Int J Clin Exp Med 2020;13(9):6850-6858
www.ijcem.com /ISSN:1940-5901/IJCEM0113688

Original Article

Effects of advanced knee osteoarthritis treatment with autologous platelet-rich plasma intra-articular injection on pain, pain mediators and inflammatory factors

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Received May 2, 2020; Accepted June 12, 2020; Epub September 15, 2020; Published September 30, 2020

Abstract: Objective: This study investigates the effects of the treatment of advanced knee osteoarthritis (KOA) with autologous platelet-rich plasma intra-articular injection on pain, pain mediators and inflammatory factors. Methods: A total of 86 patients with advanced KOA who received treatment in our hospital were divided into the observation group and the control group based on their sequence of receiving treatment (n=43 in each). The patients in the observation group were treated with autologous platelet-rich plasma intra-articular injection, while the patients in the control group were treated with the intra-articular injection of a mixture of lidocaine and compound betamethasone. The changes of VAS score, knee joint swelling score, knee joint function score and serum inflammatory factors before and after treatment were compared between the two groups. Results: The observation group had an effective rate of 86.05% for pain relief of advanced KOA, which is significantly higher than 62.79% in the control group (P<0.05). After treatment, the swollen knee joint scores of the two groups were significantly decreased, the knee function score was significantly increased, and the change of the observation group was greater than that of the control group (P<0.05). After treatment, the expression levels of pain mediators, leukotrienes and inflammatory factors in both groups decreased significantly, and the observation group decreased much more than the control group (P>0.05). Conclusion: The treatment of advanced KOA with autologous platelet-rich plasma intra-articular injection has good effects on the improvement of pain symptoms. It can effectively improve the degree and function of the swollen knee joint of patients and reduce the levels of pain mediators and inflammatory factors, so it is worthy of clinical promotion.

Keywords: Autologous platelet-rich plasma, pain, pain mediators, inflammatory factors, advanced knee osteoarthritis

Introduction

Knee osteoarthritis (KOA) is a joint disease which is primarily caused by primary or secondary degenerative disease of the cartilage of the knee joint and involves the entire knee joint tissue. Its clinical manifestations are mostly pain, stiffness, tenderness, joint swelling, and joint mobility disorders. As the disease progresses, KOA can induce joint deformities and has a high disability rate, which seriously affects the quality of life of patients [1, 2]. KOA mostly occurs in people over 40 years old, among whom the incidence of obese women is highest. As China enters into a more aged society, the incidence of KOA is on the rise [3, 4]. According to statistics bya survey [5], at least half of the people over 60 years old who underwent positive lateral X-ray examination had KOA, and 35%-50% had clinical manifestations; additionally, 80% of those who were over 75 years old had KOA symptoms. Patients with KOA often go to the doctor due to pain. Now the key problem in clinical treatment is how to effectively alleviate and maximize pain relief. Currently, most studies believe that pain mediators and leukotrienes play an essential part in the occurrence of joint pain and the progression of KOA, and the expressions of pain mediators and leukotrienes in patients with KOA are significantly increased, which is an important indicator for the objective evaluation of pain [6-8]. Moreover, because KOA is an atypical inflammatory lesion, the inflammatory response

Table 1. Comparison of the general data of the two groups of patients

Group	Sex (Male/Female)	Age ($\bar{x}$±s, age)	Course of disease ($\bar{x}$±s, year)	Kellgren-Lawrence classification	
				Level III	Level IV
The observation group (n=43)	26/17	56.79±3.88	4.47±0.69	18	25
The control group (n=43)	23/20	55.69±3.27	4.25±0.54	21	22
X^2/t	0.4269	1.4215	1.6465	0.4223	
P	0.5135	0.1589	0.1034	0.5158	

also plays an important role in the progression of its disease. The main proinflammatory factors are interleukin-1β and tumor necrosis factor-α which can accelerate the dissolution of the articular matrix to aggravate its condition. They also can promote the depolarization of nerve cells and cause pain [9]. In general, painkillers, anti-inflammatory drugs, intraarticular drug injection etc. are used for the clinical treatment of KOA. Some studies have reported [10] that intraarticular injection has better effects on advanced KOA than oral drug therapy, and it has fewer side effects. According to previous studies, platelet-rich plasma is a platelet concentrate rich in a variety of inflammatory regulators and growth factors made by collecting their whole blood after double centrifugation treatment. It has the function of inhibiting osteoclasts, and can promote the regeneration of bone matrix and chondrocytes. Moreover, as it comes from itself, it will not activate immune rejection and is highly safe [11, 12]. A large number of scholars have carried out research on the repair of joint cartilage degeneration by autologous plate-rich plasma more than 10 years ago and achieved good efficacy [13, 14]. However, so far, research on autologous platelet-rich plasma in China primarily include animal experiments and have not been widely conducted in the human body. There are few reports on the repair of human articular cartilage by autologous platelet-rich plasma, and the research results mostly focus on clinical efficacy [15]. There are few reports on the impact of autologous platelet-rich plasma on pain mediators and inflammatory factors. Therefore, this purpose of this study is to explore the effects of the treatment of advanced KOA with autologous platelet-rich plasma intra-articular injection on pain, pain mediators and inflammatory factors through treating 86 patients with advanced KOA who received treatment in our hospital with autologous platelet-rich plasma intra-articular injection.

Materials and methods

General data

A total of 86 patients with advanced KOA who received treatment in our hospital between June 2017 and June 2019 were selected as the research subjects. This study was implemented after approval by the Ethics Committee of our hospital. Among the research subjects, 49 were male and 37 were female, with an average age of (56.24±3.56) years and a course of disease (4.38±0.52) years. According to Kellgren-Lawrence classification, there were 39 cases with level III and 47 cases with level IV. Patients with advanced KOA were divided into the observation group and the control group based on the order of visit, with 43 cases in each group. There was no significant difference in the general data of the two groups of patients (P>0.05). For details, see **Table 1**.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with advanced KOA included in the study all met the relevant diagnostic criteria in the *Guidelines for the Diagnosis and Treatment of Osteoarthritis* [16]; (2) Kellgren-Lawrence classification ≥Level III, reaching the artificial joint treatment target; (3) Patients suffering from joint pain and swollen joints, and are in the onset period; (4) Blood indicators such as hemoglobin content and platelet count are at normal levels; (5) Patients who have not taken non-steroidal anti-inflammatory drugs, immunosuppressants, anticoagulants and other drugs within the past 3 months; and (6) Patients who agreed to participate in the study and signed an informed consent form.

Exclusion criteria: (1) Patients with secondary KOA; (2) Patients whose symptoms are in remission; (3) Patients with failure of multiple organs; (4) Patients with complicated autoimmune disease or malignant tumors; (5) Patients whose

hemoglobin is <11 g/L and blood platelet is $<1.5\times10^5$/L; (6) Patients with a history of intra-articular injection within the past year; (7) Patients with severe adverse reactions during treatment; (8) Patients who tool other medications during treatment.

Methods

Preparation of autologous platelet-rich plasma: The kit used to prepare platelet-rich plasma was purchased from Shandong Weigao Group Medical Polymer Products Co., LTD. (Number: 170921), and prepared carefully by the same team with double-order centrifugation technology in accordance with the operating procedures. A sample of 50 ml upper limb venous blood from patients was drawn and put it in a platelet-rich plasma preparation set centrifuge tube for the first centrifugation at 1400 r/min. After centrifugation for 10 min, the entire lower red blood cell layer was removed to the junction 3 mm below and placed it in another centrifuge tube at 1400 r/min speed for the second centrifugation, the centrifugation time was 10 min. Then, 5 ml platelet-rich plasma of the lower layer was acquired after discarding the upper platelet-poor plasma.

Treatment method: The observation group received autologous platelet-rich plasm, as an intra-a-articular injection for treatment: 1 ml prepared platelet-rich plasma for platelet count was added to 1 ml calcium chloride injection (G.Y.Z.Z. H37022037, Ruiyang Pharmaceutical Co., Ltd.) which was then added to the remaining 4 ml platelet-rich plasma to activate platelets. During intra-articular injection, patients were placed in a supine lying position, and the joint space of the lateral patella was selected as the injection point. After skin disinfection, a disposable syringe was used to puncture into the joint cavity and inject 4 ml autologous platelet-rich plasma. If a large amount of fluid was found in the patients' joint cavity, part of the fluid was extracted first. The injection of autologous platelet-rich plasma was conducted once a week for 5 weeks as a course of treatment. The patients in the control group were treated with the intra-articular injection of the mixture of lidocaine and compound betamethasone: 2 ml lidocaine (Y.Z.Z. H10960193, Jichuan Pharmaceutical Group Co., Ltd.) and 2 ml compound betamethasone (G.Y.Z.Z. H20093412, Chongqing Huabang Pharmaceutical Co., Ltd.) were mixed evenly and injected into the patients' joint cavity with the same injection method as for the observation group. The mixture of lidocaine and compound betamethasone was injected for the patients once a week, 5 times as a course of treatment.

Evaluation indexes: (1) Evaluation of pain degree: Before and after treatment, Knee joint visual analogue scale (VAS) was used for patients to score their pain by marking a point on a 10 cm long straight line with painless being (0) and severe pain being (10) at both ends according to the amount of pain they feel. The distance length is the pain intensity score [17]. (2) The treatment effect of advanced KOA was evaluated based on the VAS score and clinical symptoms before and after treatment. If the VAS decreased by 70% or more, and clinical symptoms were significantly improved, if it was scored as significantly effective. If the VAS score decreased by 30% to 70%, and clinical symptoms were improved, if it was scored as effective. If the VAS score decreased by less than 30%, and clinical symptoms had no improvement, it was scored as ineffective. Effectiveness = (significant effectiveness + effective)/the total number of cases × 1000%. (3) Evaluation of swollen knee joint: As customized by our hospital, a scoring system was approved by 2 chief physicians in pain department, where no swelling of knee joint = 0 points; the knee joint is slightly swollen and the surrounding skin texture becomes lighter = 1 point; the knee is moderately swollen, the bony signs are not obvious, and the surrounding skin texture basically disappears = 2 points; the knee joint was severely swollen and the surrounding skin was tight = 3 points. (4) Evaluation of knee joint function: According to Lysholm knee joint score, the structure and function of the knee joint were evaluated, including 8 aspects: pain, support, claudication, instability, atresia, swelling, squatting and climbing stairs. The score ranged from 0 to 100. The higher the score, the better the knee joint function.

Observational indexes: This study primarily observed the effects of two treatment methods on the pain of advanced KOA, and the secondary observation results were as follows: The changes of swollen knee joint score and knee joint function score before and after treatment in two groups of patients, and the changes in the expression levels of serum pain mediators [prostaglandin E_2 (PGE_2), 5-hydroxytryptamine (5-HT), dopamine (DA), Substance P (SP)], leu-

Table 2. Comparison of the effects of two treatment methods on the pain of advanced KOA [n (%)]

Group	Significantly effective	Effective	Ineffective	Effective rate
The observation group (n=43)	24 (55.82)	13 (30.23)	6 (13.95)	37 (86.05)
The control group (n=43)	12 (27.91)	15 (34.88)	16 (37.21)	27 (62.79)
X^2				6.1080
P				0.0135

kotrienes (LTB_4, LTC_4, LTD_4) and inflammatory factors [interleukin-1β (IL-1β)], tumor necrosis factor-α (TNF-α) before and after treatment in two groups of patients. Enzyme linked immunosorbent assay (ELISA) was used, and the operation was carried out in strict accordance with the operating instructions of the kit. The Knee Injury and Osteoarthritis Outcome Sore (KOOS) in two groups before and after treatment were compared. The score consists of symptoms, pain, daily activities, sports and entertainment functions, quality of life ,which ranges from 0-4. The higher the score, the more serious the knee osteoarthritis is. The aforementioned comparison adopts SF-36 gauge to compare scores of quality of life between the two groups, physical function (PF), Bodily Pain (BP), limitation of body role (RP), social function (SF), vitality (VT), mental health (MH), limitation of emotional role (RE), general health (GH); with 8 dimensions and 36 entries. The higher the scores of all dimensions, the higher the quality of life of patients.

Statistical methods: The data used SPSS 19.0 statistical software for statistical analysis and processing. The measurement data were all expressed in ($\bar{x} \pm s$). The paired sample t-test was used within the group before and after treatment, and the independent sample t-test was used between groups. The count data were used. Percentage means that the result is tested by chi-squared. *P<0.05* means the difference is statistically significant.

Results

Comparison of the effects of two treatment methods on the pain of advanced KOA

The effective rate of the observation group in the treatment of advanced KOA was 86.05% and that of the control group was 62.79%. The effective rate of the observation group was higher than that of the control group. The difference was statistically significant (*P<0.05*). For details, see **Table 2**.

Comparison of swollen knee joint score and knee joint function score between the two groups of patients before and after treatment

There was no statistical difference between the swollen knee joint score and knee joint function score between the two groups of patients before treatment (*P*>0.05). After treatment, the swollen knee joint scores of the two groups of patients were significantly decreased, while the knee joint function score was significantly increased, and the observation group changed more than the control group (*P*<0.05). For details (**Table 3**; **Figures 1**, **2**).

Comparison of the expression levels of serum pain mediators between the two groups of patients before and after treatment

There was no statistical difference in the serum pain mediators (PGE_2, 5-HT, DA, SP) between the two groups of patients before treatment (*P*>0.05). After treatment, the serum pain mediators (PGE_2, 5-HT, DA, SP) between the two groups of patients all decreased significantly, and the observation group decreased much more than the control group (*P*<0.05). For details, see **Table 4**.

Comparison of the expression levels of leukotrienes between the two groups of patients before and after treatment

There was no statistical difference in the leukotrienes (LTB_4, LTC_4, LTD_4) between the two groups of patients before treatment (*P*>0.05). After treatment, the leukotrienes decreased significantly compared to before treatment. The observation group decreased

Table 3. Comparison of swollen knee joint score and knee joint function score between the two groups of patients before and after treatment ($\bar{x}\pm s$, score)

Group	Time	Swollen knee joint	Knee joint function
The observation group (n=43)	Before treatment	2.13±0.49	54.73±3.84
	After treatment	0.41±0.15*	77.59±5.35*
t		22.0098	22.7628
P		0.0000	0.0000
The control group (n=43)	Before treatment	2.07±0.38	53.16±3.47
	After treatment	0.76±0.26	69.81±4.94
t		18.6568	18.0856
P		0.0000	0.0000

Note: Comparison with the control group after treatment, *$P<0.05$.

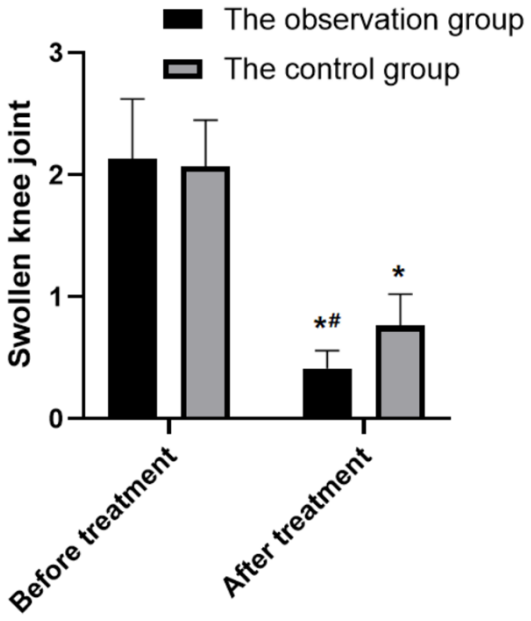

Figure 1. Comparison of swollen knee joint score between the two groups of patients before and after treatment. Comparison with the same group before treatment, *$P<0.05$. Comparison with the control group in the same period, #$P<0.05$.

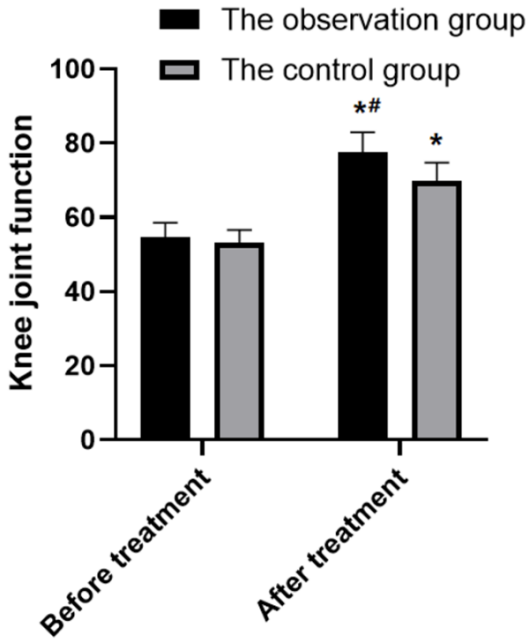

Figure 2. Comparison of swollen knee joint function score between the two groups of patients before and after treatment. Comparison with the same group before treatment, *$P<0.05$. Comparison with the control group in the same period, #$P<0.05$.

more than the control group ($P<0.05$). For details, see **Table 5**.

Comparison of the expression levels of inflammatory factors between the two groups of patients before and after treatment

There was no statistical difference in the inflammatory factors (IL-1β, TNF-α) between the two groups of patients before treatment ($P>0.05$). After treatment, the inflammatory factors (IL-1β, TNF-α) between the two groups of patients all decreased significantly, and the observation group decreased more than the control group ($P<0.05$). For details, see **Table 6**.

KOOS score comparison between the two groups of patients before and after the treatment

KOOS score of the two groups of patients was significantly reduced (P<0.05) after treatment, and the observation group decreased more than the control group. For details, see **Table 7**.

Table 4. Comparison of the expression levels of serum pain mediators between the two groups of patients before and after treatment ($\bar{x}\pm s$, score)

Group	Time	PGE_2	5-HT	DA	SP
The observation group (n=43)	Before treatment	349.75±7.36	898.64±11.58	19.12±2.67	261.37±9.14
	After treatment	263.39±5.56*	732.45±8.77*	11.33±1.84*	171.35±7.53*
t		61.3939	75.0219	15.7535	49.8467
P		0.0000	0.0000	0.0000	0.0000
The control group (n=43)	Before treatment	351.52±6.12	895.32±12.13	18.94±2.75	263.01±9.68
	After treatment	303.68±5.84	786.48±9.91	13.49±1.93	206.75±7.62
t		37.0843	45.5653	10.6374	29.9465
P		0.0000	0.0000	0.0000	0.0000

Note: Comparison with the control group after treatment, *$P<0.05$.

Table 5. Comparison of the expression levels of leukotrienes between the two groups of patients before and after treatment ($\bar{x}\pm s$, score)

Group	Time	LTB_4	LTC_4	LTD_4
The observation group (n=43)	Before treatment	56.39±3.12	132.75±9.68	91.87±7.87
	After treatment	41.67±2.12*	95.53±4.56*	72.38±5.45*
t		25.5893	22.8095	13.3507
P		0.0000	0.0000	0.0000
The control group (n=43)	Before treatment	56.58±3.34	130.81±9.42	89.48±8.66
	After treatment	46.82±2.63	99.97±5.65	75.74±6.52
t		15.0548	18.4106	8.3117
P		0.0000	0.0000	0.0000

Note: Comparison with the control group after treatment, *$P<0.05$.

Table 6. Comparison of the expression levels of inflammatory factors between the two groups of patients before and after treatment ($\bar{x}\pm s$, score)

Group	Time	IL-1β	TNF-α
The observation group (n=43)	Before treatment	94.76±5.65	16.08±3.53
	After treatment	59.15±3.27*	10.75±2.12*
t		35.7703	8.4881
P		0.0000	0.0000
The control group (n=43)	Before treatment	93.38±6.12	16.39±3.67
	After treatment	65.33±4.56	12.67±2.44
t		24.1005	5.5351
P		0.0000	0.0000

Note: Comparison with the control group after treatment, *$P<0.05$.

SF-36 score comparison between the two groups of patients before and after treatment

SF-36 score of the two groups of patients significantly increased (*P<0.05*), and the observation group decreased more than the control group. For details, see **Table 8**.

Discussion

Previous studies have confirmed that the treatment of advanced KOA with autologous platelet-rich plasma intra-articular injection can effectively reduce the clinical symptoms of osteoarthritis in patients. Filardo et al. [18]

Table 7. Comparison of KOOS scores between the two groups before and after treatment (score, $\bar{x}\pm s$)

Group	Before treatment	After treatment	T	*P*
The observation group (n=43)	112.81±7.84	45.26±12.17	30.598	0.000
The control group (n=43)	110.91±9.32	58.39±10.25	24.860	0.000
t	1.023	5.411	-	-
P	0.309	0.000	-	-

Table 8. Comparison of SF-36 scores between the two groups before and after treatment (score, $\bar{x}\pm s$)

SF-36	The observation group (n=43)				The control group (n=43)			
	Before treatment	After treatment	t	*P*	Before treatment	After treatment	t	*P*
PF	59.82±9.03	76.28±7.21*	9.341	0.000	60.18±7.22	68.22±5.96	5.631	0.000
BP	56.42±7.64	69.85±6.44*	8.814	0.000	55.84±6.45	63.21±7.02	5.069	0.000
RP	49.80±5.67	60.02±7.19*	7.319	0.000	47.93±7.05	54.29±6.12	4.467	0.000
SF	60.25±6.03	71.35±4.96*	9.322	0.000	61.25±6.58	66.72±5.84	4.077	0.000
VT	45.20±5.94	58.93±5.29*	11.319	0.000	46.27±6.43	52.37±4.82	4.978	0.000
MH	50.73±7.83	64.27±6.06*	8.967	0.000	51.08±7.05	57.26±8.33	3.713	0.000
RE	42.37±5.62	55.62±7.03*	9.654	0.000	43.95±6.08	49.22±9.47	3.071	0.003
GH	52.31±4.92	64.08±6.09*	9.858	0.000	51.84±5.26	58.96±6.43	5.620	0.000

Note: Comparison with the control group, *$P<0.05$.

found that by injecting 5 ml autologous platelet-rich plasma every 20 days, the clinical symptoms of patients with KOA were effectively improved after 3 treatments, and the subjective satisfaction rate of patients was as high as 80%. In the study by Napolitano et al. [19], 27 patients with primary osteoarthritis were injected with autologous platelet-rich plasma once a week in the joint cavity and they received the injection 3 times. The results confirmed that the patients' joint pain and function were significantly alleviated after treatment. Sampson et al. [20] found that the knee injury and osteoarthritis score of 14 patients with osteoarthritis of the knee were significantly improved after they were treated with autologous platelet-rich plasma intra-articular injection. In China the clinical research on the application of autologous platelet-rich plasma in humans is still in its infancy. Therefore, this paper attempts to study the treatment of advanced KOA with autologous platelet-rich plasma intra-articular injection. The results also show that the treatment of advanced KOA with autologous platelet-rich plasma intra-articular injection can significantly alleviate the pain and effectively improve the patients' swollen knee joint and knee joint function.

Prostaglandin E_2 (PGE_2), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) are critical cytokines that cause KOA. Woodell-May et al. [21] confirmed through research that excessive TNF-α secreted by synovial cells in joints is closely related to the occurrence and development of patients with KOA, and the high expression of TNF-α in the joint can promote the increase of PGE_2 secretion by activating polymorph nuclear cells, and then increase the permeability of blood vessels to promote the infiltration of inflammatory cells, thereby aggravating local inflammatory edema in patients. Pecchi et al. [22] confirmed that IL-1β is highly expressed in the synovial fluid of patients with KOA, and the severity of patients with KOA is positively correlated with the expression of IL-1β in synovial fluid. This study found after treatment, the expression levels of pain mediators (PGE_2, 5-HT, DA, SP), leukotrienes (LTB_4, LTC_4, LTD_4) and inflammatory factors (IL-1β, TNF-α) between the two groups of patients all decreased significantly, and the observation group decreased more than the control group ($P>0.05$). These indicate that autologous platelet-rich plasma can alleviate the pain symptoms of patients with advanced KOA and it can reduce the expression of pain mediators, leukotrienes and inflammatory factors in patients. These results suggested that autologous platelet-rich plasma alleviates pain symptoms in patients with advanced KOA and is associated with decreased expression of pain mediators,

leukotrienes and inflammatory factors in patients. On the one hand, autologous platelet-rich plasma significantly reduced the contents of peripheral blood pain mediators in patients with advanced KOA, thereby directly exerting analgesic effect; on the other hand, the inflammatory regulators in autologous platelet-rich plasma can inhibit NF-κB pathway, thereby inhibiting leukotrienes to mediate inflammatory cells to secrete inflammatory factors such as IL-1β and TNF-α, thereby raising the patients' pain threshold and indirectly exerting analgesic effect [23, 24].

In summary, the treatment of advanced KOA with autologous platelet-rich plasma intra-articular injection has good effects on the improvement of pain symptoms. It can effectively improve the degree and function of swollen knee joint of patients and reduce the content of pain mediators and inflammatory factors. However, there are certain shortcomings in this study. First, the sample size is small; and secondly, there is a lack of long-term follow-up studies. For these shortcomings, the experimental design needs to be further improved. Multi-center randomized control and long-term follow-up study will be adopted to make further explorations.

Disclosure of conflict of interest

None.

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