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Observation on the Clinical Efficacy of Platelet-rich Plasma Combined with Intra-articular Injection of Sodium Hyaluronate in the Treatment of Mild to Moderate Knee Osteoarthritis

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Abstract: *Objective*: To explore the clinical efficacy of platelet-rich plasma (PRP) combined with intra-articular injection of sodium hyaluronate in the treatment of mild to moderate knee osteoarthritis (KOA) and its effects on cartilage metabolism, oxidative stress status and cartilage structure. *Methods*: A total of 120 patients diagnosed with mild to moderate KOA in the orthopedics department of the hospital from January 2023 to October 2024 were selected and randomly divided into a control group and a study group, with 60 cases in each group. The control group was treated with intra-articular injection of sodium hyaluronate, while the study group was treated with PRP in combination on this basis. The treatment course was 4 weeks. The clinical efficacy, serum matrix metalloproteinase-13 (MMP-13), type II collagen degradation products (CTX-II), superoxide dismutase (SOD), malondialdehyde (MDA) levels and MRI-T2 mapping results of the two groups after 12 months of treatment were compared. *Result*: The total effective rate of the study group was 91.67%, which was higher than 75.00% of the control group ($p < 0.05$). After 12 months of treatment, the levels of serum MMP-13, CTX-II and MDA in the study group were all lower than those in the control group, and the level of SOD was higher than that in the control group ($p < 0.01$). MRI-T2 mapping showed that the average T2 value of cartilage in the study group was significantly lower than that in the control group, while the cartilage thickness increased significantly ($p < 0.05$). No serious adverse reactions occurred in either group. *Conclusion*: Intra-articular injection of PRP combined with sodium hyaluronate can significantly relieve pain in patients with KOA, improve joint function, inhibit cartilage degradation, reduce oxidative stress levels and promote cartilage repair. Its therapeutic effect is superior to that of sodium hyaluronate alone, and it has good safety.

Keywords: Platelet-rich plasma; Sodium hyaluronate; Knee osteoarthritis; Oxidative stress; MRI-T2 mapping; Cartilage metabolism

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1. Introduction

Knee osteoarthritis (KOA) is a chronic degenerative disease characterized mainly by degeneration of articular

cartilage and osteophyte formation. It is mainly manifested as knee pain, stiffness and limited mobility, which seriously affects the quality of life and mobility of patients [1]. Epidemiological studies have shown that approximately 10% to 20% of middle-aged and elderly people have KOA lesions to varying degrees, and the incidence rate increases significantly with age [2]. Common conservative treatment measures include oral non-steroidal anti-inflammatory drugs, functional exercises, and intra-articular injection of sodium hyaluronate, etc. However, their efficacy is limited, and some patients still experience recurrent joint pain and persistent cartilage degeneration after long-term use [3]. Platelet-rich plasma (PRP) is a high-concentration platelet-rich plasma prepared by centrifugation and concentration of autologous blood. It is rich in various active components such as platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) It can exert tissue repair and anti-degenerative effects by promoting chondrocyte proliferation, inhibiting inflammatory responses and improving local microcirculation [4]. At present, there are relatively few clinical studies on the combined application of PRP and sodium hyaluronate. This article explored its impact on patients with mild to moderate KOA.

2. Materials and methods

2.1. General information

A total of 120 patients with mild to moderate KOA who were diagnosed in the orthopedic outpatient department or inpatient department of the hospital from January 2023 to October 2024 were selected. Follow up for one year. The patients were divided into the control group and the study group, with 60 cases in each group, by the random number table method. In the control group, there were 26 males and 34 females. There were 25 male cases and 35 female cases in the research group.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

All patients met the diagnostic criteria of the "Guidelines for the Diagnosis and Non-surgical Treatment of Early Knee Osteoarthritis (2024 Edition)" [5]. It was confirmed as K-L grade I - II by imaging examination (X-ray or MRI). Knee pain for ≥ 3 months, significantly aggravated after activity; No glucocorticoids or other intra-articular injection drugs have been used in the past month. No blood system diseases or severe heart, liver or kidney function disorders; Sign the informed consent form and voluntarily accept treatment.

2.2.2. Exclusion criteria

Combined with rheumatoid arthritis, gouty arthritis or other types of joint lesions; Combined with suppurative arthritis, tuberculous arthritis or intra-articular infection; A history of severe deformity or traumatic fracture of the knee joint; Those with abnormal coagulation function or using anticoagulant drugs; Pregnant or lactating women.

2.3. Methods

The control group was treated with intra-articular injection of sodium hyaluronate injection. The patient was placed in a supine position with the knee joint flexed to approximately 30 degrees. After routine skin disinfection and laying a towel, the puncture point was selected at the outer upper edge of the patella, and a 22 G puncture needle was inserted into the knee joint cavity. After drawing out a small amount of synovial fluid and confirming its insertion into the cavity, inject 2 mL (25 mg) of sodium hyaluronate once a week for a total of 4 times.

The research group was treated with autologous PRP injection on the basis of the control group. 20 mL of elbow venous blood was collected from the patient and placed in a sterile anticoagulant tube. After centrifugation twice (the first time at 1800 r/min × 10 min, and the second time at 3500 r/min × 10 min), approximately 3 mL of platelet-rich plasma was taken from the middle layer for later use. Before injection, 2 mL of sodium hyaluronate and 3 mL of PRP are thoroughly mixed and slowly injected into the knee joint cavity at the same injection point. After the injection, the patient was instructed to lie flat for 30 minutes and avoid weight-bearing activities for 24 hours. Both drugs are injected once a week for a total of four times.

2.4. Observation indicators

2.4.1. Therapeutic effect

All patients were followed up for one year. At 12 months of treatment, the Visual Analogue Scale (VAS) and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) were used for assessment.

(1) Cure

The VAS decreased by ≥ 70% compared to the baseline, and the total WOMAC score decreased by ≥ 60% compared to the baseline, accompanied by disappearance of knee swelling and normal movement.

(2) Improvement

Meeting any of the following conditions: a 30% to 69% decrease in VAS or a 20% to 59% decrease in WOMAC, with symptoms and activity levels improving compared to before

(3) Ineffective

VAS decreases by less than 30% and/or WOMAC decreases by less than 20%, or symptoms worsen. The total effective rate (%) is calculated as (cure + improvement)/total number of cases × 100%.

2.4.2. Cartilage metabolism markers

The levels of serum matrix metalloproteinase-13 (MMP-13) and type II collagen degradation products (CTX-II) were detected using ELISA. Tests were conducted before treatment and at 12 months of treatment respectively.

2.4.3. Regulatory indicators of oxidative stress

The levels of serum superoxide dismutase (SOD) and malondialdehyde (MDA) were detected, respectively before treatment and 12 months after treatment.

2.4.4. Quantitative assessment of MRI-T2 mapping

Knee joint MRI examination was performed. The T2 mapping technique was applied to quantify the changes in cartilage signals, and the thickness and T2 value of articular cartilage were measured. Tests were conducted before treatment and at 12 months of treatment respectively.

2.4.5. Adverse reactions

All patients were followed up for one year, and the occurrence of infection, bleeding, joint effusion, and pain at the injection site during the treatment period was statistically analyzed in detail.

3. Results

3.1. Comparison of clinical efficacy

The effective rate of treatment in the study group was higher than that in the control group ($p < 0.05$). As shown in **Table 1**.

Table 1. Comparison of clinical efficacy [n (%)]

Group	n	Cure	Improvement	Invalid	Total effective rate (%)
Control group	60	23 (38.33)	22 (36.67)	15 (25.00)	45 (75.00)
Research group	60	31 (51.67)	24 (40.00)	5 (8.33)	55 (91.67)
χ^2					6.000
p value					0.014

3.2. Comparison of cartilage metabolism markers

After 12 months of treatment, the levels of serum MMP-13 and CTX-II in the study group were lower than those in the control group, as shown in **Table 2**.

Table 2. Comparison of cartilage metabolic markers levels ($\bar{x} \pm s$)

Group	n	MMP-13 (pg/mL)		CTX-II (ng/mL)	
		Before treatment	The treatment lasted for 12 months	Before treatment	The treatment lasted for 12 months
Control group	60	145.08 ± 24.87	115.65 ± 19.76	7.79 ± 1.36	5.98 ± 1.18
Research group	60	146.52 ± 25.38	96.47 ± 18.32	7.83 ± 1.42	4.92 ± 1.10
χ^2		0.314	5.514	0.158	5.090
p value		0.754	0.000	0.875	0.000

3.3. Comparison of oxidative stress indicators

After 12 months of treatment, the SOD level in the study group was higher than that in the control group, while the MDA level was lower than that in the control group ($p < 0.05$). As shown in **Table 3**.

Table 3. Comparison of oxidative stress indicators ($\bar{x} \pm s$)

Group	n	SOD (U/mL)		MDA (nmol/mL)	
		Before treatment	The treatment lasted for 12 months	Before treatment	The treatment lasted for 12 months
Control group	60	78.92 ± 9.07	95.72 ± 9.61	5.29 ± 1.05	4.12 ± 0.91
Research group	60	79.34 ± 9.12	108.46 ± 10.58	5.38 ± 1.02	3.41 ± 0.83
χ^2		0.253	6.904	0.476	4.465
p value		0.801	0.000	0.635	0.000

3.4. Quantitative imaging results of MRI-T2 mapping

After 12 months of treatment, the average T2 value of cartilage in the study group was lower than that in the

control group, and the cartilage thickness was higher than that in the control group ($p < 0.05$). As shown in **Table 4**.

Table 4. Comparison of MRI-T2 mapping indicators ($\bar{x} \pm s$)

Group	n	SOD (U/mL)		MDA (nmol/mL)	
		Before treatment	The treatment lasted for 12 months	Before treatment	The treatment lasted for 12 months
Control group	60	46.10 ± 4.52	42.91 ± 4.08	2.45 ± 0.29	2.68 ± 0.33
Research group	60	46.32 ± 4.58	40.15 ± 3.94	2.47 ± 0.31	2.86 ± 0.34
χ^2		0.265	3.769	0.365	2.943
p value		0.792	0.000	0.716	0.004

3.5. Adverse reactions

No serious adverse events such as infection, bleeding or joint effusion occurred in either group. In the study group, there were 3 cases (5.00%) with mild acid and distension at the injection site, and in the control group, there were 2 cases (3.33%). The symptoms were all relieved within 24 hours. There was no statistically significant difference ($\chi^2 = 0.209$, $p > 0.05$).

4. Discussion

KOA is a degenerative disease driven by mechanical stress, inflammatory response and metabolic abnormalities. Its core pathological features are articular cartilage degradation, synovitis and subchondral osteosclerosis. Research indicates that inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) can promote the overexpression of matrix metalloproteinases (MMPs) by activating the nuclear factor-κB (NF-κB) signaling pathway, thereby accelerating the degradation of type II collagen and proteoglycans, and causing damage to cartilage structure and functional degeneration [6]. Sodium hyaluronate, as an injection material for viscoelastic joints, can lubricate the joints, reduce friction and improve the rheological properties of synovial fluid, thereby alleviating pain and delaying cartilage wear [7]. However, sodium hyaluronate alone has limited effects on cartilage regeneration and inflammation regulation. PRP is rich in various growth factors and cytokines, and can regulate the synovial environment and cartilage metabolism balance by stimulating chondrocyte proliferation, promoting type II collagen synthesis and inhibiting the release of inflammatory factors [8].

Sodium hyaluronate provides a favorable repair environment for PRP by improving the viscoelasticity of synovial fluid, reducing friction and lowering the stress within the joint. Therefore, the PRP combined with sodium hyaluronate regimen takes into account the dual effects of “mechanical buffering” and “biological repair”, making the recovery of joint function more comprehensive. In this study, after 12 months of treatment, the levels of MMP-13 and CTX-II in the study group were lower than those in the control group, suggesting that the combination of PRP and sodium hyaluronate has a better effect in inhibiting the degradation of cartilage matrix [9]. MMP-13 is a key enzyme for degrading type II collagen, and its high expression is closely related to the degeneration of KOA cartilage. CTX-II reflects the metabolic status of type II collagen. The growth factors released in PRP can down-regulate the expression of MMP-13 and reduce the degradation of type II collagen by regulating the local inflammatory microenvironment and inhibiting the continuous activation of the NF-κB signaling pathway [10]. Meanwhile, sodium hyaluronate works together to slow down the imbalance of cartilage

metabolism by improving the viscosity of the joint cavity, alleviating mechanical friction damage and reducing the stress response of chondrocytes. In recent years, many high-quality studies abroad have further verified the clinical and imaging advantages of PRP in the treatment of mild to moderate KOA. Yoshioka et al. conducted a randomized, double-blind, placebo-controlled clinical trial and found that leukocyte-rich platelet-rich plasma (LP-PRP) used in patients with mild to moderate KOA accompanied by joint effusion or bone marrow lesions could significantly improve pain and joint function, and its efficacy was better than that of the control group, suggesting that PRP has good adaptability in various pathological conditions [11]. Aalishan et al. found based on MRI quantitative analysis that after intra-articular injection of autologous PRP in patients with moderate KOA, the T2 value of cartilage significantly decreased, and the joint pain and functional scores improved [12]. This suggests that PRP can effectively improve the hydration state of cartilage and the arrangement of collagen fibers, promoting cartilage repair, which is consistent with the MMRI T2 mapping results of this study. Favian et al. reported that after LP-PRP treatment for mild to moderate KOA, the values of cartilage T1ρ and T2 in patients decreased, and both WOMAC and VAS scores improved significantly, indicating that PRP can bring continuous benefits in both imaging and subjective outcomes [13]. The experimental study by Prathap et al. demonstrated that leukocyte-rich PRP (LR-PRP) has a more significant anti-inflammatory effect compared to leukocyte-poor PRP, and can inhibit the release of inflammatory mediators, indicating that the proportion of internal components of PRP may affect the difference in its therapeutic effect [14]. Furthermore, Elena et al. pointed out in a follow-up analysis that PRP combined with high tibial osteotomy for the treatment of patients with severe KOA can further improve joint stability and structural reconstruction, providing a new idea for the combined application [15].

The results of this study show that after 12 months of treatment, the SOD level in the study group increased and the MDA level decreased, indicating that PRP combined with sodium hyaluronate can effectively alleviate oxidative stress damage. Oxidative stress is one of the important mechanisms for the chronic progression of KOA. Excessive production of reactive oxygen species can induce chondrocyte apoptosis and promote inflammatory cascade reactions [16]. PRP can enhance the activity of antioxidant enzymes, eliminate free radicals, and alleviate lipid peroxidation reactions in cell membranes, thereby improving the microenvironment of cartilage [17]. Meanwhile, sodium hyaluronate has the ability to eliminate oxygen free radicals. When used in combination, it can further enhance the antioxidant effect. The MRI-T2 mapping results showed that after 12 months of treatment, the T2 value in the study group decreased significantly and the cartilage thickness increased, suggesting that the cartilage structure was repaired at an early stage. The T2 value mainly reflects the hydration of cartilage and the arrangement of collagen. A decrease indicates that the collagen fiber structure within the cartilage tissue becomes more complete and the water content returns to normal. PRP promotes the synthesis of type II collagen by chondrocytes, and sodium hyaluronate improves lubrication and nutrient supply. The synergy of the two can alleviate microdamage between cartilage layers and promote matrix reconstruction [18,19]. PRP is derived from autologous blood and has no risk of immune rejection or transmission, so its safety is relatively good [20].

5. Conclusion

In conclusion, the intra-articular injection of PRP combined with sodium hyaluronate can significantly relieve pain in patients with KOA, improve joint function, inhibit cartilage degradation, reduce oxidative stress levels and promote cartilage repair. Its therapeutic effect is superior to that of sodium hyaluronate alone, and it has good safety.

Disclosure statement

The author declares no conflict of interest.

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