

Traditional Chinese Medicine Involving Triple Rehabilitation Therapy for Knee Osteoarthritis in 696 Outpatient Cases: A Multi-center Randomized Controlled Trial

Jiemei Guo

Fujian Health College

Tangyan Cai

Fujian Health College

Yan Xiao

Fujian University of Traditional Chinese Medicine

Jianhui Wang

Fujian University of Traditional Chinese Medicine

Baolin Li

Fujian University of Traditional Chinese Medicine

Lulu Huang

Fujian University of Traditional Chinese Medicine

Xiao Mao

Fujian University of Traditional Chinese Medicine

Xingquan Lai

Fujian Tingzhou Hospital

Yaju Zhu

Xiaogan Chinese Medicine Hospital

Yiqiang Zhang

Fuzhou First Hospital

Shaoqing Chen

Fujian University of Traditional Chinese Medicine

Youxin Su (✉ suyouxin777@hotmail.com)

Fujian University of Traditional Chinese Medicine

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Abstract

Background: The treatment and rehabilitation of knee osteoarthritis (KOA) are important. This trial was designed to determine the effects of Traditional Chinese Medicine (TCM) involving triple rehabilitation therapy for KOA on the progression of this disease to help expand the use of this therapy.

Methods: In this multi-center, prospective, multi-factor randomized single-blinded parallel controlled clinical trial, 38 community health service centers located in Fuzhou, Guangzhou, Foshan, and Chengdu in China were randomly divided into experimental and control groups equally. A total of 722 patients who met the inclusion criteria were recruited. Health education combined with TCM involving triple rehabilitation therapy for KOA (electro-acupuncture, Chinese medicinal herb fumigation-washing, and traditional exercises) was administered in the experimental group while conventional rehabilitation therapy (physical factor therapy, joint movement training, and muscle strength training) was administered in the control group. Patients with a visual analog scale (VAS) score ≥ 4 were treated with dispersible meloxicam tablets (7.5 mg/time, once/day). The Lequesne index score, VAS score, range of motion (ROM), lower limb muscle strength, knee joint circumference, KOA symptom grading score, and the short-form 36 item health survey questionnaire (SF-36) score were measured for each patient before and at 4 checkpoints during treatment (at 2 weeks, and 4 weeks) and after treatment (at 1 month, and 3 months).

Results: The entire process was completed by 351 and 345 patients in the experimental and control groups, respectively. At all treatment checkpoints, the experimental group demonstrated better outcomes than the control group with regard to the total Lequesne index score, effective rate and rate of improvement of the total Lequesne index score, VAS score, lower limb muscle strength, knee circumference, the KOA symptom grading score, and SF-36 scores as well.

Conclusion: TCM involving triple rehabilitation therapy for KOA is suitable for patients with early or mid-stage KOA. It can alleviate KOA-related pain and swelling, improve lower limb muscle strength, and promote flexion and activity of the knee. This therapy can improve the quality of life in patients undergoing KOA, and should be popularized and made available to the broader community.

Background

Rehabilitation for knee osteoarthritis (KOA) is designed to relieve pain, delay disease progression, protect joint function, and improve quality of life. Common modern-day treatment methods include oral administration of Western medicine, physiotherapy, and surgery. Currently, clinical rehabilitation of KOA in China is mostly performed in high-acuity hospitals; however, challenges such as high implementation cost, increased burden on patients and families, and limited benefits still remain. The prevalence of the disease is increasing rapidly as the population ages ^[1], and since high-acuity hospitals can no longer meet the rehabilitation needs of patients with KOA patients, it is particularly important to explore other KOA rehabilitation programs that can be utilized in the broader community.

In Traditional Chinese Medicine (TCM), KOA is categorized as a “bi syndrome of bone;” the basic pathogenesis of the disease is “qi and blood deficiency in the liver and kidney, stagnation of wind, cold, dampness and stasis.” The principles followed by traditional medicine to treat this disease involve invigorating the liver, kidney, qi, and blood; dispelling wind and dampness; eliminating pathogenic cold and pain; and relaxing tendons and collaterals. Therapeutic methods include oral and external use of TCM, acupuncture and moxibustion, massage, and traditional exercises, among others. Based on literature review, expert consultation, and clinical application, the “TCM involving triple rehabilitation therapy for KOA” plan was created. The treatment program was approved by the Chinese public welfare industry research project of the Ministry of Finance in 2013, and the specific content of the program had been published in *Trials* [2]. This article reports the research process and the corresponding results.

Methods

1 Inclusion and exclusion criteria

1.1 Sample size estimation

The main effect index measured in patients with KOA was the Lequesne index efficiency following general hospital treatment. According to a literature review, the effective rate of the conventional treatment regimen adopted in the control group for improvement of motor dysfunction in patients with KOA was approximately 70%. Preliminary experiments showed that the effective rate of TCM involving triple rehabilitation therapy for KOA in improving motor dysfunction in patients with KOA could reach 82.3%. Taking $\alpha = 0.05$ and $\beta = 0.10$, it was expected that each group (community) should include at least 17 qualified cases ($m = 17$) based on the results of previous epidemiological investigations. Meanwhile, the individual correlation coefficient in the 0.02 allele group was estimated according to the sample content formula:

$$n = \frac{(\mu_{\alpha} + \mu_{\beta})^2 [\pi_1(1 - \pi_1) + \pi_2(1 - \pi_2)] [1 + (m - 1)\rho]}{(\pi_1 - \pi_2)^2}$$

This can be calculated as $n \approx 326.17$, taking $n = 327$; therefore, the number of communities to be observed in each group is $n = n/17 = 327/17 \approx 19$, for a total of 38 in the two groups. After considering the shedding factor, the number of cases was appropriately increased by 10%, and the total number of cases needed in the two groups was approximately 722.

1.2 Sources of patients

From March 2013 to March 2017, 722 patients with KOA with motor dysfunction who met the inclusion criteria participated in this study. The patients were recruited from 38 community health service centers in Fuzhou, Guangzhou, Foshan, and Chengdu, with 19 patients from each community.

1.3 Patient inclusion and exclusion criteria

1.3.1 Diagnostic criteria based on Western medicine

Please refer to the Chinese Medical Association orthopedics chapter, “Guidelines for the diagnosis and treatment of osteoarthritis (2007)” [3].

1.3.2 X-ray staging standard

Please refer to the Kellgren-Lawrence staging standard [4].

1.3.3 Clinical staging criteria

Please refer to Yicong Wang, Editor-in-Chief, *Bone and Joint Injury* (2007 Edition) [5].

1.3.4 TCM diagnostic criteria

Refer to the syndrome differ classification for KOA in the “Guidelines for Clinical Research of New Drugs of TCM” [6], and “Diagnostic and Efficacy Standards for TCM Syndrome” [7]; after repeated discussions, the research group reached a consensus that currently, the most common TCM syndromes in patients with KOA are liver and kidney deficiencies, and stagnation of wind, cold, and dampness. The accompanying clinical manifestations are sore waist and knees, hidden joint pain that worsens with weather changes, unfavorable joint flexion and extension, favoring heat over cold temperatures, light-red tongue with thin or thick-white coating, and a taut and thin pulse.

1.3.5 Inclusion criteria

- ☒ KOA met the diagnostic criteria.
- ☒ Patients were aged 40 to 75 years old.
- ☒ KOA was diagnosed as an early or mid-stage disease.
- ☒ KOA was accompanied by knee pain, swelling, stiffness, or a decline in the strength and endurance of muscles around the knee leading to motor dysfunction.
- ☒ KOA was in line with the TCM syndrome of liver and kidney deficiency, stagnation of wind, cold, and dampness.
- ☒ Patients agreed to participate in this study and provided informed consent.

1.3.6 Exclusion criteria

- ☒ Severe knee swelling.
- ☒ Aided muscle strength was rated as grade 2 or lower.

- ☒ History of knee trauma or knee surgery.
- ☒ Patients with heart, liver, and kidney failure, diabetic gangrene of the lower limbs, and neurological diseases.
- ☒ Patients with lower extremity dysfunction caused by spinal diseases or hip and ankle diseases, and patients who had undergone joint replacement.
- ☒ Patients with a malignant tumor or a local benign tumor of the knee joint.
- ☒ Patients with cognitive and psychological dysfunction.
- ☒ Performed traditional exercises or received massage therapy in the past month.
- ☒ Underwent arthroscopic treatment or articular cavity injection treatment within the last 6 months.
- ☒ Patients attending other clinical trials.

1.3.7 Suspension criteria

- ☒ The occurrence of serious adverse reactions or other serious disease requiring a different treatment.
- ☒ A sudden deterioration of the patient's condition.
- ☒ Patients withdrew from the study for their own reasons.
- ☒ Patients who were unable to comply after enrolling.

1.3.8 Provision for shedding cases

Patients who met the inclusion criteria and were included but then later withdrew owing to personal reasons or adverse reactions, those who had serious adverse reactions, or those who failed to complete the whole follow-up process, were considered as shedding cases.

1.3.9 Provision for adverse reactions and serious adverse reactions

Reactions such as subcutaneous hematoma; cutaneous pruritus; and rashes that coincided with the intervention, disappeared after the cessation of intervention, and reoccurred after the intervention was reinitiated were considered adverse reactions. Events such as syncope caused by needle insertion, blood phobia, skin infection, or traumatic arthritis that coincided with the intervention, disappeared after the intervention was terminated, and then reoccurred after the intervention was reinitiated were defined as serious adverse reactions. Subcutaneous hematoma, cutaneous pruritus, or rashes that only occurred once and were unrelated to treatment were only described and not listed as adverse reactions.

2 Study Design

2.1 Research Group

The study was a randomized controlled clinical cohort study. Residents within the service scope of each community health service center were allocated to one group. The 38 communities were randomly grouped according to the study area, and the experimental and control groups were divided 1:1; there were 19 communities in each group. Nineteen patients from each community health center who met the inclusion criteria for KOA were recruited, with a total of 722 patients.

2.2 Research Blinding

A single-blind method was used to blind the outcome evaluators and statistical analysts by substituting letters A and B for the groups in the report form. After the statistical analyses were completed, the project manager revealed the group codes.

2.3 Intervention Methods

2.3.1 Basic Treatment

Patients in both groups received basic treatment such as health education and drug therapy.

(1) Health Education: Face-to-face teaching between the doctors and patients and educational pamphlets were used to eliminate the fear of disease, establish correct living habits, and avoid further aggravation of the disease; topics included the incidence, potential causative factors, standardized clinical diagnosis, treatment, and rehabilitation of KOA.

(2) Drug therapy: Pain was assessed in both groups during treatment. If the visual analog scale (VAS) was ≥ 4 points, dispersible oral meloxicam tablets (7.5 mg/once a day) were administered. The drug was discontinued when the VAS was < 4 points.

2.3.2 Experimental group

Patients received basic treatment combined with TCM involving triple rehabilitation therapy for KOA (a combination of electro-acupuncture, Chinese medicinal herb fumigation-washing, and traditional exercise).

(1) Electro-acupuncture: Patients were placed in a comfortable position after which the lower limb of the affected side was routinely disinfected. The acupuncture points were selected as dubi (ST-35), neixiyan (EX-LE-4), liangqiu (ST-34), zusanli (ST-36), xuehai (SP-10), yanglingquan (GB-34), yinlingquan (SP-9), and ashi points. Sterile disposable steel needles ($\varphi 0.3 \times 40$ mm, Suzhou Medical Appliance Factory, Suzhou, China) were then inserted at the above acupoints. After reaching a certain depth, an even reinforcing-reducing method was used, along with twirling, lifting, and thrusting the needles to induce the Deqi sensation. After this, the needles were linked as pairs in GB-34, ST-34, SP-10, and SP-9 with an electronic acupuncture apparatus (SDZ-II Huatuo, Suzhou Medical Appliance Factory, Suzhou, China). The program

followed was using a dilatational wave for 30 minutes of treatment, once every other day, 3 times a week for 4 weeks.

(2) Chinese medicinal herb fumigation-washing: The prescription was changed by addition and removal of Haitongpi decoction (volume 88 of *Yi Zong Jin Jian*). Patients fumigated and washed the affected knee joint at home after receiving acupuncture therapy. After wrapping the TCM with gauze, it was added to a container with 3 liters of water, soaked for 30 minutes, and cooked for an additional 30 minutes to obtain about 2 liters of medicinal juice. The affected knee was fumigated with the medicine juice vapor and washed once the juice reached a suitable temperature of 40°C. The knee joint was repeatedly covered with a towel soaked with the medicinal juice; this action was repeated until the liquid turned cold. Fumigation and washing were performed twice a day, in the morning and afternoon, for 6 days a week over a total of 4 weeks.

(3) Traditional Exercises: Based on Tai Chi, Baduanjin, and Yijinjing, an exercise named “three-step-six-style knee exercise”^[8] was designed and practiced once a day, 6 days a week, for 4 weeks.

2.3.3 Control Group

Patients were treated with standard non-TCM therapy combined with KOA conventional rehabilitation therapy with physical factor therapy, joint activity training, and muscle strength training as outlined in the “Guidelines for the diagnosis and treatment of osteoarthritis”^[3], *Practical Rehabilitation Medicine*^[9] and “Consensus of rehabilitation experts on osteoarthritis”^[10].

(1) Physical Factor Therapy: Specific electromagnetic wave (Te Ding Dian Ci Pu, TDP) irradiation was adopted. The distance between TDP and the affected limb was maintained at 30–50 cm. It is advisable to maintain a comfortable temperature at the irradiation site. TDP was irradiated once a day for 20–30 minutes, 6 days a week, with the treatment performed for 4 weeks.

(2) Joint Movement Training: ☒ Drafting: After the patient was seated, a towel roll was padded under the popliteal fossa of the affected lower extremity, if necessary, to relieve discomfort. With the body slightly leaning backward and both hands on the bed for support, the therapist, standing in front of the patient, squatted slowly and held the far end of the patient’s leg with both hands, and then slowly and forcefully pulling the leg toward the foot end for about 10 seconds. The above movements were repeated 5 times. ☒ Passive joint movement: After the patient assumed a prone position, the therapist placed a hand on the affected side of the pelvis while holding the ankle with the other hand, causing the affected knee to bend by applying force with both arms simultaneously. This maneuver lasted for 30 seconds each time, for a total of 15 times. The range of motion (ROM) was within the range tolerated by the patient. ☒ Active joint movement: The patient was seated with the knee joint bent at 90 any significant pain. Both knees were stretched in turns, with each position held for 5 seconds each time, for a total of 10 times on each side. Joint activity training was performed once a day for 6 days a week, and the treatment was performed for 4 weeks.

(3) Muscle strength training: ☒ Straight leg lifts: The patients were placed in the supine position, with the lower limbs flat. Patients were asked to lift their limbs straight up to about 30° and hold for about 10 seconds, for a total of 15 times in groups. A 30-second break was taken after each group before proceeding to the next group of training. The training was stopped after muscle fatigue was experienced. ☒ Hip muscle contraction training: The patients were placed on their sides or in a prone position and were instructed to abduct and extend their thighs for gluteal muscle contraction training, with the same frequency mentioned above. ☒ Quadriceps isometric contraction training: The patients were placed in the supine position with both legs remaining flat on the bed. They performed active quadriceps contraction, which lasted for 30 seconds, followed by a rest period of 30 seconds. Contraction and relaxation were done together in sets of 15 and repeated 3 times. ☒ Static training: The patients were instructed to assume a semi-squat position, with the knee and hip joints bent at no less than 90°; this posture lasted for 30 seconds and was performed 15 times for each group, followed by a rest of 30 seconds, and repeated for 3 groups. ☒ Resistance muscle strength training: Sandbags were used for resistance muscle strength training to gradually increase the resistance with increase in muscle strength. The practice was carried out twice a day, 6 days a week, for 4 weeks.

2.4 Follow-Up Study

Outpatient and telephone follow-up were the main methods used. Appointments in the outpatient clinic were made with all patients after 1 month and 3 months of treatment. A telephone follow-up was conducted on one occasion, 2 months post-treatment, mainly enquiring patients about their current physical and mental state, rehabilitation and exercise status, and quality of life. We also learned about their compliance behavior, recorded the drugs or treatment utilized, and scheduled a follow-up appointment in the community clinic.

2.5 Outcome assessment

2.5.1 General information

Patients' age, gender, education, occupation, height, weight, residential floor, and course of disease were included.

2.5.2 Primary Outcomes

(1) Lequesne Index☒ The Lequesne index was used to score the severity and functional status of KOA patients^[11]; the higher the score, the more serious the clinical symptoms.

(2) Visual Analog Scale: We drew a 10 cm line with two ends indicating "painless" (0) and "extreme pain" (10), respectively, allowing the patient to draw markers consistent with the intensity of their pain.

2.5.3 Secondary outcomes

(1) Assessment of Knee ROM: A protractor method was used to measure the degree of flexion and extension of the knee joint by using the femoral external condyle as the axis, the longitudinal axis of the femur as the fixed arm, and the small head of the fibula and the external ankle.

(2) Assessment of lower limb muscle strength: The muscle strength of the knee extensor and flexor muscles was assessed by the hand muscle strength assessment method and the Lovett muscle strength classification method. The muscle strength of the extensor muscles of the knee joint was used mainly to evaluate the muscle strength of the quadriceps muscle. Muscle strength of the knee flexor muscles was mainly used to assess the muscle strength of the biceps femoris.

(3) Measurement of the knee joint circumference: A tape was used to measure the circumference of each knee 10 cm above the lower border of the patella, the midpoint of the patella, and 10 cm below the upper border of the patella. This corresponded to the upper, middle, and lower circumferences of the knee joint, respectively.

(4) KOA symptom score: The KOA symptom classification and quantification table score, according to the "Guidelines for Clinical Research of New Drugs of TCM" [6], consists of a total of 10 items, including pain, the relationship between activity and pain, and special examination items related to dysfunction. The scoring method has 0-6 points for each item, and the sum of the points of each item is calculated. The higher the score, the more serious the clinical symptom.

(5) Quality of life assessment: SF-36^[12] was used to assess the patients' quality of life, including physical and mental health, with a total of eight dimensions.

2.5.4 Safety Index

Incidence of adverse reactions and serious adverse reactions: Adverse reactions and serious adverse reactions were recorded and their relevance to treatment was evaluated.

2.6 Statistical Analyses

The statistical analysis software, SAS 8.2, was used. All statistical tests were performed on both sides. A value of $P < 0.05$ was considered to be significant, and $P < 0.01$ was considered to be extremely significant. Qualitative indicators were described by composition ratio, frequency, and frequency description. The mean and standard deviation were calculated for each measurement, and the paired t-test was used to evaluate the differences before and after treatment. The t-test (including a calculation of the 95% confidence interval) was used for comparison between small sample data sets. The rank-sum test (Wilcoxon method) was used when the variance was uneven. If the baselines between the groups were inconsistent, covariance analysis and other appropriate methods were used. The rank-sum test (Mann-Whitney method) was used for comparisons between graded data sets. Longitudinal follow-up data were obtained by using a mixed linear model.

For analysis of the main outcome indicators, we took the multi-level characteristics of the data into account and set the measurement time points as level 1, individuals as level 2, and communities as level 3. A 3-level random intercept model with the nested design longitudinal data was fitted along with a random slope model. Calibrated covariates included age, gender, community type, and severity of illness. The statistical model was also used to analyze secondary outcome indicators of the same data type. Other analytical methods for outcome measures included two groups of t-tests, the rank-sum test (Wilcoxon method), and the Chi-square test.

Missing values in this data corresponded with completely random missing (Missing Completely at Random) and the random missing (Missing at Random) descriptions. The data were filled and statistically analyzed by using the method of multiple filling (Multiple Imputation).

2.7 Quality Control Measures

(1) Strict implementation of the test principles of multi-center, random, controlled, and blind methods.

(2) Coordination of the research plan, process, and research organization implementation before the study, preparation of a unified research plan, research work manual, and case report form, filling in the instructions and filling out the sample form. Training and assessing specific programs and standard operating procedures for personnel participating in clinical research.

(3) Strict implementation of the inclusion and exclusion criteria for determining the final sample; implementation of interventions was strictly regulated following the uniform standards specified by each collaboration unit;

(4) Completion of the medical records required authenticity, timeliness, and completeness, ensuring that important information was not missed; the combined use of drugs should be recorded truthfully; research related documents should be standardized; adverse events should be reported promptly. During the implementation process, the procedures for signing all case report forms, training certificates and laboratory consumables were implemented, and the test was consistent with the original test draft; the auditors monitored the consistency of the test every 2 weeks. At the same time, the community physicians conducted a spot check on the relevant technologies used in the implementation plan.

2.8 Flowchart of cases □Figure 1□

Figure 1 Flowchart of cases

Note □: Two patients gave up on treatment due to relocation from their original home address; three patients gave up on treatment for being afraid of acupuncture; three patients believed that Chinese medicinal herb fumigation-washing was too time-consuming and troublesome, and therefore decided to quit.

Note ☒: One patient gave up on treatment due to traveling abroad with family members; one patient had an accidental fall that resulted in bone fracture and could not go on with the treatment.

Note ▲: Two patients gave up on treatment due to the loss of a close relative; one patient was unable to continue treatment due to visiting relatives abroad; three patients gave up on treatment due to private personal reasons; one patient was unable to continue treatment for a broken leg due to a car accident; one patient quit the treatment due to the inconvenience caused by relocation from their original address; three patients gave up on treatment to take care of their grandchildren; two patients could not continue treatment due to the diagnosis of a malignant tumor.

Note ■: One patient gave up on treatment due to the inconvenience caused by a change of original dwelling place.

Note ●: One patient could not be connected on the phone and follow-up could not be completed.

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Results

1 General information

A total of 722 patients with KOA were included in this study, with 361 patients in the experimental group and 361 in the control group. During the study, there were 10 and 16 cases of shedding in the experimental group and control group, respectively. Ultimately, 696 patients completed the study. There were no significant differences in age, gender, education level, occupation, height, weight, residential floor, and course of disease between the two groups ($p > 0.05$). (Table 1, 2)

Table 1 General data analysis of two groups of patients-1

2.1 Main outcome indicators2 Assessment of efficacy

Table 2 General data analysis of two groups of patients-2

2.1.1 Comparison of the total Lequesne index score between the two groups

These results indicate that TCM involving triple rehabilitation therapy for KOA is more effective at reducing the severity of KOA and improving the functional status of the knee joint in patients with KOA than conventional KOA rehabilitation therapy. (Table 3, 4, 5)

Table 3 Comparison of the total score of Lequesne Index between the two groups

Table 4 Comparison of the effective rate of improving the total score of Lequesne Index between the two groups at 4 weeks of treatment

Table 5 Comparison of the improvement rate of Lequesne Index total score between the two groups at 4 weeks of treatment

This result indicates that TCM involving triple rehabilitation therapy for KOA is more effective than conventional KOA rehabilitation therapy in reducing the knee pain in patients with KOA. (Table 7)

2.1.2 Comparison of VAS score between the two groups

Table 6 Results of mixed linear model of Lequesne Index total score These results of the mixed linear model for the Lequesne index total score showed that there were significant differences in the fixed effect between the two groups ($t = -3.371, P = 0.001$). Random effect analysis showed that there were significant differences between individuals ($Z = 37.011, P < 0.001$), time ($Z = 17.422, P < 0.001$), and communities ($Z = 3.289, P < 0.001$). (Table 6)

Table 7 Comparison of VAS scores of left and right knees between the two groups

Table 8 Results of mixed linear model of left and right knees VAS score The mixed linear model for the VAS score showed that there was a significant difference in the fixed effect between the two groups ($t = 31.570, P < 0.001$). A random effect analysis showed that there were significant differences between individuals (left knee $Z = 36.751, P = 0.000$; right knee $Z = 36.765, P < 0.001$), time (left knee $Z = 13.486, P < 0.001$; right knee $Z = 12.973, P < 0.001$), and communities (left knee $Z = 1.926, P = 0.054$; right knee $Z = 2.350, P = 0.019$). (Table 8)

2.2 Secondary outcome indicators

2.2.1 Comparison of ROM of the knee between the two groups

These results indicate that the TCM involving triple rehabilitation therapy for KOA and conventional KOA rehabilitation therapy have the same effect in improving the ROM at flexion and hyperextension. (Table 9)

Table 9 Comparison of ROM of knee between the two groups

2.2.2 Comparison of lower limb muscle strength between the two groups

These results indicate that TCM involving triple rehabilitation therapy for KOA is more effective than KOA conventional rehabilitation therapy in improving the lower limb muscle strength of KOA patients. (Table 10)

Table 10 Comparison of lower limb muscle strength between the two groups

2.2.3 Comparison of knee joint circumference between the two groups

This result suggests that TCM involving triple rehabilitation therapy for KOA can relieve knee joint swelling better than KOA conventional rehabilitation therapy. (Table 11)

Table 11 Comparison of knee joint circumference between the two groups

2.2.4 Comparison of quantitative scores of KOA symptoms between the two groups

These results indicate that TCM involving triple rehabilitation therapy for KOA could reduce the grading quantitative score of KOA symptoms to a greater extent than KOA conventional rehabilitation therapy. (Table 12)

Table 12 Comparison of quantitative scores of KOA symptoms between the two groups

2.2.5 Comparison of SF-36 score between the two groups

These results suggest that TCM involving triple rehabilitation therapy for KOA is not only superior to KOA conventional rehabilitation therapy in alleviating somatic pain, but also in improving the physiological function in patients with KOA. Moreover, the long-term efficacy of TCM therapy in improving the social and emotional function of KOA patients is also better than KOA conventional rehabilitation therapy (Table 13).

Table 13 Comparison of SF-36 score between the two groups

2.3 Safety evaluation results

No adverse reactions or serious adverse reactions were encountered in this study. Throughout the study, three patients suffered from palpitations, cold sweats, and other symptoms due to improper posture and mental tension during the electro-acupuncture treatment. However, they all felt better after taking a break. During electro-acupuncture treatment, patients were kept in the supine position and told to stay calm and relaxed. The observed nervousness, palpitation, and cold sweat symptoms in some patients did not reoccur after implementing this intervention, allowing us to dismiss these events as signs of an adverse reaction. Three patients had pruritus during Chinese medicinal herb fumigation-washing, but the symptoms resolved after the application of an anti-pruritus ointment on the affected area. After advising the patients to keep a check on the temperature and time spent applying the fumigation-washing liquid, the pruritus did not reoccur, allowing us to dismiss this event as an adverse reaction.

Discussion

The results of this study indicate that TCM involving triple rehabilitation therapy for KOA and conventional rehabilitation therapy have short-term and long-term effects on KOA. For reducing pain in patients with KOA, improving the ROM of the knee, lower limb muscle strength strengthening, enhancing knee joint function, and improving the quality of life of the patients, TCM involving triple rehabilitation therapy for KOA was found to be superior to conventional therapy. When analyzing the treatment plans, both groups of patients were treated with health education and drugs as the basic treatment in this study. More specifically, health education was used as the core treatment method advocated in the OA guidelines^[10, 13-15]. Through health educational speeches and distribution of brochures, patients were

able to develop a better understanding of KOA, including the definition, epidemiology, pathogenesis, common symptoms, diagnosis, treatment, and prevention strategies. This, in turn, could help them consciously adopt beneficial behaviors and lifestyle habits to eliminate the risk factors of KOA and improve their quality of life. Additionally, when the VAS scores were greater than 4 points, meloxicam, a typical nonsteroidal anti-inflammatory drug (NSAIDs), was administered orally for its analgesic and anti-inflammatory effects.

Conventional rehabilitation therapy of KOA includes physical factor therapy, muscle strength training, and joint activity training. Physical factor therapy involves a special electromagnetic wave (TDP) that is released after the heating of a radiation plate. It improves metabolism and adjusts the corresponding ion concentration to promote the repair of local lesions and recover body immunity^[16]. This kind of therapy is simple, safe, and effective, making it the most commonly used physiotherapy method in the community. Muscle strength training can enhance the strength and stability of the muscle and joint around the knee and delay the progression of the disease^[17]. Joint activity training can promote blood circulation, accelerate cartilage metabolism, improve cartilage nutrition, and restore or maintain normal joint activity^[18]. Both muscle strength training and joint activity training are forms of exercise therapy that can be easily performed and have no obvious adverse reactions.

TCM involving triple rehabilitation therapy for KOA combines three treatments, including electro-acupuncture, Chinese medicinal herb fumigation-washing, and traditional exercises. Electro-acupuncture functions to dredge the meridians by connecting the acupuncture instrument to the following paired acupoints: (Xuehai) SP10 and (Yinlingquan) SP9, (Liangqiu) ST34, and (Yanglingquan) GB34. This matching technique can clear the meridians, regulate the yin and yang, promote body resistance and eliminate pathogenic factors. Studies have shown that electro-acupuncture can significantly reduce KOA-related pain in patients and improve their body function, with a relatively low risk of adverse reactions^[19]. Recent research has also confirmed that electro-acupuncture can not only delay the progression of the disease by inhibiting cartilage destruction, but also promote the absorption of inflammatory substances and eliminate swelling by increasing the blood circulation. During this process, opioids that relieve pain are produced and motor function ultimately improves^[20-22].

In this study, the Chinese medicinal herb fumigation-washing was performed by the decoction of Haitongpi, which activates the liver and kidneys, strengthens muscles and bones, dispels wind and dampness, relieves pain, and relaxes muscles and collaterals. Modern pharmacology has proven that multiple herbs of this decoction have anti-inflammatory and analgesic properties. For example, naringin, the main ingredient of the *Drynaria rhizoma* (gu sui bu), can inhibit inflammation^[23]. Alkaloids and triterpenoids in *Lycopodium herba* (shen jin cao) and capsaicin, alkaloids, and triterpenoids in *Zanthoxyli pericarpium* (hua jiao) are all anti-inflammatory and analgesic agents^[24-25]. There are many kinds of alkaloids in *Aconiti radix* (chuan wu) and *Aconiti kusnezoffii radix* (cao wu) with analgesic properties that can be used in the treatment of several pain disorders^[26]. *Clematidi radix et rhizoma* (wei ling xian) inhibits the synthesis of COX-1 and COX-2, while *Carthami flos* (hong hua) inhibits the increase of IL-1

and IL-6^[27-28]. Chinese medicinal herb fumigation-washing relies on a warming effect to absorb the active ingredients of the herbs through the skin, to achieve the prevention and treatment of KOA by promoting blood circulation, dredging collateral, and soothing pain. Besides, the warming effect can reduce the excitability of nerve endings, increase the pain threshold, reduce phlegm in the surrounding connective tissue, dilate the blood vessels in the skin, and promote blood circulation. Therefore, it helps to eliminate swelling, promote the clearance of inflammatory factors, and improve the metabolism of cartilage. Numerous research studies have shown that Chinese medicinal herb fumigation-washing is an effective and safe treatment for KOA ^[29-31].

The “three-step six-style knee exercise” plan is developed from Tai Chi, Baduanjin, and Yijinjing, and is especially aimed at KOA motion dysfunction ^[8]. This exercise therapy can promote blood circulation, relax the lower limb muscles, and can strengthen the stability of the knee joint to achieve a rehabilitative effect. Some studies have shown that short-term traditional exercise is potentially beneficial for reducing pain, reducing stiffness, and improving body function^[32]. To analyze the mechanism of the “three-step six-style knee exercise” from a sports medicine perspective, the soleus, gastrocnemius, biceps femoris, and quadriceps of the lower extremities all receive isotonic training through alternating exercise movements, ultimately increasing the force and stability of the muscle. By pressing the leg and clasping the knee, the therapy improves the ROM of the knee joint, which can improve the flexion and extension of the knee joint. Additionally, by switching between forward lunge and empty step, the full-body balance and knee joint motor function is exercised in the process of transferring the center of gravity.

During the study, three patients receiving electro-acupuncture treatment experienced palpitations, cold sweat, and other symptoms caused by improper posture and mental stress, although they all felt better after taking a break. This indicated that when receiving electro-acupuncture treatment, patients should assume the supine position and remain relaxed. Three patients experienced pruritus on application of Chinese medicinal herb fumigation-washing, suggesting that patients should be instructed to keep the fumigation liquid at a suitable temperature with an adequate duration of washing so as to not cause such a reaction. Furthermore, patients should be reminded to remain vigilant for any observable skin changes during the process.

In conclusion, the TCM involving triple rehabilitation therapy for KOA integrates electro-acupuncture, Chinese medicinal herb fumigation-washing, and traditional exercises, which have the functions of dredging the meridians, harmonizing qi and blood, expelling wind and removing dampness, eliminating cold to stop the pain, improving muscle strength, and enhancing stability. Compared with the conventional rehabilitation therapy of KOA, this treatment scheme has the advantages of being simple, cheap, and having a good mass foundation. This rehabilitation program is suitable for patients with early and mid-stage KOA and can reduce the severity of knee arthritis, relieve knee joint pain, improve lower extremity muscle strength, reduce knee swelling, improve knee joint flexion and extension, and improve the quality of life of patients. Its side effects and risks are relatively minor and can be generalized and applied to the community. However, there are some shortcomings to this study. For example, we were unable to double-blind the subjects and interventionists administering KOA rehabilitation therapy.

Therefore, observer bias and measurement bias could not be completely avoided. Furthermore, the age range of the sample was wide, as subjects between 40–75 years old were included. No further stratified statistical analysis of age was carried out; only the mixed linear model analysis of the main outcome indices was performed. Therefore, the indicators may have a certain bias on the results. We plan to conduct subsequent studies in which these limitations will be addressed.

Abbreviations

KOA

knee osteoarthritis

TCM

traditional Chinese medicine

VAS

visual analog scale

ROM

range of motion

SF-36

short-form 36 item health survey questionnaire

TDP

Specific electromagnetic wave

NSAIDs

nonsteroidal anti-inflammatory drug

Declarations

Ethics approval and consent to participate

The study was guided by the Helsinki Declaration and China's Drug Clinical Trial Management Regulations. While ensuring the scientific nature of clinical trials, it fully guaranteed the dignity and rights of the subjects. Each collaborating unit was reviewed by the local medical ethics committee before patients were recruited.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare no competing interests.

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Authors' contributions

All authors participated in the clinical trial. In addition, YXS, JMG and TYC conceived of and designed the study. YJZ, YQZ, XQL and LLH were responsible for recruiting patients. JHW, SQC and BLL were responsible for clinical data collection. YX and XM provided efforts in data analysis. All authors participated in the writing and/or critical revision of the manuscript and approved the final version for submission.

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Tables

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Figures

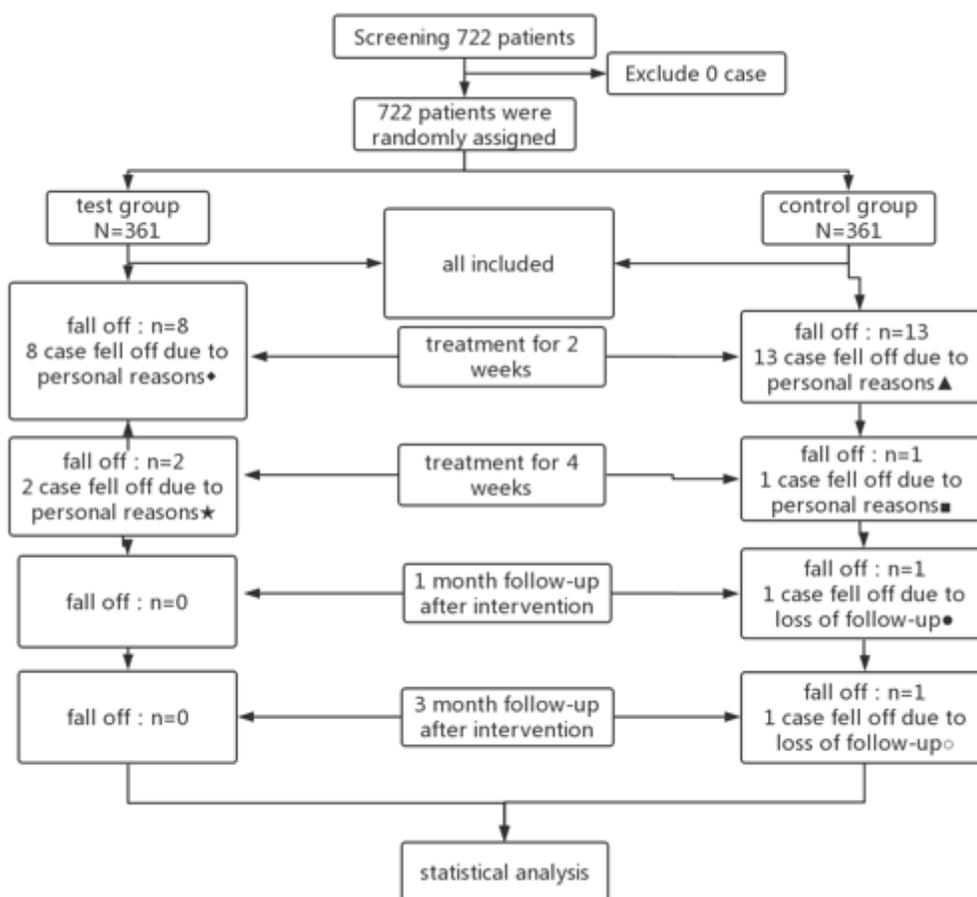


Figure 1

Cases Flowchart. Note ☒: Two patients gave up on treatment due to relocation from their original home address; three patients gave up on treatment for being afraid of acupuncture; three patients believed that Chinese medicinal herb fumigation-washing was too time-consuming and troublesome, and therefore decided to quit. Note ☒: One patient gave up on treatment due to traveling abroad with family members; one patient had an accidental fall that resulted in bone fracture and could not go on with the treatment. Note ▲: Two patients gave up on treatment due to the loss of a close relative; one patient was unable to

continue treatment due to visiting relatives abroad; three patients gave up on treatment due to private personal reasons; one patient was unable to continue treatment for a broken leg due to a car accident; one patient quit the treatment due to the inconvenience caused by relocation from their original address; three patients gave up on treatment to take care of their grandchildren; two patients could not continue treatment due to the diagnosis of a malignant tumor. Note ■: One patient gave up on treatment due to the inconvenience caused by a change of original dwelling place. Note ●: One patient could not be connected on the phone and follow-up could not be completed. Note ●: One patient could not be connected on the phone and follow-up could not be completed.

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