

Clinical Observation of Tongxuekang Capsule in Treating Knee Osteoarthritis

Ronghua Xie, Yuan Feng, Xichao Yang, Linxuan Pang, Yun Jia, Zhenbiao Wu*

Department of Clinical Immunology, Xijing Hospital, Air Force Military Medical University, Xi'an, 710032, China

Abstract: Objective: To evaluate the efficacy and safety of Tongxuekang capsule in the treatment of knee osteoarthritis. **Methods:** Single-centred, open self-control methods before and after administration were performed in different time length of 14 days, 28 days, 56 days and 84 days to observe for improvement by evaluating knee joint pain scores, WOMAC scores, and doctors and patients' scores on the overall condition of the disease before and after treatment. **Results:** A total of 34 patients with primary knee osteoarthritis from October 2016 to September 2017 were enrolled in Xijing Hospital. There were 7 males and 27 females with an average age of 54 years and an average body mass index of 25kg/m². Joint pain scores, WOMAC scores, and doctors' and patients' overall scores for the disease were significantly improved compared to prior treatment, with no significant adverse reactions in all patients. **Conclusion:** Tongxuekang capsule is safe and effective in the treatment of knee osteoarthritis and thus, can be used as a treatment option. In order to conduct further studies on the effectiveness and safety of consumption with the use of the capsule in a larger population, an increase in the sample size of the current study is necessary.

Keywords: *Tongxuekang; Osteoarthritis; Clinical treatment*

Project Fund: Shaanxi Science and Technology Coordination Innovation Project Plan 508142631047

Publication date: July, 2019

Publication online: 31 July, 2019

Corresponding Author: Zhenbiao Wu, Xieronghua1978@126.com

1 Introduction

Osteoarthritis is a common clinical common joint disease in humans. With the increasing incidence of aging, it has become an important social health problem leading to pain, loss of function and disability in the elderly. A study of 17,128 Chinese populations showed that 81% of patients with symptomatic knee osteoarthritis were over 45 years of age^[1]. Since the knee joints are important weight-bearing joints of the body, pain and morning stiffness of the knee joints often require long-term medical treatment intervention. Traditional medicines for the treatment of osteoarthritis mainly include opioid analgesics and non-steroidal anti-inflammatory drugs(NSAIDs). Opioids have a good analgesic effect, but are addictive and hence has limited the use of the drug. NSAIDs have dual anti-inflammatory and analgesic effects, but long-term use of NSAIDs can lead to gastrointestinal and renal damage and increased cardiovascular risk. In this, the safety of consumption is also a matter of attention and concern. Tongxuekang capsule is mainly a compound preparation consisting of *Liliaceae* dried rhizome of the lily plant, *Aconitum* grass, *Psammosilene tunicoides* gold iron lock and *Polygonum* grass, which has the functions of analgesic and anti-inflammatory effects, promote blood circulation, stops bleeding and so on. To further evaluate the capsule's efficacy and safety of consumption in the treatment of knee osteoarthritis, the following clinical observations were conducted.

2 Materials, objects and methods

2.1 Test design

Single-centred, open before and after administration control method; 12-week course; at baseline, 28th day and 84th day visits to the visit centre, complete relevant

laboratory tests and questionnaires; 14th day and 56th day telephone follow-ups, complete the relevant questionnaire scale.

2.2 Case selection

Inclusion criteria: meet the diagnostic criteria for knee osteoarthritis (American Society of Rheumatology ACR 1995).

Exclusion criteria: combined with other active arthritis, such as rheumatoid arthritis, gout, acute injury, etc.; previous gastrointestinal ulcers, bleeding; unstable cardiovascular disease; blood routine: $PLT < 80 \times 10^9/l$ or $Hb < 90g/l$ Or $WBC < 3.0 \times 10^9/l$; Liver function: AST or ALT exceeds the upper limit > 2 times; creatinine exceeds the upper limit of normal > 1.5 times; intra-articular drug injection within 3 months; faecal occult blood positive; 3 months other drug clinical trials; pregnant and lactating women.

Contraindications: Do not take oral or topical other non-steroidal anti-inflammatory drugs, hormones and analgesic drugs during the test; avoid injection of drugs in the joint cavity.

Efficacy evaluation target knee joint.

2.3 Drugs and methods of administration

Tongxuekang capsule, the specification is 0.2g/grain; Prescription: 0.2g, 3times/day; on the 1st, 2nd and 3rd day of the drug, take 1 capsule of the insurance capsule every morning; the course of treatment is 12 weeks. The medicine was provided by Fujian Huitian Biopharmaceutical Company.

2.4 Main efficacy indicators

1. Knee joint static pain score;
2. WOMAC score;
3. The overall evaluation of the patient's disease status;
4. The doctor's overall evaluation of the patient's disease.

The total pain of the knee joint and the overall evaluation of the disease were evaluated using the visual analogue pain scale method (VAS method, 0-100mm). The leftmost "0" means no pain, and the rightmost "100" means very painful.

WOMAC uses a questionnaire to evaluate knee osteoarthritis pain in terms of pain, stiffness, and life difficulties.

2.5 Adverse drug reactions

Monitoring blood routine, urine routine, liver function, and renal function before and after taking the drug for 4

and 12 weeks;

Record other adverse events that occurred in the subject.

2.6 Statistical methods

Self-paired t-test before and after treatment, SPSS software analysis.

3 Results

3.1 General information

In this study, patients with primary knee osteoarthritis from the Xijing Hospital outpatient department from October 2016 to September 2017 were selected. All patients who received this study were asked by the investigator for their consent signed on written informed consents.

A total of 34 cases were enrolled and 30 cases were completed; 4 cases uncompleted, 1 case was lost during follow-up, and 3 cases were withdrawn due to the lack of efficacy. There were 7 males and 27 females with an average age of 54.18 ± 8.41 years (minimum age 38 years, maximum 68 years). The average duration of disease is 9.04 ± 10.30 years (the shortest 3 months, the longest 37 years). The average body mass index is $25.20 \pm 4.60 \text{kg/m}^2$ (minimum 16.1, maximum 37)

Of the 34 patients, 33 had a history of bilateral knee pains and only 1 had a history of left knee pain. All the patients showed X-ray involvement of both knees, manifested as hyperostosis or narrowing of the gap. One patient with Sjogren's syndrome overlapped with systemic lupus erythematosus, one with Sjogren's syndrome, and one with hypertension. The complications of these 3 patients was stable. One case of previous gallstones appendicitis, one case of previous appendicitis, and both patients have undergone surgery and have recovered.

3.2 Evaluation before and after treatment

3.2.1 Joint static pain VAS score

The static pain of the joints before treatment was 53.67 ± 15.02 , and the static pain of the 14th, 28th, 56th and 84th day after treatment were 41.60 ± 15.46 , 33.96 ± 16.21 , 28.47 ± 12.44 , 24.30 ± 10.02 , respectively compared with before treatment as the baseline. The results obtained demonstrated statistical differences ($P < 0.0001$), suggesting that patients with knee pains were significantly relieved. See Table 1.

Table 1. Comparison of the joint pain VAS with the baseline

Timeline	M _{VAS(mm)} ±SD	P
0	53.67±15.02	
14th day	41.60±15.46	<0.001
28th day	33.96±16.21	<0.001
56th day	28.47±12.44	<0.001
84th day	24.30±10.02	<0.001

3.2.2 WOMAC knee osteoarthritis index score

The score of WOMAC knee osteoarthritis before treatment was 68.27±35.29, and the scores of 14th, 28th, 56th and 84th day after treatment were 60.80±32.30, 56.33±29.74,

48.13±26.47, 46.67±25.77, respectively with indication of statistical differences ($P<0.0001$), suggesting that the patient’s pain, joint stiffness, and life difficulties improved after treatment. See Table 2.

Table 2. Comparison of the WOMAC with the baseline

Timeline	M±SD	P
0	68.27±35.29	
14th day	60.80±32.30	<0.001
28th day	56.33±29.74	<0.001
56th day	48.13±26.47	<0.001
84th day	46.67±25.77	<0.001

3.2.3 Overall evaluation of patients’ comprehensive status before and after treatment

The overall score of patients with osteoarthritis before treatment was 53.76±10.88, with the score differences evaluated for the 14th, 28th, 56th and 84th

day after treatment to be 44.93±10.96, 41.40±12.36, 35.70±10.88, 32.13±12.36, respectively indicating statistical differences ($P<0.0001$), suggesting that the overall disease status of the patients improved significantly after treatment. See Table 3.

Table 3. Comparison of the overall evaluation of the OA with the baseline by patients

Timeline	M _{VAS(mm)} ±SD	P
0	53.76±10.88	
14th day	44.93±10.96	<0.001
28th day	41.40±12.36	<0.001
56th day	35.70±10.88	<0.001
84th day	32.13±12.36	<0.001

3.2.4 Overall evaluation of the general condition of the patient’s disease before and after treatment

The doctors scored 49.07±11.90 for the disease before treatment, and 41.40±11.72, 38.70±10.79, 35.60±10.08, 33.33±10.27 for the 14th day, 28th day, 56th day and

84th day after treatment, respectively with significant differences($P<0.0001$). Inthis, the doctor’s evaluation was consistent with the overall evaluation of the patient’s condition, and the overall disease status of the patient improved significantly after treatment. See Table 4.

Table 4. Comparison of the overall evaluation of the OA with the baseline by doctor

Time	M _{VAS(mm)} ±SD	P
0	49.07±11.90	
14th day	41.40±11.72	<0.001
28th day	38.70±10.79	<0.001
56th day	35.60±10.08	<0.001
84th day	33.33±10.27	<0.001

In addition to the relief of the target knee joint pain, Tongxuekang capsule also has a significant relief effect on other pain. One patient had an ankle swelling and pain, and that the ankle pain was significantly relieved after treatment. Another patient with lumbar hyperplasia and lower back pain experienced a reduction of the back pain after treatment leading to improved activity.

3.3 Safety of consumption evaluation

During the 12-week treatment observation period, there were 3 adverse events, and the incidence of adverse drug events was 10%. There was one case of calf pain and one case of alopecia. These 2 cases were not given any special treatment and no drugs were discontinued. Eventually, the symptoms were seen to be resolved spontaneously. It is interesting to point out that a 50-year-old female patient regained menstruation again after one year of menopause. Throughout this study, no serious adverse events were observed. All patients had no gastrointestinal discomfort and there were no obvious abnormalities in laboratory tests such as hematuria, liver and kidney function.

4 Discussion

Osteoarthritis is a chronic disease with joint pain and dysfunction as the main clinical manifestations. It occurs in the knee joint, hip joint and other parts, and the cause is complicated. The pathological features were articular cartilage degeneration, subchondral and marginal callus formation, secondary synovitis, joint capsule contracture, and narrow joint space. Because the disease can cause joint pain, stiffness and dysfunction, it seriously affects the quality of life of patients, especially to the elderly. In this study, the average age of patients with osteoarthritis was 54 years old, mostly females and the average body mass index was 25 kg/m², suggesting that the incidence of the disease is at approximately 50 years old. From what was observed, women and obesity are risk factors for osteoarthritis.

Traditional Chinese medicine has the effect of relieving pain and improving function. In Asia, Europe and other countries, the traditional Chinese medicine has played an important role for the treatment of knee osteoarthritis^[2,3]. For example, acupuncture and Tai Chi have been written into the OARSI guidelines^[4] and are recommended for the treatment of non-surgical knee osteoarthritis. In addition, Chinese herbal medicine has also been reported in a large number of literatures in

relieving pain and improving joint function^[5].

The current study showed that the Tongxuekang capsule has a certain effect in the treatment of knee osteoarthritis. From the second week of treatment, the patient's pain was significantly relieved, suggesting that the drug has a faster onset of treatment. The static pain scores at a timeline of four weeks, eight weeks, and 12 weeks, the overall evaluation of patients, and the overall evaluation of VAS scores of doctors all demonstrated significantly lower scoring when comparisons were made between before and after treatment. Similarly, the WOMAC scores after treatment were also lower than that before treatment, suggesting that the administration of the capsule not only provided pain relief to the patients with knee osteoarthritis but also contain a certain curative effect that is able to improve joint stiffness and functions of patients with knee osteoarthritis. In this study, the knee joint was initially focused as the target joint, but it was also observed that in two patients, apart from obtaining knee pain relief, additional relief was attained for the patients' lower back pain and ankle pain, suggesting that the drug has an additional therapeutic effect on arthritis in other areas. However, in three other patients, the improvement of conscious joint pain was not obvious after one month of treatment, and the cases were withdrawn, suggesting that the drug has obvious individual differences.

During the 12-week administration of the study, no significant adverse reactions have occurred, suggesting that it was safe to be consumed. It was worth noting that one patient regained her menstruation after experiencing menopause, which may be related to the effects of blood circulation and phlegm function produced by the drug.

Tongxuekang capsule is mainly composed of *Liliaceae* dried rhizome of the lily plant, *Aconitum* grass, *Psammosilene tunicoides* gold iron lock and *Polygonum* grass. The *Liliaceae* dried rhizome of the lily plant has anti-inflammatory and analgesic effects, inhibits vascular permeability, reduces the exudation of inflammatory mediators, and promotes the dissipation of inflammation^[6]. *Aconitum* grass has the effects of lowering serum PGE2 and histamine levels, reducing the sodium ion current on which pain transmission is dependent on, and has the effect of dilating blood vessels to promote local blood circulation and inhibiting venous thrombosis. *Psammosilene tunicoides* gold iron lock has a chain reaction that inhibits free radicals,

inhibits the synthesis and release of NO/NOS, reduces vascular permeability, and affects neurotransmitter levels in brain tissue to increase pain threshold. Animal experiments has showed that the gold iron lock has protective effect on articular cartilage of rabbit knee joint, and it is concentration-dependent, which may be related to the reduction of IL-1 β , IL-6 and TNF- α expression in cartilage tissues^[7]. *Polygonum* grass has anti-lipid peroxidation and scavenging oxygen free radicals^[8]. Based on the abovementioned pharmacological effects, the Tongxuekang capsule has anti-inflammatory and analgesic effects, and promotes blood circulation, thereby reducing pain and improving joint stiffness and function in patients with knee osteoarthritis.

Knee osteoarthritis is considered as a disorder under Chinese medicine, mainly caused by blood stasis and kidney deficiency. Compared with conventional treatment of osteoarthritis, traditional Chinese medicine has the characteristics of significantly improving symptoms and side effects, and may become a better choice for the treatment of osteoarthritis^[9].

However, this study also has some shortcomings. Because it was performed as an open study, possible influence of the placebo effect in the results generated cannot be excluded. In addition, since the sample size of the study is small, the individual difference factors may not be excluded, thereby affecting the efficacy judgment of the drug. Therefore, in order to have an in-depth understanding of the drug's treatment of osteoarthritis and in the determination of its safety as a form of long-term medication, etc., further studies

should be performed by expanding the sample size and conduct more rigorous case-control studies with the aim of providing more powerful clinical evidences.

References

- [1] Tang X, Wang S, Zhan S, et al. The prevalence of symptomatic knee osteoarthritis in China: Results from the China Health and Retirement Longitudinal Study. *Arthritis Rheumatol.* 2016, 68(3):648-53.
- [2] Brismee JM, Paige RL, Chyu MC, et al. Group and home-based tai chi in elderly subjects with backbone osteoarthritis: a randomized controlled trial. *Clin Rehabil.* 2007, 21(2):99-111.
- [3] Williamson L, Wyatt MR, Yein K, et al. Severe backbone osteoarthritis: a randomized controlled trial of acupuncture, physiotherapy (supervised exercise) and standard management for patients awaiting knee replacement. *Rheumatology (Oxford).* 2007, 46(9):1445-9.
- [4] McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of backbone osteoarthritis. *Osteoarthr. Cartil.* 2014, 22(3):363-88.
- [5] Hou P, Fu P, Hsu H, et al. Traditional Chinese medicine in patients with osteoarthritis of the knee. *J Tradit Complement Med.* 2015, 5(4):182-96.
- [6] He HJ, Zhang HY, Chen LL, et al. Advances in pharmacological action and clinical application of saponins. *Chinese herbal medicine,* 2014, 37(3):527-30.
- [7] Wang SM, Liu Y, Liu XL, et al. Protective effect and mechanism of Psammosilene tunicoides gold iron lock on articular cartilage in rabbits with knee osteoarthritis. *Shandong Medicine,* 2016, 56(16):27-9.
- [8] Zhang XY. Study on analgesic and anti-inflammatory effects of Polygonum grass. *Chinese Pharmacology and Clinical Medicine,* 2001, 17(2):19-20.
- [9] Min Y, Li J, Qing W, et al. Traditional Chinese medicine for knee osteoarthritis: An overview of systematic review. *PLoS One.* 2017, 12(12):e0189884.