

## Original Research Article

# Effectiveness and safety of an ultrasound-guided injection of platelet-rich plasma versus sodium hyaluronate in patients with knee osteoarthritis

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### Abstract

**Purpose:** To examine the effectiveness and safety of ultrasound-guided platelet-rich plasma (PRP) injection versus sodium hyaluronate injection in patients with knee osteoarthritis (KOA).

**Methods:** The clinical data of 92 patients treated at the West China Hospital Sichuan University-Ziyang Hospital between May 2020 and December 2021 were retrospectively analyzed. Patients were allocated to PRP group (ultrasound-guided PRP injection) and a hyaluronic acid (HA) group (sodium hyaluronate injection) with each group containing 46 patients. Before and after treatment, the two groups were compared in terms of visual analog scale (VAS) score, Lysholm score, levels of serum inflammatory factors, insulin-like growth factor (IGF)-1, fibroblast growth factor (FGF)-2 and WOMAC score.

**Results:** After treatment, PRP group exhibited significantly lower pain scores and higher function scores than HA group. Furthermore, PRP group exhibited lower levels of inflammation markers, higher levels of growth factors as well as better treatment efficiency and incidence of adverse reactions when compared with HA group ( $p < 0.05$ ).

**Conclusion:** Ultrasound-guided PRP therapy ameliorates pains and joint functions in KOA patients. The therapeutic effect may be associated with the regulation of cartilage performance and alleviation of inflammatory state. Therefore, PRP injection therapy combined with ultrasound guidance might also have clinical potential for other applications.

**Keywords:** Knee osteoarthritis, Ultrasound guidance, Platelet-rich plasma, Injection therapy, Therapeutic effect, Pain level, Joint function

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## INTRODUCTION

Knee osteoarthritis (KOA) refers to a common chronic illness in orthopedics, which affects middle-aged and elderly individuals, with typical clinical symptoms including joint pain, swelling and limited movement. The exact pathogenesis

of KOA is not fully understood, but factors such as advanced age, knee overload, trauma and excessive exercise may contribute to its development. As the population ages in many countries, including China, the incidence of KOA is increasing and its treatment is becoming more challenging [1].

Research has shown that early lesions in KOA patients manifest mainly as cartilage degeneration and destruction, followed by subchondral bone damage, complete loss of articular cartilage, aseptic inflammation, or osteophytes [2]. Long-term follow-up studies indicate that although KOA progresses slowly, the patient's condition tends to worsen over time. Patients with advanced KOA may experience difficulty standing after squatting, increased pain, limited mobility and limping, all of which significantly affected their quality of life. Furthermore, KOA has been linked to several cardiovascular diseases [3].

Patients with KOA often require aggressive treatment due to severe pain and limited physical activity. Conservative treatments such as joint heat, massage and oral medications are used to relieve pain and slow disease progression in mild to moderate cases, while more aggressive interventions may be necessary in severe cases [4]. In recent years, ultrasound-guided joint injection therapy has been developed as a treatment option for KOA. This therapy involves injecting specific drugs into the patient's joints under ultrasound guidance, which has been shown to effectively relieve pain and stiffness symptoms associated with KOA [5]. As a new type of drug, platelet-rich plasma (PRP) promotes tissue repair and analgesia by using a patient's own platelet concentrate obtained by centrifuging autologous whole blood. PRP is currently used to treat soft tissue pain and tendon disorders.

This research was initiated to assess the effectiveness and safety of ultrasound-guided injection therapy in KOA patients.

## METHOD

### General data

Ninety-two KOA patients who were admitted to West China Hospital Sichuan University-Ziyang Hospital, The First People's Hospital of Ziyang between May 2020 and December 2021 were retrospectively chosen as study subjects. They were allocated into two groups: PRP group (n = 46), which received ultrasound-guided PRP injections, and HA group (n = 46), which received ultrasound-guided sodium hyaluronate injections. Every procedure was implemented based on the approval of the Ethics Committee of West China Hospital Sichuan University-Ziyang Hospital, the First People's Hospital of Ziyang (approval no. 2023-230) and followed the guidelines of Declaration of Helsinki [6].

### Inclusion criteria

Patients who were diagnosed as KOA in accordance with the Osteoarthritis Treatment Guidelines [7], patients who had a knee X-ray (K-L) grading of I to III [8], patients aged between 40 and 75 years, and patients who had not received any osteoarthritis-related treatment in the three months before admission.

### Exclusion criteria

Patients with other osteoarthritic diseases, patients with a history of severe knee trauma, patients who had used anti-inflammatory drugs within one week before treatment, patients with severe mental illness, patients with liver dysfunction, and those who were allergic to the studied drugs.

### Treatments

The HA group received ultrasound-guided injections of sodium hyaluronate (Meiji Seika Pharma Co. Ltd, specification: 2.5 mL-bottle, State Drug Administration J20171041). The patients were seated with knee flexion of 90°. Ultrasound was used to detect the presence and location of fluid in the joint cavity and the medial and lateral knee areas of the affected limb were used as puncture points. After disinfecting the puncture points, lidocaine was injected into the joint cavity. If fluid was present, 2.5 mL of sodium hyaluronate was injected once a week for four weeks after retracting the fluid. The PRP group was injected with ultrasound-guided PRP injections into the joint cavity using the same method. The PRP preparation procedure was as follows: venous blood was extracted from the elbow using a 10 mL syringe (9 mL x 4 tubes) and centrifuged for 10 min under aseptic conditions (centrifugal radius: 15 cm, centrifugal rate: 1500 pm).

The whole blood was separated into three layers, and after the lower layer of cells was discharged, 2.0 - 2.5 mL of the remaining intermediate tissue was taken to obtain PRP (approximately 8 - 10 mL of PRP may be prepared from about 36 mL of whole blood). Under ultrasound guidance, the patient received a unilateral intra-articular injection of 4 - 5 mL autologous PRP and if the patient could tolerate it, the patient was asked to move passively 5 - 8 times to make the PRP diffuse fully. The puncture site was kept clean in all patients after treatment and water was avoided to prevent infection. Strenuous exercise was also avoided.

**Indices evaluated**

The study compared and observed various indicators before and after treatment in the groups. The Visual Analogue Scale (VAS) [9] was utilized for the assessment of pain levels, with patients choosing appropriate points on a 10 cm scale. Pain scores ranged from 0 - 10, with 2 or less referring to negligible pain, 3 - 4 referring to mild pain, 5 - 7 referring to moderate pain and 8 or more referring to severe pain. The Lysholm scale [10] was employed to evaluate knee function in eight areas. The scores ranged 0 - 100, with a higher score referring to better knee function. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score [11] assessed the severity of pain, stiffness and joint function. The scores ranged 0 - 96, with higher scores indicating more severe symptoms. Enzyme-linked immunosorbent assay was used to detect TNF- $\alpha$ , IL-1 $\beta$ , insulin-like growth factor (IGF)-1 and fibroblast growth factor (FGF)-2 levels in a 5 mL blood sample collected before and after treatment. The efficiency of treatment was determined by symptom relief. Markedly effective treatment resulted in complete disappearance of symptoms, with no pain, swelling, or restricted activity; Effective treatment partially relieved symptoms, with no pain or substantial reduction in swelling and slightly restricted activity; Ineffective treatment resulted in no relief or worsening of symptoms, with severe pain and inability to move. Treatment efficiency was computed using Eq 1.

$$E = ((ME+EC)/TC)100 \dots\dots\dots (1)$$

where E = Efficiency; ME = Markedly effective; EC = Effective cases; TC = Total cases. The incidence of adverse reactions such as increased pain, knee swelling, itching at the injection site and fever, was compared between the HA and PRP groups.

**Statistical analysis**

All data was processed and analyzed utilizing Statistical Package for the Social Sciences

(SPSS) 24.0 (IBM, Armonk, NY, USA). A two-sided test was conducted, with a *p*-value < 0.05 denoting statistical significance. For quantitative data, normality was tested utilizing the Kolmogorov-Smirnov test. A variance test or t-test was used in indicators with normal distribution, with results expressed as mean  $\pm$  standard deviation (SD). Kruskal-Wallis rank sum test was employed in indicators without normal distribution and results are expressed using the median and quartiles. The chi-square test was used for comparison of qualitative data between the groups.

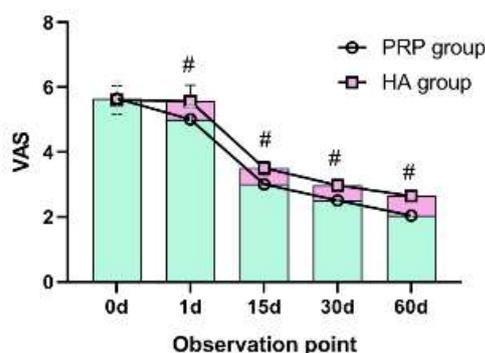
**RESULTS**

**Baseline information**

The baseline information including gender, age, BMI, K-L classification and side of the affected knee in the two groups showed no significant differences between the two groups (*p* > 0.05; Table 1).

**VAS scores**

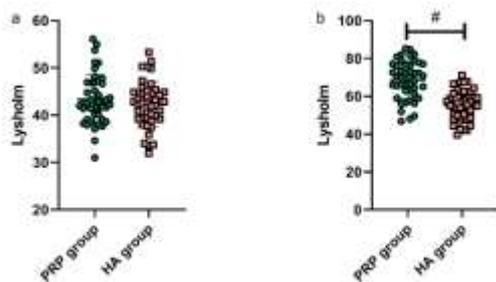
Both groups exhibited no significant differences in VAS scores before treatment (*p* > 0.05; Figure 1). The PRP group had decreased VAS scores at the first day of treatment and exhibited lower VAS scores than the HA group (*p* < 0.05).



**Figure 1:** Analysis of changes in VAS scores before and after treatment. #*P* < 0.05 vs HA group

**Table 1:** Comparison of general information between the two groups (n=46)

General information		PRP group	HA group	t <sup>2</sup> $\chi$	P-value
Gender	Male	15	18	0.425	0.514
	Female	31	28		
Age (years)		59.01 $\pm$ 5.99	60.38 $\pm$ 7.23	0.990	0.325
BMI (kg/m <sup>2</sup> )		21.38 $\pm$ 2.29	21.32 $\pm$ 1.81	0.139	0.890
Duration of disease (year)		4.05 $\pm$ 1.02	4.33 $\pm$ 1.12	1.254	0.213
K-L classification (Grade)	I	15	14	0.067	0.967
	II	15	16		
	III	16	16		



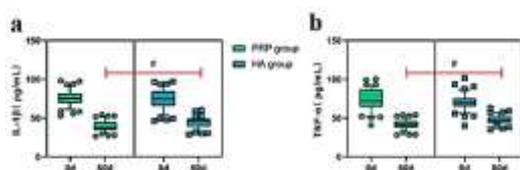
**Figure 2:** Comparison of Lysholm scores between the two groups. (a) Before treatment (b) group after 2 months of treatment. # $P < 0.05$  vs HA group

**Lysholm scores**

Both groups exhibited no statistically significant differences in the Lysholm scores before treatment ( $p > 0.05$ ). At 2 months after treatment, both groups exhibited markedly higher Lysholm scores than those before treatment ( $p < 0.05$ ; Figure 2).

**Serum inflammatory factor levels**

Both groups exhibited no statistically significant difference in IL-1 $\beta$  and TNF- $\alpha$  levels before treatment ( $p > 0.05$ ). However, both groups exhibited improved inflammatory status after treatment and had lower levels of IL-1 $\beta$  and TNF- $\alpha$  than those before treatment ( $p < 0.05$ ). In addition, the levels of both IL-1 $\beta$  and TNF- $\alpha$  were lower in the PRP group than in the HA group at 60 days after treatment ( $p < 0.05$ ); Figure 3).



**Figure 3:** Analysis of changes in the levels of serum inflammatory factors before and after treatment. (a) IL-1 $\beta$  and (b) TNF- $\alpha$  before treatment # $P < 0.05$  vs the HA group

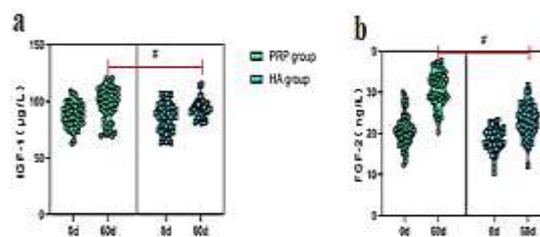
**Growth factor levels**

Before treatment, both groups exhibited no significant differences in serum IGF-1 and FGF-2

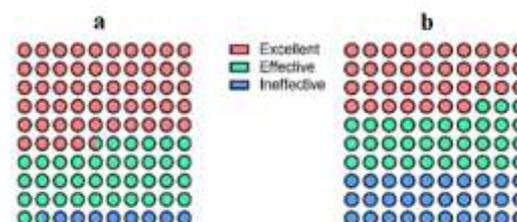
levels ( $p > 0.05$ ). After treatment, IGF-1 and FGF-2 levels were elevated in both groups ( $p < 0.05$ ) and were much higher in the PRP group ( $p < 0.05$ ; Figure 4).

**Treatment efficacy**

The PRP group (91.31 %) exhibited higher treatment efficiency than HA group (69.57 %), showing significant differences ( $p < 0.05$ ), see Table 2 and Figure 5.



**Figure 4:** Changes in IGF-1 and FGF-2 levels before and after treatment. (a) IGF-1 and (b) FGF-2 levels in the two groups before treatment ( $p > 0.05$ ), and the IGF-1 and FGF-2 levels in the PRP group were higher than those in the HA group after treatment # $P < 0.05$  vs the HA group



**Figure 5:** Comparison of treatment efficiency between the two groups. The treatment efficiency of the PRP group was 91.31% (a), which was higher than that of the HA group (69.57 %) (b), showing statistically significant difference ( $p < 0.05$ ).

**WOMAC scores of patients**

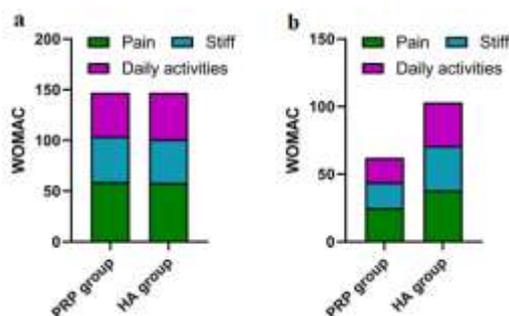
Both groups exhibited no statistically differences in WOMAC scores before treatment ( $p > 0.05$ ). The PRP group had significantly lower WOMAC score in each dimension and total scores than the HA group after treatment ( $p < 0.05$ ) (Figure 6).

**Table 2:** Comparison of treatment efficiency between two groups of patients [n (%)]

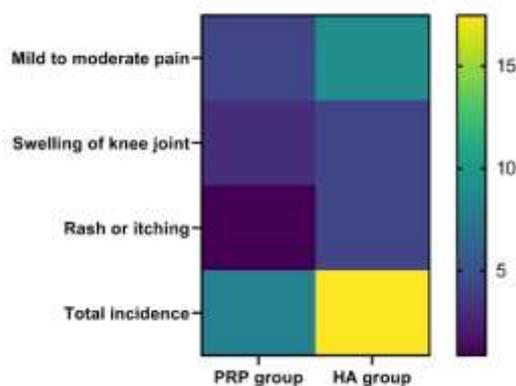
Group	Number of patients	Markedly effective	Effective	Ineffective	Effective rate
PRP	46	25 (54.35)	17 (36.96)	4 (8.69)	42 (91.31)
HA	46	17 (36.96)	15 (32.61)	14 (30.43)	32 (69.57)
$\chi^2$	-	-	-	--	6.901
$P$ -value	-	-	--	--	0.008

## Incidence of adverse reactions

In the PRP group, patients (46) had a total of 233 injections, of which 10 (4.29 %) had mild to moderate knee swelling, 7 (3.00 %) had knee swelling and 2 (0.86 %) had injection site rash or itching. Forty-six (46) cases in the HA group underwent a total of 235 injections, of which 21 (8.94 %) had mild to moderate knee swelling, 10 (4.26 %) had knee swelling, and 2 (0.86 %) had injection site rash or itching. The PRP group had lower incidence of adverse reactions than the HA group ( $\chi^2 = 9.039$ ,  $p = 0.003$ ; Figure 7).



**Figure 6:** Comparison of WOMAC scores between the two groups. There was no statistically significant difference between the two groups (a) before treatment in WOMAC scores ( $p > 0.05$ ), and (b) after treatment



**Figure 7:** Comparison of the incidence of adverse reactions between the two groups.  $P$ -value = 0.003 versus HA group

## DISCUSSION

Knee osteoarthritis is a degenerative disease primarily influencing middle-aged and elderly people, which is characterized by degeneration of knee cartilage tissue and bone hyperplasia, resulting in joint swelling, pain, and limited mobility [12]. The disease's pathogenesis is complex and the knee's cartilage tissue plays a vital role in its course. When overloaded, traumatized, or strained, knee cartilage tissue

becomes damaged and prone to degeneration and loss, which affects the knee joint's function [13]. The current treatment for KOA aims to delay cartilage tissue degeneration and supplement symptomatic treatment with analgesics and anti-inflammatory drugs. Although intra-articular injection is currently a commonly used treatment, there are still discussions on the injection of drugs. Researchers are exploring more scientific, safer and more effective intra-articular injection methods and drugs remain the primary direction of KOA research [14].

PRP injection on knee joint function and inflammatory factors in KOA patients. The result indicated that both groups showed significantly higher knee function scores and lower VAS scores after treatment. However, patients treated with PRP injection had higher knee function scores and lower VAS scores compared to sodium glass injection, indicating that PRP injection significantly improves knee function and reduces pain in patients. PRP provided meaningful pain reduction and functional improvement for up to six months without the risk of serious adverse reactions and complications. The greatest advantage of PRP over other drugs is that it is an autologous substance. Therefore, PRP increased joint fluid viscosity and joint cavity lubrication. After injection, PRP alleviated the frictional forces generated during bone and joint activities, increased cushioning during joint activities, weakened joint stress, and promoted joint function recovery and pain reduction in patients. The study confirmed that after treatment, both groups exhibited significantly lower serum TNF- $\alpha$  and IL-1 $\beta$  levels compared with pre-treatment levels.

Patients treated with PRP injection had greater reductions in serum levels of inflammatory factors than those treated with sodium glacial injection. Both groups showed reduced WOMAC scores after treatment, with greater reductions in patients treated with PRP injection. Tumour necrosis factor-alpha (TNF- $\alpha$ ) and IL-1 $\beta$  are pro-inflammatory cytokines. While TNF- $\alpha$  decreases the rate of proteoglycan production in the knee joint and induces cartilage degeneration, IL-1 $\beta$  has strong pro-inflammatory activity and also induces the expression of pro-inflammatory mediators, thus exacerbating the immune response. Interleukin-1 beta (IL-1 $\beta$ ) also induces the secretion of degradative proteases in synovium and cartilage, thereby accelerating the breakdown of cartilage matrix [15].

The analysis showed that PRP contains a high concentration of autologous antibodies which may be directly injected into the patient's joint

cavity, participating in the immune response and inhibiting the production of inflammatory cells, thus improving the body's inflammatory response. This may be one of the essential reasons why the pain intensity in the PRP group were lower than those in the HA group after treatment [16]. It has been noted that PRP contains a high concentration of active growth factors, which stimulate the differentiation and proliferation of chondrocytes and promote cartilage matrix synthesis [17].

The study group had higher levels of IGF-1 and FGF-2 after treatment than the control group. As previously mentioned, cartilage damage is a significant cause of KOA. The addition of PRP alleviates or even improves cartilage damage, which positively impacts the acceleration of patients' recovery [18]. In this study, it was found that ultrasound-guided PRP injection improves patients' clinical symptoms by inhibiting inflammatory reactions, accelerating cartilage matrix synthesis and reducing pain levels. These effects ultimately improved the treatment outcome.

### Limitations of this study

This study has some limitations. The number of patients were few and treatment duration was short.

## CONCLUSION

The findings of this study demonstrate that ultrasound-guided PRP injection is an effective intervention for patients with KOA. It significantly improves pain symptoms and joint function during follow-up. This improvement may be due to the ability of PRP to alleviate the patient's inflammatory state and regulate cartilage performance. Therefore, ultrasound-guided PRP injection has a potential as a therapeutic intervention for KOA.

## DECLARATIONS

### Acknowledgements

None provided.

### Funding

None provided.

### Ethical approval

The study was approved by the Ethics Committee of West China Hospital Sichuan

University-Ziyang Hospital, the First People's Hospital of Ziyang, China (approval no. 2023-230).

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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