and non-healing fractures.

PRP is a biologically active component obtained by concentrating platelets through centrifugation, with platelet content higher than that in serum. PRP contains alpha granules, which play a crucial role in tissue healing by releasing numerous growth factors and transforming factors, including transforming growth factor-β, vascular endothelial growth factor, and platelet-derived growth factor [12]. PRP exhibits anti-inflammatory, chemotactic, and anti-apoptotic effects, inducing cell migration, promoting proliferation and differentiation, and altering the microenvironment of damaged sites. It possesses significant regenerative potential and has been widely used in orthopedic injuries and related conditions in recent years [13, 14]. A meta-analysis by Li et al. [15] indicated that in patients treated with PRP injection for delayed healing and non-union of long bones, 85.8% showed bone consolidation after treatment. The PRP group had a higher healing rate than the control group, and the average bone healing time was also shortened.

The above two treatment modalities both belong to minimally invasive and non-invasive cutting-edge regenerative medical technologies, showing precise therapeutic effects. The combination of both in this study was found to enhance the treatment outcomes. Seabaugh et al. [16] found that applying ESWT after PRP treatment can stimulate platelets to release various growth factors on reaching the injured area, promoting the tissue healing process. Based on this, the present study used musculoskeletal ultrasound for precise determination of the fracture end positions, facilitating PRP injection and ESWT treatment at the fracture ends. Ultrasound assessment of fracture healing is non-invasive, ionizing radiation-free, and real-time [17]. Sun et al. [18] demonstrated that the accuracy of ultrasound in diagnosing fracture healing in long tubular bone fractures treated with shock wave therapy could reach 95.5%, with sensitivity of 91.7% and specificity of 100.0%. It is an effective method for pre-operative assessment, intraoperative positioning, and post-operative follow-up. In this study, patients treated with ESWT combined with PRP under musculoskeletal ultrasound guidance showed higher scores for bone callus and fracture lines than the ESWT group and PRP group. Follow-up ultrasound revealed a significant reduction in the maximum distance between the fracture ends. During the process, we also observed

variable numbers of dot or streak-shaped blood flow signals and the formation of bone callus images within the fracture ends. The combination treatment shortened the treatment cycle for patients and improved the healing rate. Therefore, in this study, we believe that the combination of ESWT and PRP under ultrasound guidance has unique therapeutic efficacy in patients with non-union fractures and may become an important alternative therapy in the future. This study, however, also has some limitations. First, the sample size is relatively small, and second, long-term follow-up was not conducted, thus potentially introducing errors.

Conclusion

ESWT, PRP, and the combined treatment of ESWT + PRP can effectively improve fracture healing in patients with non-union fractures in the limbs. The combined use of these two treatment modalities shows more significant efficacy compared to the singular use of ESWT or PRP alone. ESWT and PRP have become attractive options for the treatment of non-healing fractures, with ESWT combined with PRP emerging as a promising alternative for non-union treatment.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflicts of Interest: Nil. **Source of Support:** None.

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