Tropical Journal of Pharmaceutical Research April 2024; 23 (4): 777-782
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i4.14

Original Research Article

Effect of intra-articular injection of sodium hyaluronate on knee function and inflammatory state in knee osteoarthritis patients

Lei Zhu, Yuxi Wei, Jun Zhang*
Orthopedics, Renmin Hospital, Hubei University of Medicine, Shiyan, Hubei, China

For correspondence:* ***Email:* *jiuyongtao5@126.com*

Sent for review: 26 April 2023 *Revised accepted: 23 March 2024*

Abstract

Purpose: *To investigate the effect of intra-articular sodium hyaluronate injections in knee osteoarthritis (KOA) patients.*
Methods: *110 patients with KOA admitted to Renmin Hospital, Hubei University of Medicine, Shiyan, China from September 2019 and October 2021 were enrolled in this study. Each patient was assigned a number based on the time of admission, and the patients were randomly divided into control and study groups. Total effectiveness (efficacy), and visual analog scale (VAS) scores in both groups were evaluated. Also, the levels of inflammatory factors, viz, IL-6, TNF-α, and TLR4 were investigated using enzyme-linked immunosorbent assay (ELISA)*
Results: *The total effectiveness in the study group was significantly higher compared to control group ($p < 0.05$), while the visual analog scale (VAS) scores of the study group were significantly lower than those of the control group one week and three months after treatment ($p < 0.05$).*
Conclusion: *Intra-articular injection of sodium hyaluronate relieves pain, restores knee function, and reduces joint inflammation. Future long-term studies utilizing a larger number of patients from multiple centers will be required to validate treatment effects, potential for relapse, and recurrence of symptoms.*

Keywords: *Knee osteoarthritis, Intra-articular injection, Sodium hyaluronate, Knee joint function, Inflammatory*

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Knee osteoarthritis (KOA) is a joint disease caused by degenerative pathological changes [1,2]. Joint tenderness and discomfort are likely to cause joint pain during prolonged periods of cold weather, fatigue, and temperature fluctuation. In addition, joint pain and movement disorders worsen as a result of joint damage or reduced mobility [3]. Osteoarthritis (OA) is categorized into primary knee arthritis and secondary knee arthritis, based on their etiology. It is generally believed that the cause of primary OA is a combination of systemic and local factors, including cartilage nutritional metabolism and stress imbalances. Secondary knee arthritis occurs as a result of secondary changes in the knee caused by primary disease such as sagittal joint irregularities, joint surface irregularities, injuries, mechanical wear, metabolic diseases,

© 2024 The authors. This work is licensed under the Creative Commons Attribution 4.0 International License

joint instability, infections, etc [4,5]. Initially, clinical symptoms are slow to appear, as patients gradually experience knee swelling, knee pain and discomfort during daily activities. It is also possible for patients to suffer from swelling and fluid retention, resulting in their inability to move flexibly or even at all. The incidence of this disease is mildly associated with gender; however, it is higher in elderly people [6,7]. The incidence of OA varies from region to region in China. The rate of symptomatic OA is higher in rural areas compared to cities, and is significantly higher in southwest and northwest China compared to north and eastern China, with a total incidence rate of 8.1 % [8]. In clinical practice, in order to cure knee OA, it is necessary to determine a treatment protocol that is tailored to the patient's condition.

Treatment is usually divided into four levels which may include; relieving pain, slowing down disease progression, resolving deformity, improving or restoring joint function; in advanced stages, surgical treatment is required [9]. A neurotransmitter analgesic drug called celecoxib is most commonly used in clinical settings. The principal aim of this medication is to alleviate the symptoms and signs of OA, rheumatoid arthritis, and the treatment of acute pain in adults. In addition to having anti-inflammatory and analgesic properties, it improves knee movement in patients [10,11]. However, clinical evidence suggests that patients may develop drug resistance after long-term use, resulting in adverse effects on subsequent therapy.

As a polymer polysaccharide biomaterial, sodium hyaluronate is formed by repeated alternation between N-acetylglucuronic acid and sodium hydroxide [12,13]. In addition to lubricating and preventing spasticity, it enhances joint contracture, prevents cartilage degeneration and surface changes, improves pathological synovial fluid, improves dripping and sliding function, further stabilizes the muscles and ligaments around the knee joint, and promotes knee joint recovery [14,15]. Despite this, there are very few studies on the use of sodium hyaluronate in knee arthritis. This study investigated the effect of intra-articular injections of sodium hyaluronate in treating KOA and thus provides relevant data for future research.

METHODS

Subjects

A total of 110 patients with KOA from September 2019 and October 2021 were enrolled, comprising 51 males and 59 females. The subjects were randomly divided into control and study groups consisting of 55 patients each. This study was carried out after approval by the Medical Ethics Committee of Renmin Hospital, Hubei University of Medicine, Shiyan, China (approval no. 109237j/7) and conducted following the Declaration of Helsinki [16].

Inclusion criteria

Patients who met the diagnostic criteria for knee osteoarthritis (KOA) with confirmation using X-ray or MRI imaging.

Exclusion criteria

Patients with serious functional diseases affecting the heart, brain, liver, kidneys, etc; patients who were unconscious or unable to communicate normally, as well as those with advanced bone lesions or significant skeletal abnormalities other than KOA.

Treatments

Control group

Control group received 200 mg of celecoxib capsules (approval no. J20140072, Pfizer Pharmaceutical Co. Ltd) orally, with warm water once a day for 5 weeks.

Study group

Study group received intra-articular injections of sodium hyaluronate as described below: The patient was in supine position, with the knee joint exposed at 15 ° of flexion, and the lateral edge of the patella, or the lower angle of the patella, was selected as the puncture point. After inserting the needle, a pump was applied. In the event of an effusion in the joint, the effusion was removed and sodium hyaluronate was injected. The patient was injected once a week with 2.5mL sodium hyaluronate (approval no. H20054738, Xi'an Libang Pharmaceutical Co., Ltd.).

Following injection, sterile cotton balls were placed at the eye of the needle for 30 s to allow for disinfection, and thereafter the sterile dressing was applied. The treatment lasted for 5 weeks. In both groups of patients, traditional Chinese medicine (TCM) fumigation and washing treatments were administered (study group received treatment 3 - 7 days after each sodium hyaluronate injection). The following herbs were mixed in 2 L of water and left to soak for 30 min; 15 g *Achyranthes bidentata*, 15 g frankincense, 15 g myrrh, 15 g clematis, 30 g rattan, 30 g Shenjincao, 15 g *Rhizoma drynariae*, 15 g

Fangfeng, 15 g Cao Wu, 15 g safflower, 15 g Chuanwu, 15 g blood scorpion, 30 g Tougu grass, 30 g Pittosporum bark, and 15 g Angelica.

The preparation was boiled, transferred to a small basin, and a towel was then placed in the basin and applied to the affected area for approximately 20 min, after which the towel was changed and the process repeated for 30 mins, and the treatment lasted for one month.

Evaluation of parameters/indices

Clinical efficacy/effectiveness

Clinical efficacy was classified as markedly effective (clinical symptoms disappeared at end of treatment), effective (clinical symptoms improved at end of treatment), and ineffective (no clinical symptoms improved).

Pain

The visual analogue scale (VAS) was used to assess pain in the patients prior to and after treatment. Based on a scale of 0-10, a score of 0-3 was considered mild pain, hardly noticeable pain, but without an impact on daily life, 4 to 6 was deemed moderate pain, obvious but bearable, and > 7 was considered severe and unbearable pain.

Knee joint function

This study used the Lysholm Knee Joint Scoring System (LKSS) for assessing lameness and pain, with a total score of 100 points. The knee function is proportional to the score.

Inflammatory status

Blood samples (5 mL) were taken from each group before and after treatment, centrifuged for 15 min at 3000 rpm, and serum was separated. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and Toll-like receptor 4 (TLR4).

Statistical analysis

GraphPad Prism 8 software (GraphPad Software, San Diego, CA, USA) was used to present figures, and Statistical Packages for Social Sciences (SPSS 24.0, IBM, Armonk, NY, USA) software was used for data analysis. Measurement data was presented in mean ± standard deviation (SD) and an independent sample *t*-test was used for inter-group comparison. Count data was presented in frequencies and percentages (n, %), and the chi-square test (χ^2) was used for comparison. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data

There was no significant difference in baseline data in both study and control groups ($p > 0.05$) (Table 1).

Clinical efficacy

Total effective rate of study group was significantly higher compared to control group ($p < 0.05$) (Table 2).

Pain

There was no significant difference in VAS in both groups before treatment ($p > 0.05$). However, at 1 week and 3 months after treatment, the VAS score of study group was significantly lower ($p < 0.05$) (Figure 1).

Knee joint function

There was no significant in Lysholm point in both groups ($p > 0.05$) before treatment. However, Lysholm point in study group was significantly higher compared to control group after treatment ($p < 0.05$) (Table 3).

Inflammatory state

There was no significant difference in inflammatory factors in both groups before treatment ($p > 0.05$). However, levels of IL-6, TNF-α, and TLR4 were significantly lower in study group compared to control group ($p < 0.05$) (Table 4).

Table 1: Baseline data (N = 55 in each group, mean ± SD)

Group	Gender		Age (years)		Course of disease		Educational level	
	Male	*Female*	*Scope*	*Mean age*	*Scope*	*Mean age*	*High school and below*	*Undergraduate and above*
Study	26	29	45-78	58.27±3.68	0.5-5	2.32±0.51	31	24
Control	25	30	46-80	58.59±3.41	0.8-5	2.45±0.54	29	26
T-value	-	-	-	0.473	-	1.298	-	-
P-value	-	-	-	0.637	-	0.197	-	-

Table 2: Clinical efficacy (*N = 55 in each group;* N, %)

Group	Markedly effective	Effective	Ineffective	Total effective rate
Study	25(45.45)	28(50.91)	2(3.64)	53(96.36)
Control	20(36.36)	24(43.64)	11(20.00)	44(80.00)
χ^2		7.066		
P-value		0.008		

Note: Total effective rate = markedly effective rate + effective rate

Table 3: Lysholm points (mean ± SD)

Group	Pre-treatment	Post-treatment
Study	62.45±3.56	85.23±5.21
Control	62.87±3.41	74.65±4.85
T-value	0.632	11.023
P-value	0.529	<0.001

Table 4: Comparison of inflammatory factor levels (mean ± SD)

Period	Inflammatory factor	Group		*T*-value	*P*-value
		Study	***Control***		
Before treatment	IL-6	317.56±40.28	318.08±39.54	0.068	0.946
	TNF-α	24.56±3.21	24.98±3.15	0.693	0.490
	TLR4	18.64±5.94	18.32±6.01	0.281	0.779
After treatment	IL-6	213.15±23.56*	256.45±30.21*	8.382	<0.001
	TNF-α	11.09±2.30*	15.38±2.48*	9.406	<0.001
	TLR4	11.32±4.93*	15.95±5.03*	4.875	<0.001

Note: **P* < 0.05 compared to control group

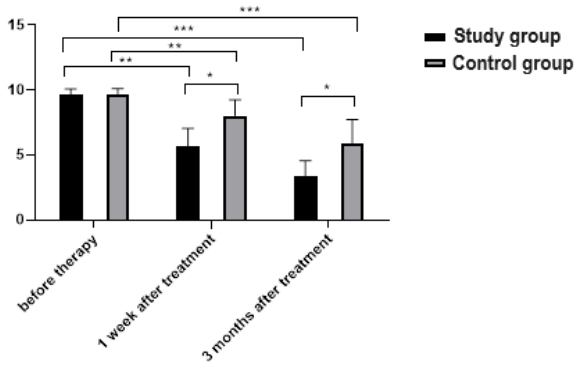

Figure 1: Visual analogue score of study and control groups. *Note: *P* < 0.05 between the two groups, ***p* < 0.05 within the same group before and one week after treatment, ****p* < 0.05 within same group before and three months after treatment

DISCUSSION

Knee osteoarthritis (KOA) most commonly affects the knee. Pain, muscle weakness, stiffness, instability, and reduced mobility are common symptoms of KOA ultimately affecting patient's ability to live independently, and hindering quality of life [16]. Sodium hyaluronate is one of the components of cartilage matrix, which consists primarily of glucuronic acid and acetyl hexose. It is a non-ethnic glycosaminoglycan, which is injected into the articular cavity of patients. Thus, it alleviates symptoms related to synovial fluid loss in the intra-articular joint, maintains level within normal limits while protecting the joint, restores cartilage structure, promotes joint function, recovery, and easing symptoms [17]. Therefore, the purpose of this study was to investigate the effects of intra-articular injection of sodium hyaluronate in treating KOA. The results indicated that the overall treatment efficacy of study group was significantly higher. Celecoxib is a highly selective COX inhibitor, and one of the commonly prescribed orthopedic drugs in clinical practice. It relieves inflammation, pain, and at same time, it is associated with a high risk of adverse reactions [18,19]. However, sodium hyaluronate is composed of alternating n-acetyl glucosamine, which is a primary component of joints. It is commonly used in the treatment of various skin lesions in clinics. It is used to treat middle-aged and elderly KOA by lubricating and protecting cartilage, improving contracture, and preventing cartilage degeneration. The results of this study indicated that VAS scores in study group one week after treatment and 3 months after treatment were significantly lower, and the Lysholm score was significantly higher. It is believed that patients with KOA have a lower sodium hyaluronate content in their joints than that of healthy people [22]. It has been demonstrated that exogenous injection of sodium hyaluronate restores knee function, reduce friction, lubricate joints, and ease pain among patients. Additionally, sodium hyaluronate has a relatively strong affinity with

knee cartilage, which allows it to adhere rapidly to the surface of the cartilage to provide protection, slows down development of cartilage degeneration and decreases metabolic disorder of cartilage tissue. By improving clinical efficacy, and reducing penetration of proteoglycan into cartilage matrix, it is able to slow down the injury process, accelerates healing and regeneration of cartilage, and enhances knee joint functionality in patients. This is similar to previous studies that sodium hyaluronate is effective in relieving pain, reducing complications, and enhancing joint mobility [17]. Inflammatory factors (IL-6 and TNF-α) may cause knee joint injury and aggravates joint pain, TLR4 promotes the synthesis of inflammatory factors and its presence enhances disease healing. The results of this study indicate that IL-6, TNF-α, and TLR4 levels after treatment were significantly lower in study group compared to control group. In addition to functional exercise, there is evidence to suggest that sodium hyaluronate significantly reduces inflammatory substances in joints and prevents progression of arthritic conditions. The results demonstrated that injection of sodium hyaluronate into the synovial fluid lubricated joints, removed joint pain substances, reduced excretion of inflammatory substances. Furthermore, the fumigation and purging of Qi and blood with TCM improves blood circulation within joint tissues and accelerates the clearance of endogenous inflammatory substances. Studies suggest that the therapeutic effect of integrating TCM and Western medicine is more effective in reducing pain in the treatment process as well as promoting the restoration of knee joint function as quickly as possible [20]. Both groups were treated with TCM fumigation procedures which included promoting blood circulation and dredging collaterals, warming tendons and strengthening bones, removing arthralgia, and removing stasis. *Pittosporum* bark, *Fangfeng*, among other substances contained in the prescription, reduce swelling, relieve pain, warm the meridians, dredge collaterals, dispel Qi and eliminate blood stasis, while *Achyranthes* and *Rhizoma drynariae* strengthen bones and tendons, promote blood circulation and prevent complications. Tendon grass activates tendons and veins, penetrates bone and clear meridians, myrrh and frankincense encourage the smooth movement of blood and Qi. Additionally, safflower, *Angelica sinensis* and blood scorpion relieve cold and pain, warm meridians, promote blood circulation; Cao Wu and Chuanwu, reduce swelling and pain, expel cold and disperse dampness. Multiple drug combinations eliminate complications, dispelling wind and easing pain, strengthening muscles and bones, as well as facilitating joint mobility [21]. A good way to make TCM efficient is the application of heat to fumigate and wash the drugs. This creates a better environment for the drugs to perform. It is also used in combination with sodium hyaluronate to achieve the purpose of simultaneous treatment of bones and muscles.

Limitations of this study

The limitations of this study include the limited sample size, single-center approach, and lack of objective measures such as biomarkers of inflammation which may potentially affect the generalizability of the results. This study employed a short-term follow up which did not provide more comprehensive information on the treatment effects and the potential for relapse or recurrence of symptoms. Also, the lack of placebo control and the presence of potential confounding factors (concomitant medications or other interventions) group made it difficult to determine whether the observed effects were specifically due to the treatment or reflected natural disease progression or placebo effects.

CONCLUSION

Intra-articular injection of sodium hyaluronate improves knee function and reduce pain and joint inflammation, and is, therefore, a potentially safe and effective treatment option for KOA. Future long-term studies utilizing a larger number of patients from multiple centers will be required to validate treatment effects, potential for relapse, and recurrence of symptoms.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This study was approved by approval by the Medical Ethics Committee of Renmin Hospital, Hubei University of Medicine, Shiyan, China (approval no. 109237j/7).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Lei Zhu and Yuxi Wei contributed equally to the study.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. *Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee osteoarthritis: A primer. Perm J 2017; 21: 16-183.*
2. *Hussain SM, Neilly DW, Baliga S, Patil S, Meek R. Knee osteoarthritis: A review of management options. Scott Med J 2016; 61(1): 7-16.*
3. *Kan HS, Chan PK, Chiu KY, Yan CH, Yeung SS, Ng YL, Shiu KW, Ho T. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J 2019; 25(2): 127-133.*
4. *Sharma L. Osteoarthritis of the knee. N Engl J Med 2021; 384(1): 51-59.*
5. *Jang S, Lee K, Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. Int J Mol Sci 2021; 22(5): 2619.*
6. *Brophy RH, Fillingham YA. AAOS clinical practice guideline summary: management of osteoarthritis of the knee (Nonarthroplasty), Third edition. J Am Acad Orthop Surg 2022; 30(9): e721-e729.*
7. *Deyle GD, Allen CS, Allison SC, Gill NW, Hando BR, Petersen EJ, Dusenberry DI, Rhon DI. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. N Engl J Med 2020; 382(15): 1420-1429.*
8. *Perlman A, Fogerite SG, Glass O, Bechard E, Ali A, Njike VY, Pieper C, Dmitrieva NO, Luciano A, Rosenberger L, et al. Efficacy and safety of massage for osteoarthritis of the knee: a randomized clinical trial. J Gen Intern Med 2019; 34(3): 379-386.*
9. *Lin X, Zhi F, Lan Q, Deng W, Hou X, Wan Q. Comparing the efficacy of different intra-articular injections for knee osteoarthritis: A network analysis. Medicine (Baltimore) 2022; 101(31): e29655.*
10. *Codazza S, Ferrara PE, Gueli G, Ferriero G, Ronconi G. The management of knee osteoarthritis in elderly: results from a national survey compared to ESCEO guidelines. Eur Rev Med Pharmacol Sci 2022; 26(1): 24-32.*
11. *Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP injections for the treatment of knee osteoarthritis: A meta-analysis of randomized controlled trials. Cartilage 2021; 13(1): 364S-375S.*
12. *Benner RW, Shelbourne KD, Bauman SN, Norris A, Gray T. Knee osteoarthritis: Alternative range of motion treatment. Orthop Clin North Am 2019; 50(4): 425-432*
13. *Deyle GD, Allen CS, Allison SC, Gill NW, Hando BR, Petersen EJ, Dusenberry DI, Rhon DI. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. N Engl J Med 2020; 382(15): 1420-1429.*
14. *Siddiq MAB, Clegg D, Jansen TL, Rasker JJ. Emerging and new treatment options for knee osteoarthritis. Curr Rheumatol Rev 2022; 18(1): 20-32.*
15. *Allaeys C, Arnout N, Van Onsem S, Govaers K, Victor J. Conservative treatment of knee osteoarthritis. Acta Orthop Belg 2020; 86(3): 412-421.*
16. *Ferreira RM, Torres RT, Duarte JA, Gonçalves RS. Non-pharmacological and non-surgical interventions for knee osteoarthritis: A systematic review and meta-analysis. Non-pharmacological and non-surgical interventions for knee osteoarthritis: A systematic review and meta-analysis. Acta Reumatol Port 2019; 44(3): 173-217.*
17. *Tang JZ, Nie MJ, Zhao JZ, Zhang GC, Zhang Q, Wang B. Platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. J Orthop Surg Res 2020; 15(1): 403.*
18. *Zou Y, Hu S, Yang X, Wang W, You H, Hu B, Zhang D. Effects of the combination of loxoprofen sodium and sodium hyaluronate on osteoarthritis and knee function. Trop J Pharm Res 2022; 21(9): 2025-2030.*
19. *Cho SK, Choi S, Kim H, Song YJ, Jung SY, Jang EJ, Sung YK. COX-2 inhibitor use as an early treatment option for knee osteoarthritis patients in Korea: A population-based cross-sectional study. J Korean Med Sci 2022; 37(18): e148.*
20. *Wang M, Liu L, Zhang CS, Liao Z, Jing X, Fishers M, Zhao L, Xu X, Li B. Mechanism of traditional Chinese medicine in treating knee osteoarthritis. J Pain Res 2020; 13: 1421-1429.*
21. *Zhou G, Zhang X, Gu Z, Zhao J, Luo M, Liu J. Research progress on the treatment of knee osteoarthritis combined with osteoporosis by single-herb Chinese medicine and compound. Front Med (Lausanne) 2023; 10: 1254086.*