

The effectiveness of intra-articular hyaluronic acid injection combined with oral nonsteroidal anti-inflammatory drugs in the treatment of knee osteoarthritis

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Abstract: Knee osteoarthritis (KOA) is a chronic disease with limited clinical treatment and easy recurrence. This study analyze the effectiveness of intra-articular hyaluronic acid (HA) injection combined with oral nonsteroidal anti-inflammatory drugs (NSAID) in treating KOA, providing scientific basis for improving the therapeutic effect of this disease. 100 KOA patients admitted to our hospital from December 2021 to December 2023 were divided into control group ($n=50$) and study group ($n=50$). Both groups were treated with oral NSAID, study group were added with intra-articular HA injections. The pain scores (VAS), knee osteoarthritis indicator score (WOMAC), knee osteoarthritis outcome score (KOOS), Lysholm score, knee joint range of motion, inflammatory indicators, clinical efficacy and adverse reactions were compared among both groups. After treatment, all indicators in both groups remarkably improved ($P<0.05$). The KOOS score, Lysholm score, knee mobility and clinical efficacy in study group were remarkably higher than control group, and VAS score, WOMAC score and inflammatory factor level were less than control group ($P<0.05$). No significant discrepancies in the adverse reactions among both groups ($P>0.05$). The efficacy of the combined treatment is remarkable without increased adverse reactions and deserves to further popularize its use in the clinic.

Keywords: Knee osteoarthritis; hyaluronic acid; non-steroidal anti-inflammatory drugs; pain; inflammatory factors

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INTRODUCTION

Knee osteoarthritis (KOA) is a chronic and progressive osteoarthritis/osteodystrophy, which feature are pain, stiffness, swelling and limited joint activity. It is highlighted by features such as degeneration of articular cartilage and osteophytes. The pain increases with the progress of the disease, and there is also joint swelling and deformity, which seriously affects the quality of life of the patients. Due to the destruction of articular cartilage, reactive hyperplasia and other pathological changes are also known as hyperplastic, hypertrophic arthritis, it is also referred to as hyperplastic or hypertrophic arthritis (Zhu *et al.*, 2024). Clinical manifestations in the early stage include pain in the knee joint when going up and down the stairs, limitation of activities, etc. The condition worsens when there is a lot of activity and can be relieved after resting. If delayed treatment or improper treatment leads to aggravation of the condition, joint deformity will occur and even lead to disability (Zhou *et al.*, 2021). KOA was characterized by degeneration of articular cartilage, destruction of articular cartilage, subchondral ossification, osteochondroplasia at the joint margin, spur formation, contracture of articular capsule, synovial inflammation, ligamentous relaxation or contracture and deformity of joint (Liew *et al.*, 2023). The incidence of KOA increases with age. Old Age is a recognized risk factor for KOA. The positive correlation among the incidence of KOA and age, the severity of

symptoms and the degree of joint degeneration are also positively correlated with age, with primary KOA being more common in the elderly (Driban *et al.*, 2020).

The etiology and pathogenesis of KOA have not been unified, so there is no cure for knee joint osteoarthritis. The current treatment of KOA is to relieve or eliminate pain and delay the loss of joint function, the goal is to correct existing deformities and improve the qualities of life of patients with KOA (Geng *et al.*, 2023). The main treatment methods in modern medicine are surgical treatment, non-drug treatment and drug treatment (Primorac *et al.*, 2020). Among them, surgical treatment is suitable for the patients whose conservative treatment is ineffective, the knee joint has long-term pain, the knee joint function cannot be improved, and the quality of life is seriously affected. The purpose of the operation is to improve the pain symptoms, improve the knee joint functions and correct knee joint deformity. The surgical treatment of KOA, including cartilage repair, arthroscopic debridement, osteotomy and artificial joint replacement, is expensive and carries surgical and anesthetic risks, long-term functional exercise is required after operation (Madry, 2022). Non-drug therapy is mainly for patients with mild symptoms, such as exercise therapy and weight loss therapy, can relieve knee pain, improve knee function, is the clinical treatment of choice (Vaghela *et al.*, 2020). In addition, drug therapy usually includes NSAID, analgesics, intra-articular injections and anti-anxiety drugs. Drug therapy for KOA has the advantages of wide access to medication, excellent therapeutic effect

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and convenient use, it is therefore a commonly used treatment in clinical practice (Kwak *et al.*, 2023).

The NSAID is valid in the treatment of KOA. It can effectively relieve pain and restore the function of the knee joint. It is the first choice in the treatment of KOA. They can be divided into topical and systemic applications (Zeng *et al.*, 2021). Topical medications are recommended to be used as a priority, presumably as gel patches, plasters, emulsions, etc. made from a variety of NSAID. Local external medications have a rapid onset of action and are very effective for mild to moderate pain, while avoiding gastrointestinal adverse effects. For moderate to severe pain, a combination of topical medications and oral NSAID is recommended (Wolff *et al.*, 2021). Systemic application of drugs include: Oral Drugs, injections, suppositories, etc., of which oral drugs are most commonly used. Systemic drugs, including aspirin and salicylic acid, have the pharmacological effect of inhibiting the activity of Cyclooxygenase and inhibiting the chemical synthesis of prostaglandins, thereby reducing inflammatory reaction, to achieve anti-inflammatory pain, protection of articular chondrocytes effect. However, it should be noted that the efficacy and adverse reactions of oral drugs vary from patient to patient and should be taken under the guidance of the drug instructions (Wang *et al.*, 2022). NSAIDs commonly used in clinical practice are selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and erliximab. Compared with traditional NSAIDs, these drugs have fewer gastrointestinal adverse effects and are widely used (Tai and McAlindon, 2021). If oral medication does not achieve the ideal therapeutic effect, it can be combined with intra-articular drug injection to control the development of the disease. Intra-articular drug injection can effectively alleviate the symptoms of knee joint pain, to improve knee joint movement, glucocorticoid, sodium hyaluronate, medical chitosan, growth factors and platelet-rich plasma are commonly used (Xie *et al.*, 2023). Sodium hyaluronate, also known as hyaluronic acid (HA), can also improve knee joint pain, improve knee joint function and protect articular cartilage, it is recommended for patients with early and intermediate KOA (Jin *et al.*, 2022).

At present, the clinical efficacy of oral NSAID in osteoarthritis treatment has been studied, but there are few reports about the treatment of KOA by intra-articular HA injection combined with oral NSAID. In this study, a synergistic therapeutic strategy of "local micro environmental modulation + systemic inflammation suppression" was innovatively proposed, combining the viscoelastic replenishment mechanism of intra-articular injection of HA with the systemic anti-inflammatory effect of celecoxib, a selective COX-2 inhibitor, to target the pathology of KOA. By evaluating the effects of the combination therapy on inflammatory factors (e.g., IL-6, TNF- α) and functional scores (e.g., WOMAC scores), we

provide clinical evidence for new multi-mechanism combinations for individualised treatment of KOA.

MATERIALS AND METHODS

Selection criteria

Inclusion criteria

(1) The diagnosis of KOA was in accordance with the diagnostic criteria of KOA in the guidelines for the diagnosis and treatment of osteoarthritis (2007 edition)(Sun *et al.*, 2019); (2) recurrent knee pain within a month; (3) X-ray showed osteophyte formation and narrowing of joint space; (4) morning stiffness less than or equal to 30 minutes; (5) bone friction sound during activity; (6) normal cognitive function; (7) patients and their family members signed the informed consent agreement.

Exclusion criteria

(1) Those who do not meet the above-mentioned KOA diagnostic criteria and inclusion criteria; (2) complicated with severe cardiovascular, hepatic, renal, gastrointestinal and hematopoietic diseases; (3) allergic to the drugs and ingredients of this experiment; (4) those who have major neurological and psychiatric diseases and cannot take medicine regularly; (5) others did not meet the study conditions.

Study design

This study is a systematic clinical retrospective study conducted simultaneously in multiple clinical centres, aiming to comprehensively and accurately systematically assess and integrate the efficacy of intra-articular injection of HA combined with oral NSAIDs in the treatment of KOA, and to provide a scientific basis for the clinical relevant medication regimen. Between December 2021 and December 2023, patients with KOA were collected from the orthopaedic department, rheumatology and immunology department, and emergency department of our hospital. The patients were screened according to strict inclusion and exclusion criteria, and their age was limited to 40-70 years old. Finally, 100 patients were successfully screened. Subsequently, these 100 patients were allocated to two groups of 50 patients each. The Control group was treated with oral NSAIDs, and the Study group was treated with intra-articular injection of HA combined with oral NSAIDs, so as to form a control, and through the comparison and analysis of the data of the two groups in the process of treatment, to explore the real efficacy of the combined treatment programme. The flowchart is demonstrated in fig. 1.

Treatment methods

The control and study group were treated with NSAID therapy, COX-2 inhibitor celecoxib capsule (0.2g/capsule, PfizerInc, approval number: J20120063), 1 capsule/time, 1 time/day, for 3 weeks. Study group added HA injection into knee intra-articular.

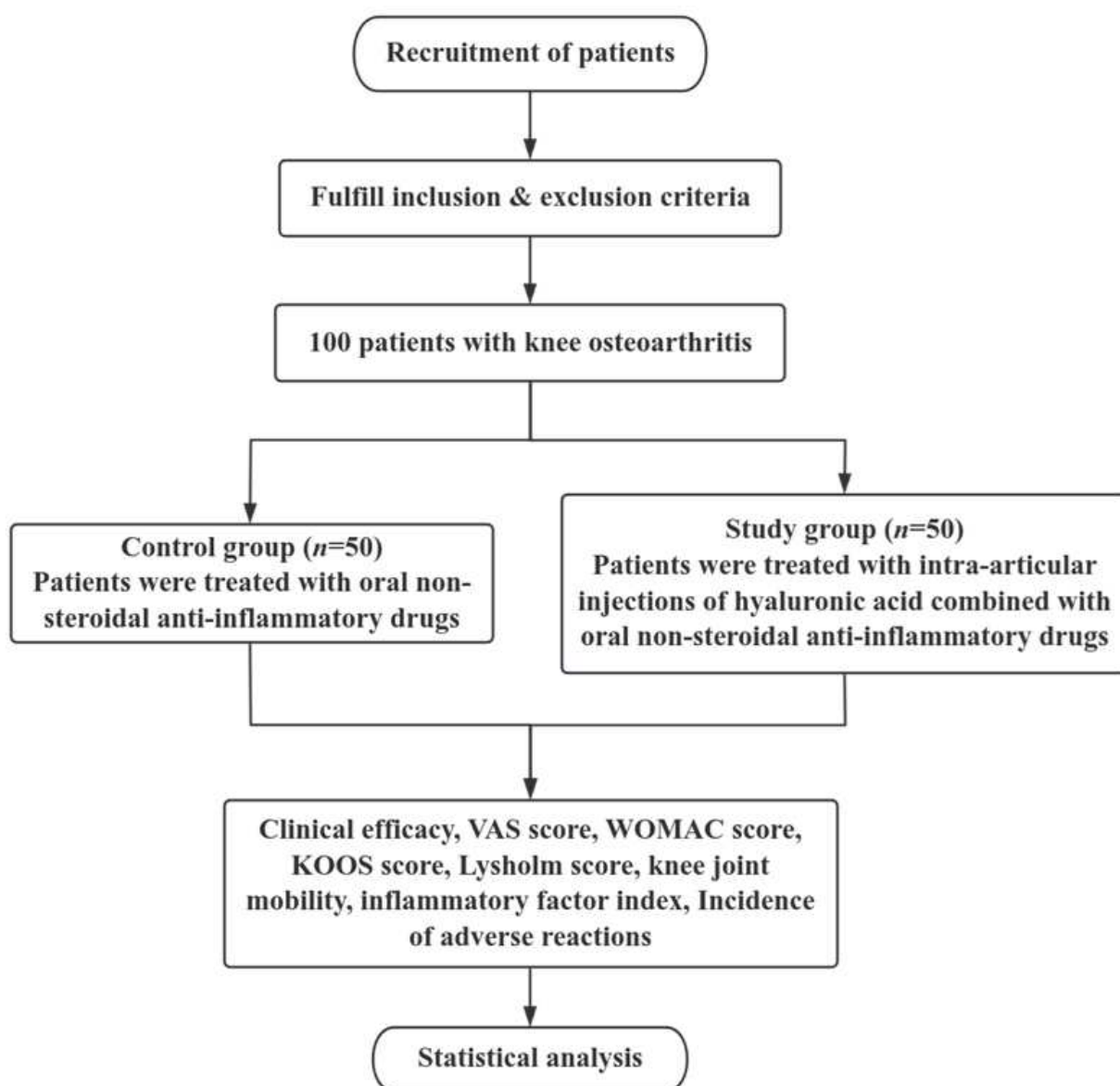


Fig. 1: Flowchart of the treatment process

All patients received articular injection in the outpatient articular injection room of our hospital, and the entire course of treatment was completed by the same technician to ensure consistency. All patients received standard intra-cavitary injection of knee joint, that is, patients were placed in supine position, knee joint was extended straight, and lateral puncture of suprapatellar bursae was taken. The puncture site was routinely disinfected with iodophor and punctured into the joint cavity with injection needle no.5. After blood withdrawal, 2% lidocaine was injected into the joint cavity for local anesthesia. After successful anesthesia, the joint effusion was sucked out and 2.5 mL HA (Baibao, 2.5mL / 25mg /branch, Shanghai Jingfeng Pharmaceutical Co., LTD.) was injected into the joint cavity, and the puncture site was covered with sterile dressing after needle withdrawal. Moderate passive

flexion of the knee promotes uniform distribution of the drug to the articular cartilage and synovial surface. The injection was given once a week for 3 consecutive weeks.

Evaluation index of curative effect

Pain score

With reference to the report of Samma *et al.* (2021), the degree of knee pain in the both groups was examined by Visual analog score (VAS). The VAS score ranged from 0 to 10, with 0 indicating no pain and 10 indicating the most severe pain.

Knee osteoarthritis indicator score

According to the report of Li *et al.* (2022), Western Ontario and McMaster Universities score (WOMAC) was used to evaluate the improvement of knee joint function.

WOMAC included three aspects: Pain (5 items), stiffness (2 items), function (17 items), each item ranges from 0 to 4 points, 0 indicates no symptoms, 4 indicates the most severe symptoms, the total score is 0 to 96 points, the higher the score, the worse the knee function.

Knee osteoarthritis outcome score (KOOS)

According to Larsen *et al.* (2023), KOOS scores, including pain symptoms, activities of daily living, sports and recreation ability, and knee joint related quality of life, were performed pre- and post-treatment in both groups.

Lysholm knee function score (Lysholm score)

Lysholm score was employed to estimate knee pain and knee function in the two groups (Huang *et al.*, 2022). The Lysholm knee joint score scale includes 8 items such as walking up and down stairs and knee joint weakness. The score is 0 to 100 points, and the lower the score is, the worse the knee joint function is.

Knee range of motion

When the muscles of the patients were without Lokmoat dynamic support and the muscles were completely relaxed pre- and post-treatment, external force was applied to measure the range of motion of the knee joint after the knee joint. The range of motion of the knee joint was measured by L-ROM method (Cevei *et al.*, 2022), and the results were recorded and analyzed.

Inflammatory factor index

With reference to the research method proposed by Kanlioglu Kuman *et al.* (2021) and modified, inflammatory factor indexes were observed in the two groups of patients. 5 mL of elbow vein blood specimen was drawn from patients in fasting state, centrifuged at 3000 r/min for 10 min, and the supernatant was taken after serum separation. Serum samples were detected by ELISA in the clinical laboratory of our hospital, and the levels of post-operative serum test indexes were recorded respectively. Human interleukin-6 (IL-6) ELISA Kit (PI330, Shanghai Beyotime Biotechnology Co., Ltd.), human interleukin-17 (IL-17) ELISA Kit (PI550, Shanghai Beyotime Biotechnology Co., Ltd.), human tumornecrosis factor- α (TNF- α) ELISA Kit (97072ES96, Shanghai Yeasen Biotechnology Co., LTD., Ltd.) and human transforming growth factor- β (TGF- β) ELISA Kit (ml064258, Shanghai Enzyme-linked Biotechnology Co., Ltd.) analyzed serum levels of IL-6, IL-17, TNF- α and TGF- β .

Clinical effect

The clinical effect of the both groups of patients was estimated. The evaluation criteria of curative effect were divided into three levels: obvious, effective and ineffective. Obvious effect was defined as recovery of joint function, disappearance of symptoms and unrestricted activity. All symptoms and joint function

were improved, and some activities were limited and effective. Clinical symptoms do not change, unable to normal activities as ineffective. Total effective rates = (apparent + effective) / total cases $\times$ 100%.

Adverse event rate

The number of patients with knee joint infection, swelling and hematoma during treatment was counted, and the incidence of adverse reactions was analyzed.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 27.0 statistical software. Measurements data conformed to normal distribution were ($\bar{x} \pm s$). Comparisons among the two groups were examined using the independent samples *t* test, and counting data is expressed as rate (%) using χ^2 test, with $P < 0.05$ meaning the discrepancy was statistically significant.

RESULTS

Basic information

The general characteristics of the participants revealed that the patients randomly assigned to the control and study groups were similar in most demographic and clinical variables. The mean age of participants in both groups was also similar, 57.80 ± 7.36 years in the control group and 57.20 ± 6.83 years in study group ($P = 0.732$). Males accounted for 54% of the control group and 48% of study group ($P = 0.754$), so no differences in the gender distribution of patients among the both groups. In addition, body weight and body mass index were similar in both groups of patients as presented in table 1. Together, these results demonstrate that the randomization process achieved the important goal of evenly distributing participants into the both groups, and that any observed results and effects of study findings cannot be attributed to differences in baseline characteristics.

VAS score and WOMAC scores

The comparison of VAS scores and WOMAC scores among the both groups was presented in fig. 2. Pre-treatment, VAS scores in the control and study group were 6.75 ± 1.35 and 6.73 ± 1.30 score, respectively, with no significant differences ($P = 0.940$, 95%CI: -0.546~0.506). The WOMAC scores of both groups were 58.48 ± 5.95 and 58.61 ± 6.47 score, respectively, with no significant differences ($P = 0.917$, 95%CI: -2.337~2.597). Post-treatment, the VAS scores of study group (3.10 ± 1.05 score) was remarkably decreased compared to control group (4.49 ± 1.38 score) ($P < 0.001$, 95%CI: 0.903~1.877), the WOMAC score of the study group was 29.11 ± 5.33 score, which was below of the control group 40.94 ± 7.86 score ($P < 0.001$, 95%CI: 9.165~14.495). It illustrated that the pain of patients could be remarkably reduced and improve the patient's knee function post-treatment, and the relief effect of study group is better.

KOOS score

The comparison of the results of KOOS scores among the both groups were presented in table 2. Pre-treatment, KOOS scores of pain, daily activities, sports and recreation, and quality of life were not remarkably different among the control and study group ($P>0.05$). The scores of the both groups post-treatment were increased compared to pre-treatment. The scores of the study group were 74.06 ± 11.78 , 68.72 ± 11.22 , 57.04 ± 6.82 and 67.23 ± 11.75 score, respectively, which were remarkably improved compared to control group 61.77 ± 11.37 , 60.75 ± 7.60 , 44.23 ± 7.05 and 59.21 ± 6.70 score ($P<0.001$), respectively, indicated that the knee injury of the patients was remarkably improved post-treatment, and the improvement extent of the study group was better.

Lysholm score and knee range of motion

The comparison of the results of Lysholm scores and knee range of motion among the both groups are presented in fig. 3. Pre-treatment, Lysholm scores of the control and study group were 68.29 ± 3.95 and 68.26 ± 4.53 score, respectively, with no significant differences ($P=0.972$, 95%CI: $-1.717\sim 1.657$). The knee joint motion of the control and study group was $115.27\pm 6.22^\circ$ and $115.15\pm 7.51^\circ$, respectively, with no significant difference ($P=0.931$, 95%CI: $-2.857\sim 2.617$). Post-treatment, the both groups scores were remarkably improved compared to pre-treatment. The Lysholm score of study group was 90.49 ± 4.79 score, which was above to control group 80.90 ± 4.49 score ($P<0.001$, 95%CI: $-11.433\sim -7.747$), the knee range of motion of study group was $135.19\pm 5.32^\circ$ above to $126.05\pm 5.54^\circ$ in control group ($P<0.001$, 95%CI: $8.624\sim 12.936$). It indicated that the treatment could significantly improve the patients knee joint function and improve the patients' knee joint mobility, and the patients in the Study group had better knee joint improvement.

Inflammatory factor indicators

The results of inflammatory factor index analysis among the both groups were presented in table 3. Pre-treatment, no significant differences in IL-6, IL-17, TNF- α and TGF- β contents among the both groups (all $P>0.05$). Post-treatment, the inflammatory index content in both groups was remarkably decreased compared to pre-treatment, and the inflammatory factor index content in the study group was 11.22 ± 1.89 pg/mL and 10.59 ± 1.70 pg/mL, 20.02 ± 2.86 pg/mL and 31.48 ± 4.69 μ g/mL, respectively, were remarkably below in 16.80 ± 2.11 pg/mL and 12.95 ± 2.36 pg/mL, 30.44 ± 3.18 pg/mL and 34.40 ± 5.58 μ g/mL, respectively, in control group (both $P<0.05$), illustrated that the anti-inflammatory ability of both groups was remarkably improved post-treatment, and the anti-inflammatory effect of the study group was better.

Clinical efficacy

The clinical effective analysis results of the both groups are presented in fig. 4. Total effective rates of the control

group was 76.0% (38/50) and that of the study group was 90.0% (45/50), which was remarkably improved compared to control group ($P<0.05$), illustrated that the efficacy of the study group was better.

Occurrence of adverse reactions

The adverse reactions of patients in both groups during treatment, such as infection, swelling and blood accumulation, were observed in varying degrees, as presented in table 4. The adverse reactions incidences was 8.0% (4/50) in the control group and 6.0% (3/50) in the study group, and no remarkable discrepancy in the adverse reactions among the both groups.

DISCUSSION

Knee swelling and pain are the prominent symptoms of KOA in the acute phase. At the same time, the disease is also a common cause of knee joint dysfunction and deformity. It is an inflammatory disease about the whole synovial joint, include synovium, fat pad under patella, meniscus, ligament around joint and subchondral bone (Sanchez Lopez *et al.*, 2022). Although conservative therapy can alleviated the symptomatic of KOA to some extent, it is very easy to relapse. Long-term patients with KOA have sleep disturbances and are prone to depressive due to chronic ache, which is the most common and serious consequence, and chronic ache limits physical activities, while physical inactivity can lead to increased knee pain and weight gain, creating a vicious cycle (Wojcieszek *et al.*, 2022). There are currently no drugs that can stop the progression of KOA or reverse the existing damage, and current treatments can only delay the disease progress, so early interventions are needed to reduce the knee joint pain and relieve the disease symptoms (Jang *et al.*, 2021).

HA is one of the components of joint synovial fluid and cartilage matrix, which can play a role in lubricating and reducing friction between tissues. Intra-articular injection of HA can restore the concentration of intra-articular HA to normal, and at the same time eliminate pain caused by joint movement and soft tissue sliding friction by stimulating endogenous HA synthesis, play a role in relieving pain and anti-inflammatory, and contribute to the repair of cartilage injury (Chavda *et al.*, 2022). HA can protect the damaged cartilage to prevent the deterioration of the disease, and can also help repair the damage of cartilage after forming a polymer with glycoprotein. Moreover, HA has viscous-inducing properties, which can stimulate endogenous HA expression in synovium and increase the viscoelasticity of intra-articular tissues. A number of studies have proved that intra-articular HA injection can effectively relieve knee pain, improve joint function, and delay the development of the disease (Mao *et al.*, 2023; Migliorini *et al.*, 2024). NSAID, glucocorticoids, analgesics and

Table 1: Baseline characteristics of patients in each group

Parameter	Control group (n=50)	Study group (n=50)	t/χ^2	P
Age (years)	57.80±7.36	57.20±6.83	-0.423	0.674
Gender (Male/Female)	27/23	24/26	0.360	0.548
Body mass index (kg/m ²)	25.06±2.55	24.81±2.89	-0.459	0.648
Lesion site (single/double)	31/19	30/20	0.042	0.838
Duration of illness (month)	15.75±2.11	16.01±1.80	0.663	0.509

Table 2: Comparison of KOOS scores

norm	time	Control group (n=50)	Study group (n=50)	t	P	95%CI
Pain	Pre-treatment	29.16±5.72	29.48±4.89	0.301	0.764	-1.792~2.432
	Post-treatment	61.77±11.37*	74.06±11.78*	5.308	<0.001	7.695~16.885
Daily activities	Pre-treatment	46.88±8.27	47.44±7.62	0.352	0.726	-2.596~3.716
	Post-treatment	60.75±7.60*	68.72±11.22*	4.159	<0.001	4.167~11.773
Sports and recreation	Pre-treatment	31.87±5.71	30.43±6.58	-1.169	0.245	-3.885~1.005
	Post-treatment	44.23±7.05*	57.04±6.82*	9.234	<0.001	10.057~15.563
Quality of life	Pre-treatment	39.61±6.44	39.23±7.89	-0.264	0.793	-3.238~2.478
	Post-treatment	59.21±6.70*	67.23±11.75*	4.193	<0.001	4.224~11.816

Note: “*” represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 3: Comparison of inflammatory factors

norm	time	Control group (n=50)	Study group (n=50)	t	P	95%CI
IL-6 (pg/mL)	Pre-treatment	28.51±2.01	28.29±2.07	-0.539	0.591	-1.03~0.59
	Post-treatment	16.80±2.11*	11.22±1.89*	-13.929	<0.05	-6.375~-4.785
IL-17 (pg/mL)	Pre-treatment	55.31±7.97	54.12±7.31	-0.778	0.438	-4.225~1.845
	Post-treatment	12.95±2.36*	10.59±1.70*	-4.862	<0.001	-3.176~-1.544
TNF- α (pg/mL)	Pre-treatment	57.35±4.57	58.63±4.76	1.372	0.173	-0.572~3.132
	Post-treatment	30.44±3.18*	20.02±2.86*	-17.227	<0.001	-11.62~-9.22
TGF- β (μ g/mL)	Pre-treatment	64.69±3.89	65.55±4.11	1.075	0.285	-0.728~2.448
	Post-treatment	34.40±5.58*	31.48±4.69*	-2.833	<0.05	-4.966~-0.874

Note: “*” represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 4: Occurrence of adverse reactions

Group (n=50)	Infection	Swelling	Hematoma	Total incidence (n, %)
Control group	1	2	1	4 (8.0)
Study group	1	1	1	3 (6.0)
χ^2			0.307	
P			0.579	

other drugs are commonly used in clinical treatment of KOA. Among them, the most commonly used oral drugs are NSAID, which have antipyretic, analgesic and anti-inflammatory effects and are the first-line drugs for OA, reducing pain, improving stiffness, and improving joint function (Giaretta *et al.*, 2024). Celecoxib is widely used in clinical practice, mainly to relieve the symptoms and signs of osteoarthritis, and has a certain effect on patients with acute pain (Cheng *et al.*, 2021). The 2018 KOA treatment expert consensus points out that NSAID are the commonly used drugs for the KOA treatment (Chan *et al.*, 2023), among which selective COX-2 inhibitors, such as celecoxib and imrecoxib, have relatively small gastrointestinal side effects. Celecoxib capsules are selective COX-2 inhibitors that have remarkably reduced side effects compared to conventional NSAID (Cruz *et*

al., 2022). Relevant studies have found that celecoxib can inhibit apoptosis, promote chondrocyte growth and protect chondrocytes in knee osteoarthritis (Du *et al.*, 2020; Timur *et al.*, 2020). Therefore, in this study, celecoxib was selected as the control group to treat KOA, and intra-articular HA injection combined with oral celecoxib capsule was selected as the study group to treat KOA, and the efficacy of the two groups was compared and analyzed.

The results showed that post-treatment, the indexes of the two groups of patients were better than pre-treatment ($P<0.05$). Post-treatment, the total effective rates of 90.0% (45/50) in the study group was above to the 76.0% (38/50) in control group ($P<0.05$), indicating that the combined treatment in study group had a remarkable

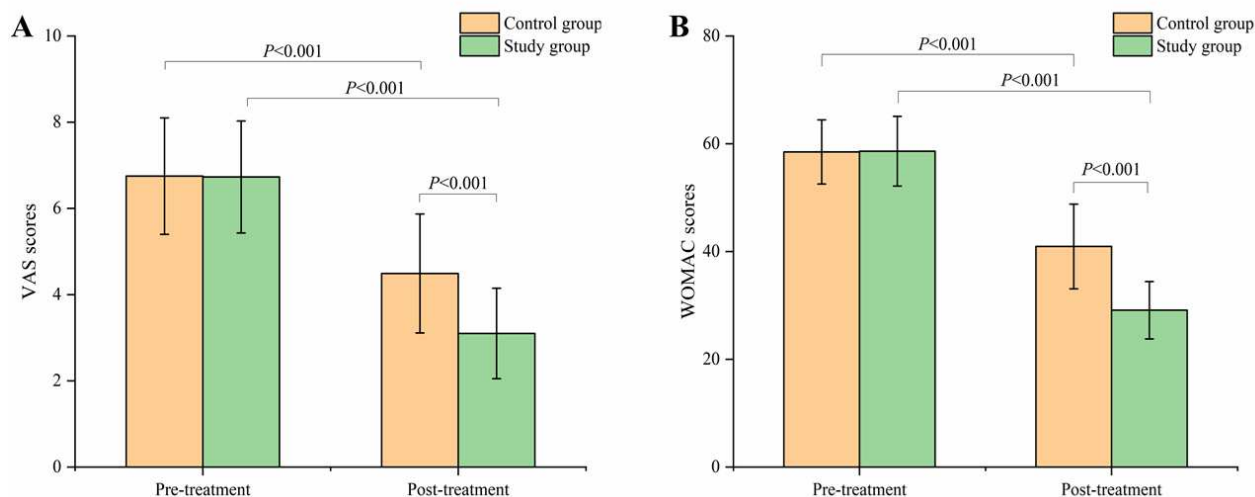


Fig. 2: Comparisons of VAS scores and WOMAC scores (fig. A represents VAS scores, fig. B represents WOMAC scores)

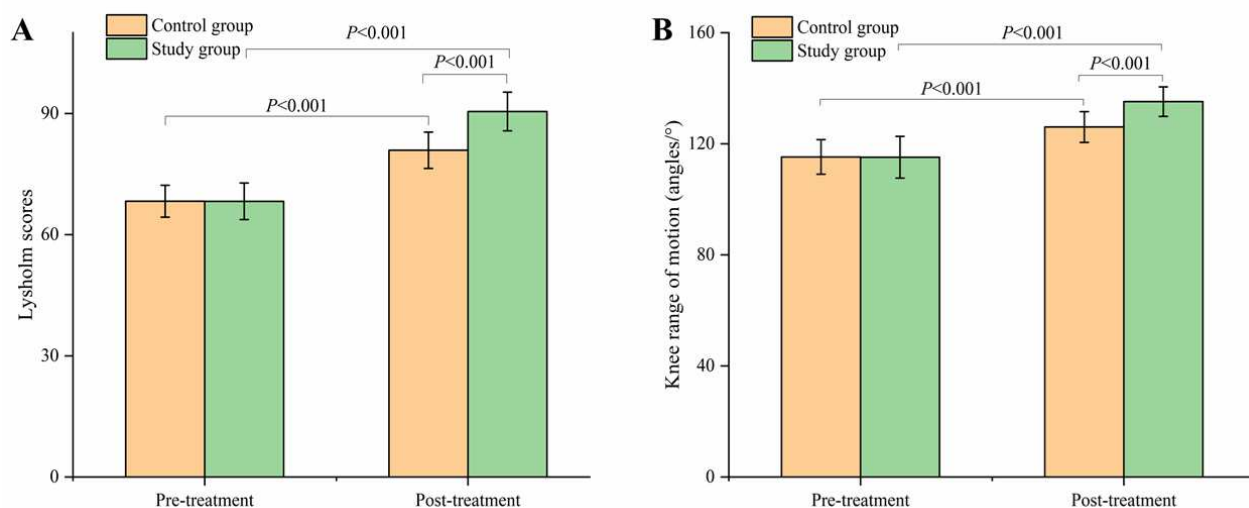


Fig. 3: Comparison of Lysholm scores and knee range of motion (fig. A represents Lysholm scores, fig. B represents knee range of motion)

clinical effect. In terms of physiological indexes and functional scores before and post-treatment, the changes of study group patients were more obvious, and the KOOS score, Lysholm score and knee motion of study group patients were remarkably above in control group ($P<0.05$), VAS scores and WOMAC scores were below in control group ($P<0.05$). In summary, all scores of patients in the study group were remarkably better to the control group ($P<0.05$), illustrated that intra-articular HA injection combined with oral celecoxib capsule in the treatment of KOA can remarkably reduce pain, improve knee joint motion, improve knee joint function and remarkably improve the quality of life of patients with KOA. This conclusion is consistent with the study reported by Xu *et al.* (2020) on intra-articular ketorolac and corticosteroid injection in the treatment of KOA. At the same time, KOA is often accompanied by changes in inflammatory factors, and the results showed that the

level of inflammatory factors in the study group was remarkably below in the control group post-treatment ($P<0.05$), indicating that the combined treatment of the two can remarkably reduce the clinical inflammatory response in KOA patients. In addition, the adverse reactions incidence was 8.0% (4/50) in the control group and 6.0% (3/50) in the study group, with no significant differences among the both groups ($P>0.05$). Najm *et al.* (2021) reported similar conclusions in study on the treatment of KOA by intra-articular corticosteroid injection. After the disease, KOA patients often feel muscle weakness, abnormal gait in daily activities, difficulty in walking, and decreased movement ability in life (Iijima *et al.*, 2020), in this study, the results of intra-articular HA injection combined with oral celecoxib capsule in the treatment of KOA showed that this therapy can effectively relieve patients pain degree, improve the knee joint function and inflammatory response of patients,

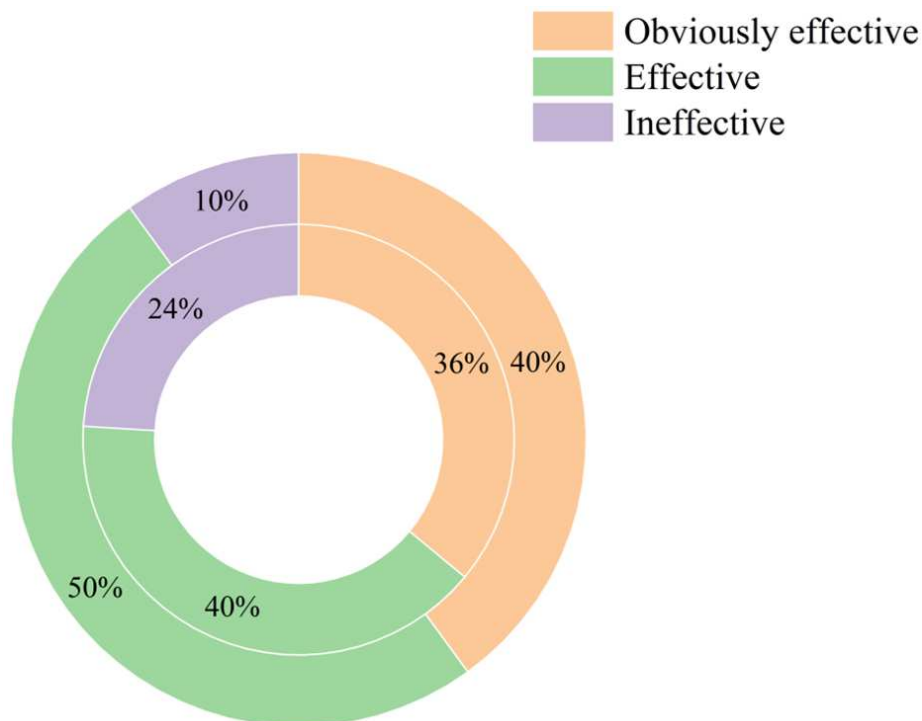


Fig. 4: Clinical efficacy diagram (the proportion of efficacy of the inner and outer rings in the control group and the research group, respectively)

and effectively promote the improvement of patients' quality of life.

CONCLUSION

In this study, KOA was treated by intra-articular injection of HA combined with oral celecoxib capsule, in order to provide a new reference for the treatment of this type of disease. The results showed that intra-articular HA injection combined with oral NSAID in the treatment of KOA is precise, which can effectively relieve the pain degree of patients, improve the bone and joint functions, reduce the degree of osteoarthritic inflammation, and also provides a new reference method for related clinical treatment. However, this study has some shortcomings, such as small sample size and short treatment cycle. Due to limitations, other specific inflammatory indicators could not be added. In the later stage, multi-center, large-sample and high-quality clinical studies can be continued for verification.

Ethical approval

This study was approved by Jiujiang University Affiliated Hospital's Ethics Committee. Ethical approval number is JJUAH-EC-2020-0105.

Authors contribution

[Sijun Ruan]: Developed and planned the study, performed experiments, and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.

[Sijun Ruan]: Participated in collecting, assessing, and interpreting the data. Made significant contributions to data interpretation and manuscript preparation.

[Xiqing Cheng]: Provided substantial intellectual input during the drafting and revision of the manuscript.

Data Availability statement

The data that support the findings of this study are available from the corresponding author, upon request.

Conflict of interest

The authors declare that they have no financial conflicts of interest.

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