Research Paper

Efficacy of Intra-Articular Injection of Chitosan in Conjunction with Traditional Chinese Medicine Guidance Therapy in Knee Osteoarthritis

LIWEI YU, TINGYA WANG[1], JUN HUANG[2] AND XIAOBEI ZHANG[2]*

Department of Traditional Chinese Medicine Tuina, Huadong Hospital Affiliated to Fudan University, Shanghai 200040, [1]Department of Acupuncture and Moxibustion Tuina Traumatology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 201306, [2]Department of Anesthesiology, Jia Ding Hospital of Traditional Chinese Medicine, Shanghai 201801, China

To figure out the effectiveness of chitosan intra-articular injection in conjunction with traditional Chinese medicine guidance therapy in treating knee osteoarthritis. Between October 2019 and May 2023, we conducted a randomized study involving 128 individuals with knee osteoarthritis who were treated at our hospital. These individuals were assigned to either the observation group or the control group. The control group received chitosan intra-articular injections, while the observation group received traditional Chinese medicine guidance therapy in addition to the control group's treatment. To evaluate the function and symptoms of the knee joint, multiple metrics were employed, including the Western Ontario and McMaster Universities osteoarthritis index score, visual analog scale, synovium thickness, and the distance covered in a 6 min walking test. The occurrence of adverse reactions was also monitored, and an assessment was conducted on the overall effectiveness rate in both study groups. A notable disparity was observed in the overall effectiveness rate between the observation group and the control group, with the observation group displaying a significantly higher rate. Moreover, the outcomes of the Western Ontario and McMaster Universities osteoarthritis index score, visual analog scale score, and 6 min walking distance in the observation group were considerably better than those recorded in the control group. The observation group displayed a significant reduction in synovium thickness in the knee joint compared to the control group. Additionally, the occurrence of adverse reactions, including dizziness and headache, abdominal pain and diarrhea, red and swollen skin, as well as joint swelling, was significantly lower in the observation group as opposed to the control group. The utilization of chitosan intra-articular injection along with traditional Chinese medicine guidance therapy has proven to be an effective strategy for managing knee osteoarthritis. This comprehensive treatment approach not only yields a significant improvement in the overall effectiveness rate but also enhances knee joint function while minimizing the occurrence of adverse reactions. It holds great promise and should be considered for broader adoption.

Key words: Chitosan, intra-articular injection, traditional Chinese medicine guidance therapy, knee osteoarthritis, physical therapy

Characterized by the degeneration of articular cartilage, narrowing of the joint space, and the formation of secondary bone spurs, Knee Osteoarthritis (KOA) is a persistent degenerative condition that mainly affects the knee joints[1-3]. Its symptoms primarily include knee joint deformity, swelling, pain, limited mobility, and atrophy of the surrounding tissues. In severe cases, it may lead to inward or outward curvature of the knee joint, resulting in disabilities and a reduced quality of life. Current treatment methods for osteoarthritis mainly involve medication, physical therapy, and surgical interventions[4,5]. However, these traditional methods only provide symptomatic relief and do not cure the condition. Furthermore, certain medication treatments may carry the potential for side effects and risks. As a result, the exploration of an effective and safe treatment approach has emerged as a prominent

***Address for correspondence**
E-mail: 15711648124@126.com

subject of current research[6].

In recent years, intra-articular injection of chitosan and traditional Chinese medicine guidance therapy has gained attention and recognition from clinicians and researchers as potential treatments for osteoarthritis. Chitosan, a natural biopolymer, possesses good biocompatibility and biodegradability, making it highly suitable for tissue repair and regeneration. It can stimulate the proliferation and differentiation of chondrocytes, promoting cartilage repair and regeneration. Intra-articular injection of chitosan directly targets the articular cartilage, exerting protective and reparative effects, thus slowing down the progression of osteoarthritis[7]. Additionally, traditional Chinese medicine guidance therapy, based on unique theories and extensive clinical practices, aims to adjust the body's qi and blood circulation, enhance the supply of nutrients to the joints, alleviate pain and inflammation, and improve joint function and quality of life.

This study seeks to assess the therapeutic efficacy of combining intra-articular injection of chitosan with traditional Chinese medicine guidance therapy for the management of osteoarthritis. A selected number of osteoarthritis patients will undergo the proposed treatment plan. Through the observation and evaluation of changes in joint function, pain relief, adverse reactions, and other indicators over a certain period, the effectiveness of this therapy will be assessed[8,9].

MATERIALS AND METHODS

General information:

A total of 128 patients were recruited from our hospital between October 2019 and May 2023 for inclusion in this study. The patients were divided into two groups; an observation group (65 cases) and a control group (63 cases). The observation group had an age range of 52 y to 73 y, with an average age of (63.73±5.67) y, including 37 males and 28 females. The control group had an age range of 53 y to 73 y, with an average age of (63.26±5.78) y, including 34 males and 29 females. No significant difference in general information between the two groups ($p>0.05$) was observed, indicating that the groups were comparable in terms of demographic and baseline characteristics.

Inclusion and exclusion criteria:

Inclusion criteria: Meet the relevant diagnostic criteria for KOA in the "Chinese guidelines for the diagnosis and treatment of osteoarthritis (2021 edition)"[10,11]; exhibit typical symptoms such as swelling, pain, stiffness, and limping in the knee joint; no contraindications to traditional Chinese medicine guidance, intra-articular injection of chitosan, or other treatment methods; good compliance and ability to cooperate with the treatment; voluntary participation in this study and approval of the research protocol by the hospital's ethics committee.

Exclusion criteria: Concurrent systemic musculoskeletal disorders; autoimmune diseases, inflammatory diseases; receiving other therapeutic drug interventions before enrollment; liver or kidney dysfunction, pregnant or lactating women; patients with missing or incomplete baseline and clinical examination data.

Dropout criteria: Failure to strictly follow the treatment protocol of this study; need for adjustment of treatment plan due to changes in the condition and voluntary withdrawal from the study during the course of treatment.

Treatment methods:

The control group received intra-articular injection of medical-grade chitosan (Shanghai Qisheng Biopharmaceutical Co., Ltd., Medical Device Registration No. 20173640026, concentration 12 mg/ml). The injection site was sterilized, and local surface anesthesia was performed using lidocaine. A supine position was adopted by the patients, with their knee joint flexed at an angle of 45°. The puncture point for injection was carefully determined on the medial side of the patellar ligament, situated below the patella. Prior to administering the medication into the joint cavity, any existing joint effusion was aspirated. Following the injection, the knee joint underwent passive flexion and extension movements, performed approximately 5-6 times to facilitate proper dispersion of the medication within the joint cavity. This injection protocol was repeated at intervals of 2 w over a total period of 3 mo.

The observation group received traditional Chinese medicine guidance therapy in addition to the treatment given to the control group. The traditional Chinese medicine guidance therapy referred to Wei's knee joint guidance method in traumatology[12], which is a simple and effective functional rehabilitation exercise. It consists of five techniques, as follows:

Bouncing knee guidance: The patient stands with

both feet together, knees flexed. The patient bends forward and places the palms above the patella on both knees. Both knees are forcefully extended backward from the flexed position to the extended position. The position of the feet also moves backward during the sudden extension. It is normal to hear joint sounds or experience slight pain during the abrupt extension. Each exercise consists of one flexion and one extension. Mild cases perform 5-10 exercises per session, while severe cases perform fewer exercises. The exercise is performed 2-3 times per day.

Hesitation knee guidance: The patient stands in front of a wall with the feet shoulder-width apart. The heels are approximately one foot's length away from the wall. The patient squats down against the wall, placing both hands on the knees, and breathes naturally for about 10 times before slowly standing back up. It is normal to experience a feeling of qi retrogression or having heavy and sore knees during the exercise. Generally, squatting is performed around 5 times per session, and the exercise is performed 2-3 times per day.

Harmonizing knee guidance: The patient stands with both feet and knees together, and then semi-flexes the lower limbs at the knee, slightly leaning the waist and hips back. Both palms are placed on the patella on both knees. In the first step, the hands rotate clockwise from left to right. In the second step, the hands rotate counterclockwise from right to left. The rotation should be gentle and smooth, following the body's natural movements, without excessive force that may cause friction around the knee joint. The hands should be tightly pressed on the patella to effectively facilitate the rotation. Each rotation direction is performed 5 times, and generally, 3-5 exercises are performed per session. The exercise is performed 2-3 times per day.

Buttoning knee guidance: This technique can be performed in a sitting or supine position. In the sitting position, the patient sits on a bench with the knees placed outside the edge of the bench. In the supine position, the patient lies on the bed with the knees placed outside the edge of the bed. The knee joint undergoes continuous flexion and extension using the strength of the lower limbs, with emphasis on the flexion movement. Each extension and flexion together is considered one repetition. Generally, about 30-50 repetitions are performed per session, focusing on the affected side only when there is unilateral involvement or on both sides simultaneously when both knees are affected.

Dismissing knee guidance: The patient sits with the knee joint fully extended, contracts the quadriceps muscle in the front of the thigh, and extends the foot as much as possible. The entire lower limb is slowly lifted and held for about 15 s before slowly lowering it down. Each lifting and lowering is considered one repetition. Generally, 30 repetitions are performed per session, and the exercise is performed 2-3 times per day.

Among these techniques, bouncing knee and hesitation knee guidance are generally suitable for patients with mild knee joint pain and less obvious swelling. Harmonizing knee, buttoning knee, and dismissing knee guidance are suitable for patients with mild or severe KOA.

Observation indicators:

Knee joint function evaluation: The prognosis scores of the two patient groups were statistically compared 3 mo after treatment. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate the knee joint symptoms and activity function of the patients[13]. This index consists of three parts; pain, joint stiffness, and daily activities, with a total of 24 items. Each item is scored on a 5-point scale, and the total score is 96. A higher score indicates more severe symptoms.

Knee joint pain level: The knee joint pain levels of the two patient groups before and after 3 mo treatment were assessed and compared using the Visual Analog Scale (VAS). This scale ranges from 0 to 10, with lower scores indicating milder pain.

6 Min Walk Distance (6MWD): The 6MWD of the two patient groups before and after 3 mo treatment was measured and compared.

Synovium thickness: The thickness of the synovium and the depth of knee joint effusion were measured using musculoskeletal ultrasonography. The operating procedures followed the guidelines for musculoskeletal ultrasound examinations issued by the European society of musculoskeletal radiology ultrasound subcommittee and the "Illustrated guide to musculoskeletal ultrasound intervention"[14,15].

Adverse reactions: The occurrence rates of adverse reactions during treatment were observed and compared between the two patient groups.

Evaluation of therapeutic efficacy:

After the completion of the treatment course, the clinical efficacy of the two patient groups was observed and evaluated, and the total effective rate was calculated for comparison. The evaluation of therapeutic efficacy followed the guidelines of the "Expert Consensus on Stepwise Treatment of KOA" (2018 edition)[16].

Significant improvement: The patient's swelling, pain, stiffness, limping, and other symptoms and signs are reduced to disappearance, and knee joint mobility is restored to normal.

Effective: The patient's symptoms and signs show significant improvement, and knee joint mobility is noticeably improved.

Ineffective: There is no significant improvement in the patient's symptoms and signs after treatment.

The total effective rate=(Significant improvement+effectiveness) patients/total number of patients in each group×100 %

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) 25.0 software was employed for statistical analysis. Count data were expressed as percentages (%) and analyzed using the Chi-square (χ^2) test. Measurement data were presented as mean±standard deviation (x±s) and analyzed using the t-test. $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Upon completion of the 3 mo treatment regimen, the observation group exhibited 39 cases of significant improvement, 21 cases of effectiveness, and 4 cases of ineffectiveness, resulting in an overall effective rate of 92.3 %. In comparison, the control group recorded 31 cases of significant improvement, 17 cases of effectiveness, and 15 cases of ineffectiveness, yielding a total effective rate of 76.2 %. Importantly, the overall effective rate of the observation group was significantly superior to that of the control group ($p<0.05$), as shown in Table 1.

The baseline data analysis revealed no significant distinctions between the two groups prior to treatment ($p>0.05$). Following the intervention, both the observation and control groups demonstrated substantial enhancements in WOMAC scores, VAS scores, and 6MWD measurements ($p<0.05$). Moreover, the observation group exhibited significantly superior improvements in WOMAC scores, VAS scores, and 6MWD measurements compared to the control group ($p<0.05$) as shown in Table 2.

TABLE 1: COMPARISON OF CURATIVE EFFECT

Group (n)	Significant improvement	Effectiveness	Ineffectiveness	Overall effective rate
Observation (65)	39 (60.0)	21 (32.3)	4 (6.2)	60 (92.3)
Control (63)	31 (49.2)	17 (27.0)	15 (23.8)	48 (76.2)
χ^2				7.89
p				0.005

TABLE 2: COMPARISON OF CURATIVE EFFECT

Group (n)	WOMAC score (point)		VAS score (point)		6MWD (m)	
	Before	After	Before	After	Before	After
Observation (65)	56.04±12.45	38.11±8.95*	6.40±1.27	0.92±0.50*	208.87±14.20	399.51±23.23*
Control (63)	56.79±12.69	47.35±9.04*	6.24±1.05	1.65±0.48*	208.54±14.24	298.10±22.64*
t	0.336	5.812	-0.764	8.449	-0.131	-25.004
p	0.737	0.000	0.446	0.000	0.896	0.000

Note: Compared with pre-treatment, *p<0.05

TABLE 3: ADVERSE REACTIONS

Group (n)	Synovium thickness (mm)		t	p
	Before	After		
Observation (65)	5.60±1.10	3.69±0.74	2.967	0.004
Control (63)	5.45±1.14	4.14±0.95	7.16	0.000
t	-0.752	3.024		
p	0.454	0.003		

TABLE 4: ADVERSE REACTIONS n (%)

Group (n)	Dizziness and headache	Abdominal pain and diarrhea	Red and swollen skin	Joint swelling	Overall incidence
Observation (65)	1 (1.5)	1 (1.5)	0 (0)	0 (0)	2 (3.1)
Control (63)	2 (3.2)	3 (4.8)	2 (3.2)	2 (3.2)	9 (14.3)
χ^2					5.117
p					0.024

Prior to treatment, no noteworthy variances in synovium thickness were observed between the two groups. Following the intervention, a significant reduction in synovium thickness was evident in both groups ($p<0.05$). Furthermore, the observation group exhibited a significantly smaller thickness of the synovium compared to the control group after treatment ($p<0.05$) as shown in Table 3.

Throughout the treatment period, both the observation and control groups encountered adverse reactions including dizziness, headache, abdominal pain, diarrhea, skin redness, and joint swelling. The overall incidence rates were 3.1 % (2/65) in the observation group and 14.3 % (9/63) in the control group, revealing a statistically significant difference ($p<0.05$) as shown in Table 4.

Osteoarthritis, also known as degenerative joint disease or age-related osteoarthritis is a chronic joint condition characterized by degenerative changes in articular cartilage and secondary bone remodeling. It primarily affects the middle-aged and elderly population, with a prevalence of over 50 % in individuals aged 65 and above[17]. Currently, there is no definitive method to halt the progression of osteoarthritis, and existing treatment approaches can only slow down its progression[18,19].

Guidance therapy is an important treatment method in traditional Chinese orthopedics. It has a long history and is documented in the ancient Chinese medical text "Huangdi Neijing"[20]. The concept of guidance, also known as "Dao Yin," involves combining breath regulation and body movements to promote the smooth flow of the body's qi and blood, as well as enhance flexibility and agility. In this study, we observed that the observation group (treated with intra-articular chitosan injection combined with traditional Chinese guidance therapy) achieved significant therapeutic efficacy compared to the control group (treated with intra-articular chitosan injection alone) in the management of osteoarthritis. The overall treatment efficacy rate in the observation group was significantly higher than that in the control group, indicating a positive impact of traditional Chinese guidance therapy in the treatment of osteoarthritis.

In terms of improvement in knee joint function, the observation group demonstrated significantly better outcomes compared to the control group. This could be attributed to the ability of traditional Chinese guidance therapy to adjust the body's yin-yang balance, promote qi and blood circulation, and improve joint function. These findings are consistent with previous research results, supporting the application of traditional Chinese guidance therapy in the management of osteoarthritis[21]. Additionally, patients in the observation group exhibited greater reductions in pain intensity and improvements in the 6MWD compared to the control group. Pain reduction is a crucial treatment goal in osteoarthritis, and traditional Chinese guidance therapy may achieve this by improving blood and qi circulation, and activating the meridians. The 6MWD is an important indicator for assessing patient's physical abilities and quality of life. The improved walking distance in the observation group post-treatment may be attributed to the enhanced joint function and reduced pain achieved through traditional Chinese

guidance therapy. Furthermore, this study found a significant decrease in synovium thickness in both groups after treatment, with a greater reduction observed in the observation group. This suggests a positive effect of traditional Chinese guidance therapy in reducing synovium reactions, which may be closely related to its anti-inflammatory properties. Another notable finding is that the occurrence rate of adverse reactions during treatment was significantly lower in the observation group compared to the control group. This suggests advantages in terms of safety for traditional Chinese guidance therapy, as it can reduce the risk of adverse reactions. However, further research is needed to investigate the safety and long-term effects of traditional Chinese guidance therapy.

Although this study demonstrated the potential of intra-articular chitosan injection in conjunction with traditional Chinese guidance therapy in the management of osteoarthritis, there are some limitations to consider. First, the study design was single-center with a relatively small sample size, requiring multicenter studies with larger sample sizes to validate the results. Secondly, the follow-up period in this study was relatively short and long-term efficacy and safety need to be further monitored and evaluated.

Funding:

The work was supported by Natural Science Research Project in Jiading District, Shanghai (No: JDKW-2020-0031).

Author's contributions:

Liwei Yu and Tingya Wang have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Lu S, Yang J, Zhang L. Effect of diclofenac sodium sustained release capsule combined with traditional Chinese medicine and rehabilitation exercise training on primary knee osteoarthritis. J Baotou Med Coll 2022;5:38.
2. Chen DI, Shen J, Zhao W, Wang T, Han L, Hamilton JL, *et al.* Osteoarthritis: Toward a comprehensive understanding of pathological mechanism. Bone Res 2017;5(1):1-3.
3. Nelson AE. Osteoarthritis year in review 2017: Clinical. Osteoarthritis Cartilag 2018;26(3):319-25.
4. Guo SC, Huang J. Advances in the treatment of knee osteoarthritis. J Inner Mongolia Med Coll 2021;32:3327.
5. He R. Progress in diagnosis and treatment of knee osteoarthritis. Med Dietetic Ther Health J 2021;19(11):2.
6. Xing D, Wu H, Yu N. Expert consensus on the application of medical chitosan in articular cavity injection (2018 version). Chin J Joint Surg 2018;12(2):3.
7. Xia H. Clinical analysis of chitosan intra-articular injection combined with manipulation in the treatment of degenerative knee osteoarthritis. Med Health 2023;4:4.
8. Yu S, Wang Y, Zheng M. Observation on the curative effect and satisfaction of Zheng's massage guidance combined with characteristic health education on knee osteoarthritis in community. Sichuan Tradit Chin Med 2017:35(10):3.
9. Niu Xi, Ye Yi, Qiu Z. Research progress of guidance in the prevention and treatment of knee osteoarthritis. Rheum Arthritis 2019;8(12):5.
10. Zhao Xi, Zhu C, Tang J. Comparison of clinical efficacy of chitosan and sodium hyaluronate in the treatment of knee osteoarthritis. Chin Med J 2021;56(6):4.
11. Fan Z, Wang G, Li C. Interpretation and evaluation of Chinese guidelines for diagnosis and treatment of osteoarthritis (2021 Edition). Chin J Evid Based Med 2022.
12. Yan W, Xi X, Xu Y. Experience of Wei's Traumatology department in the treatment of knee osteoarthritis. J Beijing Univ Tradit Chin Med 2021:51-4.
13. Copsey B, Thompson JY, Vadher K. Problems persist in reporting of methods and results for the WOMAC measure in hip and knee osteoarthritis trials. Qual Life Res 2019;28(2):335-43.
14. Zhu C, Zheng H. Application of high frequency ultrasound in the treatment of knee joint under the guidance of high frequency ultrasound. J Interv Radiol 2020;29(11):1.
15. Wang HM, Liu JN, Zhao Y. Progress on integrated Chinese and Western medicine in the treatment of osteoarthritis. Chin J Integr Med 2010;16(4):378-84.
16. Wang Bo, Yu N. Consensus of experts on step treatment of knee osteoarthritis (2018 edition). Chin J Joint Surg 2019.
17. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. Lancet 2011;377(9783):2115-26.
18. Xie H, Wang B, Fu W. Evaluation of platelet-rich plasma combined with sodium hyaluronate in the treatment of knee osteoarthritis during arthroscopy. Chin J Clin 2020;48(3):4.
19. Hao F, Lin J. Interpretation of the guidelines for diagnosis and treatment of osteoarthritis (2007 Edition). Chin J Clin 2010;7:3.
20. Xia X. The origin of guidance in the pre-Qin and Han dynasties. J Tradit Chin Med 2015;4(6):2-8.
21. Jiang Y, Feng F. Clinical application of traditional Chinese medicine massage guidance in the treatment of knee osteoarthritis. China Rural Health 2017;16:1.

This article was originally published in a special issue, "Exploring the Role of Biomedicine in Pharmaceutical Sciences" Indian J Pharm Sci 2024:86(1) Spl Issue "136-141"