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Original Article

Platelet-rich plasma therapy in refractory knee osteoarthritis combined with infection

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Abstract: Objective: To clarify the clinical efficacy of platelet-rich plasma (PRP) in the treatment of patients with refractory knee osteoarthritis (KOA) combined with infection. Methods: Between June 2014 and June 2016, 60 refractory KOA patients with infection (non-pyogenic infection) admitted to Ningbo NO.6 Hospital were recruited in this study. The patients were randomly assigned to receive either PRP plus antibiotics (A group, n=30) or sodium hyaluronate and antibiotics (B group, n=30). The Visual Analogue Scale (VAS) and Lysholm Knee Scale scores of the patients in both groups were documented and compared before treatment, at 1 mon and 3 mon after treatment, respectively. Under the guidance of B ultrasound, synovial fluid was drawn from the articular cavity of each patient in both groups before and after treatment for detection of the proportions of white blood cells in synovial fluid; venous blood was also drawn from each patient before and after treatment for measurement of C-reactive protein (CRP); finally, the treatment of KOA with infection were assessed. Results: One month after treatment, the VAS scores of patients in both A group and B group were decreased, with more significant decrease in A group; the Lysholm knee scores were increased, with more remarkable increase in A group; infection was under control in both groups; the proportions of white blood cells in synovial fluid and the CRP levels in venous blood were reduced, with marked reductions in A group (both $P<0.05$). Three months after treatment, the VAS scores of patients remained a decreasing trend in both groups, with a slighter rise in B group and a more significant drop in A group than those at 1 month; the Lysholm knee score was decreased in B group, contrary to a remarkable increase in A group; the infection symptoms of patients in both groups were alleviated substantially when compared with those before treatment; the proportions of white blood cells in synovial fluid and the CRP levels in venous blood of patients were increased in B group versus those at 1 month, in contrast to a striking decrease in A group (all $P<0.05$). Conclusion: PRP was effective in the treatment of refractory KOA with infection. The long-term outcomes are better with longer duration of treatment.

Keywords: Osteoarthritis of the knee, platelet-rich plasma, injection of the articular cavity

Introduction

Knee Osteoarthritis (KOA) is a degenerative disease of the knee for which degeneration of cartilage in the knee joint causes structural disorder associated with subchondral bone osteophytes and gonarthromeningitis which leads to destruction or even deformity of the knee joint, ultimately to joint dysfunction [1]. KOA is one of the main causes of knee pain and dysfunction in the middle-aged and elderly population [2, 3]. Infection is a common comorbidity in the development of KOA [4, 5]. KOA patients with infection account for 8 to 27% of the KOA patients who visit the clinic for joint pain treatment, and KOA with infection brings greater challenges to the treatment [5].

In recent years, there are a variety of methods for treating KOA with infection. Nevertheless, all of the methods are symptomatic treatment, only aiming to alleviate pain and dysfunction of patients. Their long-term efficacy is poor, unable to prevent or delay the procession of joint degeneration [4-8]. Platelet-rich plasma (PRP) is a platelet concentrate prepared by isolating autologous whole blood, rich in a sea of growth factors. Additionally, multiple studies have shown an essential role of growth factors in the natural repair of bone and potent osteogenesis and anti-infection of PRP [9-11]. PRP has drawn increasing attention from clinicians and experts. In this study, for the purpose of finding better treatment methods, we explored the therapeutic effect of PRP in refractory KOA patients with infection.

Materials and methods

Patients

This study was approved by the Medical Ethics Society, and the eligible patients were informed of the possible risks of treatment and alternative regimens in case of poor efficacy and provided written informed consent. Between June 2014 and June 2016, 60 patients with refractory KOA with acute or chronic infection admitted to Ningbo NO.6 Hospital were recruited in this study. Patients ranging in age from 55 to 75 years old were included if they met the diagnostic criteria for KOA (the pain or swelling in the knee joint of over 4 months and insignificantly resolved symptoms and pain in the knee joints after 3 months of conventional oral medication), concomitant infection (the symptoms of red and swelling heat pain in the joint, and elevated C-reactive protein (CRP) levels in the venous blood and up-regulated white blood cell count in synovial fluid), KOA of stage II and III [12, 13].

Exclusion criteria included KOA surgery; severe organ dysfunction in the heart, the lungs, the brain, the livers, the kidneys and other important organs; other disease involving in the knee, including rheumatoid arthritis and joint tumor; pyogenic infection of the knee joint (joint puncture with pyogenic secretion or systemic fever) and infection in other parts of the body, such as lung infection; previous intra-articular douching or injection therapy within 3 months before enrollment in this study; an allergy to the study drugs; ineligible patients with disease judged by other investigators, such as coagulation disorders and platelet disorders.

Randomization

A total of 60 patients were eligible for enrollment, including 43 males and 37 females. They were randomly assigned to receive either PRP plus antibiotic therapy (A group, n=30) or sodium hyaluronate added to antibiotic therapy (B group, n=30) [14].

Study treatment

A group: PRP was prepared firstly in the following procedure: a venous blood sample (20 mL) was drawn from each patient and put into an anticoagulant tube by an operator. The same operator prepared PRP (4 mL) with a PRP preparation package by means of the double-centrifugation technique, with the entire procedure performed in the sterile environment. Placed in a supine position, the patient had the knee joint bent at approximately 60-70°. The collateral joint space of the patellar ligaments was located under the guidance of B-ultrasound. After conventional sterilization and draping, a puncture was performed along the located site and 4 mL of PRP plus 1 mL (40,000 units) of gentamicin were injected into the knee articular cavity.

B group: The same procedure for drug injection was performed in the patients of B group, and the drugs injected were 4 mL of sodium hyaluronate and 1 mL of (40,000 units) gentamicin.

After drug injection, the affected knee joints of the patients in both groups were moved passively 20 times to allow the drugs fully distributing throughout the joints. The patients were instructed to conduct normal activities except for physically strenuous one. The treatment was conducted once a week for a cycle of 4 weeks.

Efficacy evaluation

Visual analogue scale: A horizontal line (10 cm) was drawn on a paper, with one end indicating 0 point and the other end 10 points. Each patient was instructed to mark the scores on the horizontal line according to their own pain, with higher score indicating more severe pain. The Visual Analogue Scale (VAS) scores were measured and documented before treatment, at 1 and 3 months after treatment, respectively.

Lysholm knee scale: The Lysholm Knee Scale, an internationally common knee scoring scale for evaluating the knee functions, is subdivided into eight subscales of pain, swelling, stair-climbing, limp, support, locking, instability and squatting (on a scale of 100 points, with lower score indicating worse function of the knee joint. The Lysholm knee scores of all the patients were measured and documented before treatment, at 1 month and 3 months after treatment, respectively.

CRP level in the venous blood: Significantly elevated CRP levels in the venous blood have been confirmed in KOA patients with infection

Table 1. Baseline characteristics of patients

Variable	Gender		Mean age (year)	Disease staging		Infection	
	Male	Female		II	III	Acute	Chronic
A group (n=30)	14	16	65.45±5.76	13	17	15	15
B group (n=30)	12	18	66.23±4.87	14	16	17	13
P	0.856		0.476	0.645		0.723	

Table 2. Comparison of evaluation indexes between the two groups

Variable	VAS score	Lysholm knee score	CRP (mg/L)	White blood cells count (*10^9/L)
A group	8.51±0.558	31.87±3.114	34.61±9.554	8.71±1.169
B group	8.8+0.547	30.6±4.067	34.91±9.155	8.84±1.286
P	0.865	0.574	0.265	0.431

Note: VAS, Visual Analogue Scale; CRP, C-reactive protein.

Table 3. Changes in the VAS and Lysholm scores after treatment

Variable	1 month after treatment		3 months after treatment	
	VAS score	Lysholm score	VAS score	Lysholm score
A group	4.25±0.573	65.33±5.984	3.39±0.401	76.8±5.943
B group	5.62±0.444	57±6.036	6.83±0.445	47.67±5.421
P	0.036	0.027	0.004	<0.001

Note: VAS, Visual Analogue Scale.

as compared with those of the KOA patients without infection [15]. Therefore, we selected CRP as a marker for determining the presence or absence of infections and the therapeutic effect of the patients. A venous blood sample (3 mL) was drawn by an operator from each patient before treatment, 1 and 3 months after treatment, respectively. The CRP level in the venous blood was measured by the same operator using the immunoturbidimetric assay, with normal reference values of less than 8.00 mg/L.

White blood cell count in synovial fluid: Synovial fluid (1 mL) was drawn from the articular cavity of each patient before treatment, 1 and 3 months after treatment under the guidance of B ultrasound, and the white blood cell count was detected under a microscope, with normal values lower than (0.2-0.7) *10^9/L.

Safety

Immediate alternative methods were adopted for infection control at the presence of symptom of pyogenic infection in the patients of either group, and the affected cases were considered as invalid. If severe adverse events (hepatic and renal injury) occurred during treatment, immediate discontinuation or other regimens (e.g. surgery) were performed and the affected cases were considered as invalid.

Statistical analysis

All the statistical data were analyzed with the use of the SPSS software, version 17.0, with the results of the analyses expressed as mean ± standard deviation. Between-group comparisons of measurement data at multiple time intervals were compared using the analysis of variance (ANOVA) with repeated measures and Bonferroni post hoc test; comparisons of measurement data at distinct time interval were analyzed with the use of univariate ANOVA. Count data were compared with the use of the chi-square test. A *P* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The demographic characteristics including gender, age, disease severity and disease staging were largely well balanced between A group and B group, as were the clinical characteristics of pain, knee function score and infection assessment before treatment (P>0.05, **Table 1**).

Evaluation indexes

The VAS scores, the Lysholm knee scores, the CRP levels and white blood cell count in synovial fluid were basically similar between the two study groups before treatment (P>0.05, **Table 2**).

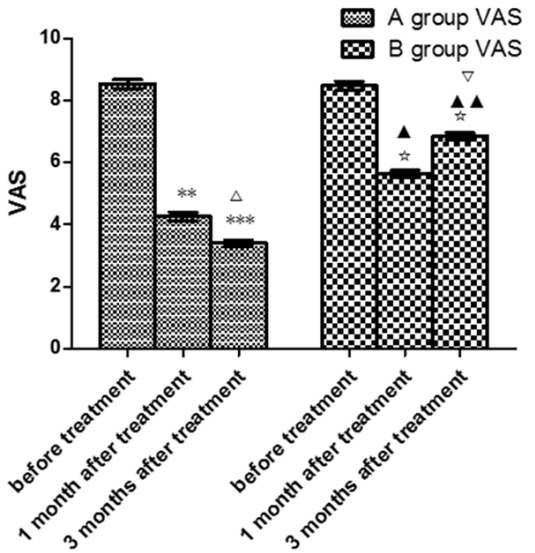

Figure 1. VAS scores of both groups before and after treatment VAS, Visual Analogue Scale. The VAS score in A group was more significantly decreased after than before treatment (**P<0.01, ***P<0.001); The VAS score in A group was lower at 3 months than at 1 month after treatment (ΔP<0.05); The VAS score in B group was lower after than before treatment (☆P<0.05); The VAS score in B group was higher at 3 months than at 1 month after treatment (▽P<0.05); The VAS score in A group after treatment decreased more significantly than that in B group (▲P<0.05, ▲▲P<0.01).

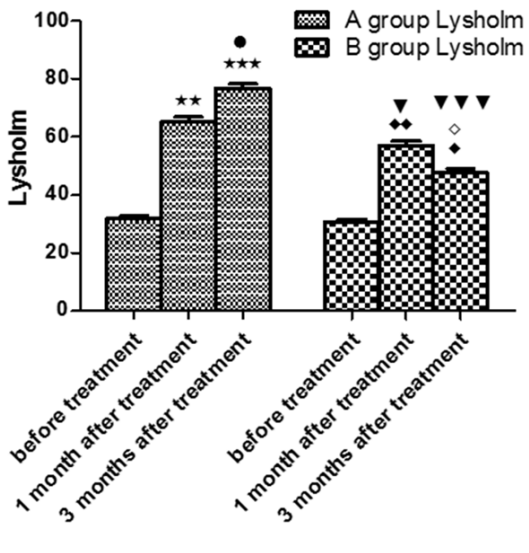

Figure 2. Changes in Lysholm scores of A and B groups. The Lysholm score in A group after treatment was increased considerably versus that before treatment (★★P<0.01; ★★★P<0.001); The Lysholm score in A group was higher at 3 months after treatment than at 1 month (•P<0.05); The Lysholm score in B group was increased remarkably versus that before treatment (◆P<0.05; ◆◆P<0.01); The Lysholm score in B group was lower at 3 months after treatment than at 1 month (◇P<0.05); The Lysholm scores after treatment rose more strikingly in A group than in B group (▼P<0.05; ▼▼▼P<0.001).

Efficacy

Changes in the VAS and Lysholm scores: One month after treatment, the VAS scores were decreased in both A group and B group compared with those in both groups before treatment (P=0.004, 0.025, respectively), with more significant reduction in that of A group (P=0.036); higher Lysholm scores favoring A group (P=0.027) were noted in both groups (P=0.008, 0.009, respectively). Three months after treatment, the VAS score dropped in A group (P=0.016), but the Lysholm score was increased in A group (P=0.014) when compared with those at 1 month; conversely, the VAS score in B group rose (P=0.037), although still lower than that before treatment (P=0.032); the Lysholm score was decreased (P=0.029), but still higher than that before treatment (P=0.019), as shown in **Table 3**, **Figures 1** and **2**.

Changes in CRP levels and white blood cell counts: One month after treatment, the CRP levels and white blood cell counts were decreased in both A group and B group (P=0.004/<0.001, and 0.007/0.004, respectively), with more significant decrease in A group (P=0.021/<0.001); the symptoms of infection were relieved greatly. Three months after treatment, the reductions in A group were more remarkable (P=0.027), but increases were seen in B group (P=0.018; **Table 4**, **Figure 3**).

Discussion

The specific mechanisms of the onset and development of KOA remain unclear. More recent studies have been focused on investigating the effects of cytokines on KOA. Interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and other cytokines promote inflammation reaction and accelerate the degeneration of articular cartilage, thereby accelerating the progression of KOA [16]. In contrast, the platelet-derived growth factor (PDGF), the transforming growth factor-β (TGF-β), the vascular endothelial growth factor (VEGF) and other growth factors play crucial roles in natural repair of bone, as they stimulate the generation of bone cells and restore impaired bone and joint tissues [17-19].

Table 4. Standardization of CRP and white blood cell counts after treatment

Variable	1 month after treatment		3 months after treatment	
	CRP (mg/L)	WBC (*10^9/L)	CRP (mg/L)	LC (*10^9/L)
A group	16.98±3.625	3.42±0.571	10.78±2.147	1.45±0.571
B group	21.8±4.12	4.93±0.661	27.18±1.838	6.13±0.81
P	0.021	0.018	<0.001	<0.001

Note: CRP, C-reactive protein; WBC, white blood cell count.

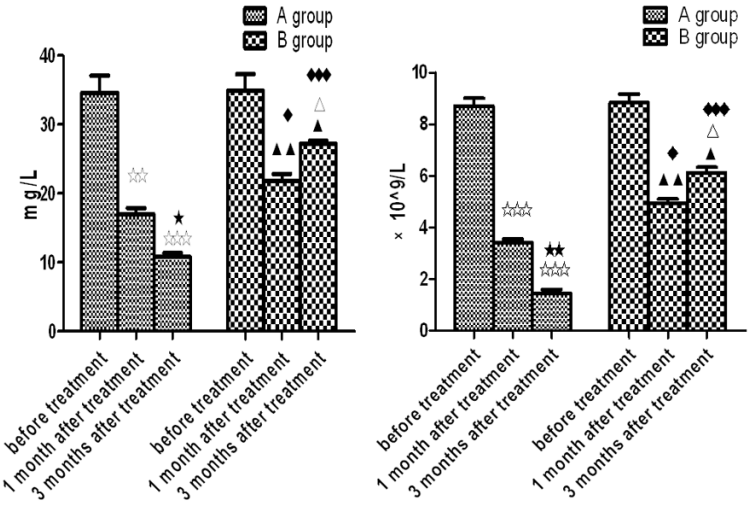

Figure 3. Changes in the CRP levels and white blood cell counts in synovial fluid CRP, C-reactive protein. Panel Left shows CRP levels, and Panel B white blood cell counts. The CRP levels and white blood cell counts in synovial fluid in A group were reduced more remarkably before than after treatment (☆☆P<0.01; ☆☆☆P<0.001); The CRP levels and white blood cell counts in synovial fluid in A group were lower at 3 months than at 1 month (★P<0.05; ★★P<0.01); The CRP levels and white blood cell counts in synovial fluid in B group were reduced more remarkably before than after treatment (▲P<0.05; ▲▲P<0.01); The CRP levels and white blood cell counts in synovial fluid in B group was higher at 3 months than that at 1 month (△P<0.05); The CRP levels and white blood cell counts in synovial fluid after treatment were lowered more strikingly in A group than in B group (◆P<0.05; ◆◆◆P<0.001).

The infection following KOA is frequently bacteria-induced. The infection profile is closely related to the toxicity and quantity of bacteria and the immunity of the organism. Previous studies indicate the above-mentioned KOA-related inflammatory cytokines and growth factors play decisive roles in a sea of diseases associated with infection including pneumonia with infection, influenza, and helicobacter pylori infection; IL-1, IL-6, TNF-α and other inflammatory cytokines promote the onset and development of infection [20-22]. Moreover, PDGF, TGF-β, VEGF and other cytokines control and manage infection [23, 24]. Therefore, we held that the study on the management of KOA with infection could be explored from inhibition of cytokines IL-1, IL-6, and TNF-α and promotion of growth factors PDGF, TGF-β and VEGF.

PRP, a platelet concentrate, contains plenty of PDGF, TGF-β, VEGF, insulin-like growth factor (IGF), epidermal growth factor (EGF) [25]. The growth factors stimulate the repair and regeneration of bone tissues, control and manage infection. Therefore, theoretically, PRP in the treatment of KOA with infection is supported by sufficient evidence. The complicated course of disease, a long treatment duration of KOA, and varied individual effect lead to poor effectiveness of oral medication in many patients. In some patients, the disease even progresses into refractory KOA [26, 27]. When KOA is complicated with infection, it is more difficult to treat; oral medication cannot achieve a good effect. Although surgical treatment is more advantageous in KOA patients with pyogenic infection, surgery-associated traumas are so severe that elderly patients are unable to tolerate. Consequently, in recent years, the intra-articular injection therapy has been used in practice. The technique is associated with smaller traumas, improved safety, a higher degree of acceptance, and better efficacy, primarily applied for treating stage II or III patients. Therefore, in this study, we chose intra-articular injection of PRP in the management of refractory KOA patients with infection, with an aim to provide more clinical evidence for PRP in treatment and control of KOA and infection.

Sodium hyaluronate is a common agent used in intra-articular injection for the treatment of KOA. Numerous studies have validated the therapeutic effect of sodium hyaluronate on KOA, but its effect on infection control is controversial; in the treatment of knee osteoarthritis, sodium hyaluronate use results in pain

relief in KOA patients; but it fails to achieve infection control in KOA patients with infection [28, 29]. In the current study, we found that for refractory KOA patients with infection, PRP was more effective than sodium hyaluronate at 1 month after treatment. Additionally, the patients with PRP achieved better infection control than controls, suggesting that PRP is effective for both KOA and infection. The therapeutic effect of sodium hyaluronate for KOA and infection began to decline at 3 months after treatment, with increased VAS pain scores, reduced Lysholm knee scores and elevated CRP levels and white blood cell counts in synovial fluid. Conversely, the curative effect of PRP at 3 months was improved compared with that at 1 month, which confirms that short-term outcomes are favorable with PRP, the long-term outcomes are more favorable over time, and the infection control with PRP is also significantly better than that at 1 month after treatment. This implies there is a synergy of PRP and antibiotics, which enhances the therapeutic effect on infection. All these further prove that PRP has a good therapeutic effect on infection. Therefore, the findings of our current study substantiated the effectiveness of PRP in the treatment of refractory KOA with infection, and its long-term outcomes were better than its short-term outcomes.

For the sake of time limitation, in the current study, we only compared the therapeutic effects at 1 and 3 months after treatment. Moreover, the lack of long-term follow-up resulted in the difficulty in confirming the long-term outcomes of PRP in the treatment of KOA and infection. Therefore, additional studies are required for validation.

Disclosure of conflict of interest

None.

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