

Effect of Acupotomy in Knee Osteoarthritis Patients: Study Protocol for A Randomized Controlled Trial

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Study protocol

Keywords: acupotomy, needle-knife, knee osteoarthritis, study protocol, randomized controlled trial

Posted Date: August 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-35085/v1>

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Version of Record: A version of this preprint was published at Trials on April 20th, 2021. See the published version at <https://doi.org/10.1186/s13063-021-05247-z>.

Abstract

Background

Symptomatic knee osteoarthritis patients are common in China. Pharmacologic therapy is not the first recommendation because of its safety issues. Non-pharmacologic therapy, such as lifestyle adjustments, weight loss, and proper exercise is strongly recommended to use in knee osteoarthritis. But the adherence rate is very poor. Acupotomy therapy, as an effective treatment for knee osteoarthritis, is lack of high quality randomized controlled trials. This study set out to investigate the efficacy of acupotomy in patients with knee osteoarthritis.

Methods

136 patients will be enrolled in the First Affiliated Hospital of Guangzhou University of Chinese Medicine, and assigned into acupotomy group or sham acupotomy group according to the block randomization number. The acupotomy group will receive 2 sessions of acupotomy for 2 weeks(once a week). The sham group will receive 2 sessions of sham stimulation for 2 weeks□once 2 week. All the patients will use indomethacin cream externally. The primary outcome is the WOMAC index and the secondary outcomes are VAS, plantar pressure distribution test, X-ray examination, musculoskeletal ultrasound, maximum knee circumference, and joint mobility. We will measure them at baseline, one week after the end of treatments, the third month and sixth month follow up.

Discussion

As we know, this is the first single-blinding and sham controlled design in acupotomy research. We aim to prove the efficacy of acupotomy in treating knee osteoarthritis.

Trial registration

Chinese Clinical Trial Registry: ChiCTR2000033047(2020-5-18).

Background

As the 11th highest contributor to global disability, knee osteoarthritis (KOA) triggers burdensome pressure for society and family ^[1]. In China, symptomatic knee osteoarthritis patients are common ^[2]. Symptomatic knee osteoarthritis will cause pain and impaired knee function. 3.9% of knee osteoarthritis patients are suffering from these severe torments, which leads them to disability easily ^[3]. The pharmacologic therapy is not recommended because of its limited efficacy and safety issues ^[4]. Non-pharmacologic therapy has been used a lot in treating knee osteoarthritis ^[5]. For instance, Lifestyle adjustments, weight loss, and proper exercise are the first line recommended methods ^[6]. However, patients with these treatments usually have poorer adherence ^[7]. Thus, we are seeking for an effective non-drug therapy with better adherence to treat knee osteoarthritis.

Acupotomy therapy is a special technique of acuthery. Unlike standard acupuncture needles, acupotomy therapy will use a needle-knife with a thicker diameter and flat needle. This needle-knife can enter deep tissues to loosen adhesion. Acupotomy therapy has been used to treat knee osteoarthritis for many years, because of its longer treatment session and satisfying effect in clinical practice. Although previous studies [8-10] have showed the efficacy of acupotomy therapy, there is no high-quality clinical research in this field. The sloppy designs of past studies are detrimental to the power of their conclusion.

Therefore, we design a randomized, single blinding, sham controlled trials to explore the efficacy of acupotomy therapy in treating knee osteoarthritis patients.

Methods

Study Design

Based on the Declaration of Helsinki, we will design a parallel, block randomization, single-blinding, sham controlled trials. The study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines (Additional file 1). This study will be performed in the First Affiliated Hospital of Guangzhou University of Chinese Medicine from June 2020 to June 2023 (Figure 1). We will recruit volunteers via advertising, posters and contacting community doctors, and enroll those who meet inclusion criteria.

Fig. 1 Flowchart of the study design.

Inclusion Criteria

- (1) Patients meeting the I, II, and III levels of Kellgren-Lawrence's radiological diagnostic criteria [11];
- (2) The score of pain visual analog scale is above 4 points in the past month;
- (3) Age is between 40-70 years old;
- (4) Those who have not taken other related treatment drugs or adopted related treatment methods within 2 weeks;
- (5) Participants should provide informed consent.

Exclusion Criteria

- (1) Pregnant or lactating women, or women with a pregnancy plan during the trial;
- (2) Patients with infectious diseases or serious diseases, such as cardiovascular, cerebrovascular, liver, kidney, hematopoietic system;
- (3) Patients with local infection, ulceration, vascular nerve damage or deep abscess in the knee joint;

- (4) Patients with a history of severe knee trauma, or who have undergone surgery or arthroscopy;
- (5) Patients with other diseases that cause knee pain, such as tumors, knee joint tuberculosis, rheumatoid arthritis, gouty arthritis, etc.;
- (6) Patients who have taken oral corticosteroids or received intra-articular knee injection treatment within 1 month; or have participated in other clinical trials within 3 months;
- (7) People who are allergic to the medical devices involved in this trial; contraindications to the use of indomethacin plaster, such as those with a history of allergy to indomethacin, those with liver and kidney dysfunction (alanine aminotransferase (ALT), aspartate amino acid transaminase (AST) is more than 2 times the normal value, and the blood creatinine (cr) is more than the normal value). Patients who have induced asthma, urticaria or allergic reactions after taking aspirin or other non-steroidal anti-inflammatory drugs may have nonsteroidal Patients with a history of gastrointestinal bleeding or perforation after anti-inflammatory drugs, patients with active gastrointestinal ulcer bleeding, or patients with previous recurrent ulcers / bleeds, patients with severe heart failure, perioperative coronary artery bypass surgery, etc. ;
- (8) Patients with bleeding tendency, such as long-term use of warfarin, aspirin and other anticoagulants;
- (9) People with an abuse history of sedative hypnotics, opioid analgesics, and alcohol;
- (10) Patients who cannot cooperate with relevant experiments and measurements.

Intervention

Acupotomy group

The patients are in a supine position with the knee flexed 30 ~ 45 °. A cushion is placed below the knee. The physicians will select 6 points from a point set as follow. The point set contains 8 points, including the upper point and lower point medial collateral ligament of the affected knee joint, the upper point and lower point lateral collateral ligament, the subpatellar ligament points, the upper point of the patella, the muscle insertion of the popliteal muscle, and the medial popliteal fossa stimulation points. We will stimulate 6 points for unilateral knee pain and 12 points for bilateral knee pain (Table 1).

After standard disinfection, the physicians will operate Hanzhang Ⅹ type No.4 straight needle knife (Beijing Huaxia Needle Knife Medical Equipment Factory) to run acupotomy therapy (Figure 2). All these physicians have more than 5 years of acupotomy experience and will be retrained 16 hours before the study begins.

The incision line is consistent with the longitudinal axis of the lower limb. The body of needle-knife is perpendicular to the skin. The doctor operates according to the procedures of fixed point, orientation, pressure and penetration. When the needle knife reaches the target depth, the doctors perform a manual operation. After the operation, the needle-knife is pulled out, and local hemostasis is applied for 3

minutes. The wound was disinfected with iodine and the needle eye was covered with a band-aid. Patients receive acupotomy therapy 2 sessions for 2 weeks—once a week—.

Table 1. the location of point set

Fig 2. the needle-knife

Sham acupotomy group

Patients assigned to sham acupotomy group will receive the mock acupotomy, which will be performed just like real acupotomy, but without manual stimulation to achieve any real effect. The needle-knife will pierce through the skin only and stay under the skin for 10 seconds to simulate manipulation time. Patients will receive 2 sessions of sham acupotomy for 2 weeks—once a week—.

All the patients of two groups are allowed to use drugs. Clinicians will give patients indomethacin cream (manufacturer: Nipro Pharma Corporation Saitama Site Plant 2, import drug registration number H20181060) for external use, once daily after 24 hours of acupotomy. They will receive indomethacin cream 12 times in total.

Outcome Measurement

We had selected both clinical outcomes and surrogate outcomes to assess the efficacy of acupotomy. All the outcomes will be measured at baseline and one week after the end of treatment. Besides, we will follow up for WOMAC index and VAS in the 3rd month and 6th month after the end of treatment (Table 2). Before the study begins, we will train the related investigators.

Table 2. Study schedules. T1-T3: from the first treatment period to the third treatment period. W7: one week after the whole treatment period; M3: the 3th month; M6: the 6th month

Primary Outcome

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC index is always used to assess knee osteoarthritis symptoms^[12]. The scale includes 24 items in three parts, including 5 pain items, 2 stiff items, and 17 joint function items. The scoring record uses a 10cm long visual analog scale scoring rule. The two ends are 0-point and 10-point. 0 points indicate that the item is asymptomatic, and 10 points indicates the most serious degree of the item.

Secondary Outcome

Visual Analog Scale (VAS)

VAS scale is a commonly used scale to reflect the degree of body pain^[13]. A 10 cm length VAS scale will be used. The two ends are 0-point and 10-point respectively. The 0 presents painless and 10 shows the

most severe pain which is intolerable.

Plantar Pressure Distribution Tests

Plantar pressure distribution tests can observe the function of patients' knee joints^[14]. This test uses the Plantar Pressure Distribution Test System (Belgium RSscan Footscan1.0m). A rehabilitation technician will in charge of measurement. We will collect balance parameters (foot angle and subtalar joint mobility) to assess the stability of knee joint medial and lateral. The bigger balance parameters indicate the worse stability. Besides, impulse parameters, known as the ratio of the heel and forefoot, will be used to analyze knee buffering stability. The larger the ratio, the stronger the stability.

X-ray examination

Interrogation of the results of the patient's front and lateral knee X-rays was performed by an imaging physician. This measurement aims to monitor whether there are existences of osteophyte formation, joint space narrowing, subchondral sclerosis, cartilage degeneration, osteoporosis, valgus deformity, and varus deformity.

Musculoskeletal Ultrasound

Ultrasonography has also been proven as a useful tool in monitoring knee osteoarthritis treatment effectiveness^[15]. Specialized ultrasound doctors will collect data via Philip HP SONOS 5500 ultrasound imaging machine. We will pay attention to the knee joint fluid volume and synovial film thickness. These data will show us the degree of damage and repair of knee.

Maximum Knee Circumference

This indicator is used to assess the soft tissue lesions around the knee joint^[16]. When conducting the assessment, the patients will be asked to lie supine with the knee joint straight. The doctor will use a soft ruler to measure the circumference of the knee joint along the upper and lower pole of the patella, of the metatarsal bone, and measure around the knee joint.

Joint Mobility

Joint mobility is also used to check knee function^[17]. The arthrometer will be used to measure knee mobility. The patient being tested is positioned on his/her side with the affected leg being measured facing upwards. First, the lateral femoral condyle is positioned over the center of rotation of the arthrometer. Then position the fixed arm along the middle of the femoral joint, and fix the movable arm along the fibula. Lastly, let the patient extend the knee joint as much as possible, and then bend the knee as much as possible, and measure the flexion and extension motion range by moving the movable arm.

Sample Size

Referring to a previous study ^[18], we determined that the change in the WOMAC index before and after treatment in the acupotomy group was 16.34 ± 4.19 . Then the change in the WOMAC index before and after treatment in the sham acupotomy group was 14.2 ± 4.19 , and the effect size was 2.14 ^[19]. The sample sizes should provide 80% of statistical power and significance level of 0.05.

We calculated the sample sizes of 124 with repeated measurement design via the SAS software package (version 9.4, Tokyo, Japan). Considering the 10% loss of patients during the research, we had decided to enroll 136 participants finally.

Randomization

A biostatistician will generate a block random number list at a ratio of 1: 1 via Stata 14.0 software package. The block size is not discovered until study finishing because of allocation concealment. An independent staff, who does not take part in the performance period of this study, will seal the random number by the opaque envelopes. Then the primary investigator will save these envelopes and open one of them when a participant is enrolled.

Blinding

This study takes a single-blind approach. The operators will mock the procedure of standard acupotomy therapy in the sham acupotomy group. The operators pierce through the skin only and do not stimulate the relevant ligaments and muscles. The needle-knife will stay under the skin for 10 seconds without any manipulation. At the same time, this experiment will blind other folks (data administrators, biostatisticians, programmers, measurement evaluators, etc.) to minimize performance bias.

For the sake of protecting the rights of the subjects, we will approve free acupotomy treatment for the sham acupotomy group at the end of the trial.

Date Management and Monitor

We will train all the staff to ensure data quality. The researchers will fill the data in the Case Report Forms (CRF) and sign it. CRF does not allow alteration directly. The researchers must report to the primary investigator if they need to alter the CRF. Any changes in CRF need to be signed and dated. Data administrators will enter data into the computer. The CRF and the computer will be locked in the research center, while the primary investigator keeps the key only. The original data will be kept in the research center rather than publish. The data can be access through research center if someone applies with reasons.

The data monitoring and management committee is composed of the Scientific Research Department of the First Affiliated Hospital of Guangzhou University of Chinese Medicine. They independently review and monitor research data. The South China Acupuncture Research Center Clinical Sub-center will form a quality monitoring committee. These committees will visit our clinical research center every 6 months to review and monitor the trial. The study group will run a conference to review this trial every month.

Safety Monitor

Acupotomy therapy may trigger adverse events including dizziness and local hematoma. When dizziness occurs during treatment, the doctor should stop the treatment immediately. Then the doctor will lay down on the pillow, and take warm water to take the service. If hematoma remains after treatment, the patient will apply a local cold compress, and switch to a hot compress at 24 hours to promote the dissipation and absorption of blood stasis. If an adverse drug reaction occurs, the drug should be discontinued. Active clinical observation and symptomatic treatment should be carried out.

Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine will monitor the safety of this trial and furnish us with advices (e.g., endpoint adjustment) if it is necessary. When an adverse event occurs in a patient, the researchers should record the detail, such as time, severity, duration, treatment measures, and event outcomes. The responsible doctor will determine the causal relationship between the treatment method and the adverse event, and decide to continue or terminate the study. Relevant information must be reported to the ethics committee on the same day.

The following are the criteria for terminating the study: (1) the subject has a serious adverse event or the subject has requested to suspend participation in the trial, or the trial operator believes that it is necessary for the subject to suspend the trial;(2) during the study, the subject is found to have a systemic disease that could not be detected before the start of the clinical trial;(3) for other reasons, researchers believe that patients are not suitable for continued treatment;(4) patients receive privately other interventions that may affect outcomes.

Statistics Analysis

Per-protocol subjects' analysis and intention-to-treat analysis were used to analyze the efficacy. The safety analysis set is used to analyze the safety evaluation.

We will develop a statistical analysis plan with a statistician. The statistician R 3.4.3 software package is used to performs descriptive statistics, exploratory analysis and dropout analysis. The result is statistically significant when the P-value is less than 0.05. In the intention-to-treat analysis, when the data is missing, the last observation is used for interpolation. Then we will select sensitive analysis for the result.

For continuous variables that obey normal distribution and meet homogeneity of variance, we will use Student's t-test. if continuous variables cannot meet the condition mentioned above, the Mann-Whitney test or Wilcoxon test will be used. A chi-square test will be performed for discrete or categorical variables. When analyzing data from repeated measurements, we will use analysis of variance or analysis of covariance.

For safety analysis, we will use descriptive analysis at first. Subsequently, the incidence of adverse reactions between the two groups will be compared. The causality for the severity of adverse reactions and the needle-knife operation should be considered in the comparison. If there are a large number of

adverse reactions, the relationship with the intervention time and baseline characteristics should be analyzed.

Discussion

Knee osteoarthritis is a chronic disease with pain, swelling, stiffness, restricted movement, popping or deformity^[20]. It is associated with gender, age, body weight, physical activity, occupation and biochemical factors etc^[21]. There are three views of knee osteoarthritis pathological mechanism^[22]. First of all, mechanical loading causes changes in biological stress, which can damage knee cartilage. Furthermore, synovial inflammation induces cartilage to secrete too much matrix metalloproteinase, which can damage knee cartilage. In addition, some adipokines, such as leptin and adiponectin, are known as one of the pathological mechanisms in triggering cartilage impaired.

Different guidelines had provided different suggestions of clinical practice in knee osteoarthritis^[23]. The physicians always use paracetamol (acetaminophen) and NSAIDs (celecoxib, indomethacin, etc.) to deal with knee osteoarthritis problems according to the guidelines^[4, 24-26]. But patients cannot use these drugs for long time. Paracetamol (acetaminophen) does a little work for patients' pain and stiffness and physical function^[27]. Besides, paracetamol (acetaminophen) brings hepatotoxicity^[28] and induces adverse reactions in kidney, cardiovascular and gastrointestinal tract with a long-term use^[29]. NSAIDs will increase the risks of adverse cardiovascular outcomes^[30] and upper gastrointestinal complications^[31]. Hence, non- pharmacologic therapies play an essential role in knee osteoarthritis treatment^[32]. Traditional Chinese Medicine can also make a contribution in this field, such as acupuncture^[33], moxibustion^[34], Taiichi and massage^[35]. Compared with other non-drug therapies, acupotomy therapy is a better choice for the treatment of knee osteoarthritis. It is less frequent, which is good for persistence. Besides, acupotomy not only can relief pain but also improve patients' joint mobility.

As a special type of acuthery, acupotomy therapy can improve knee osteoarthritis symptoms via different pathways. Knee biomechanical will be restored by acupotomy due to its function of biological street adjustment^[36]. Acupotomy can also curb inflammation^[37-38]. The reduction of IL-1 β , IL-6, and TNF- α suppress the expression of MMP-1, MMP-3, and MMP-13, which is conducive to knee cartilage. In a word, acupotomy therapy promotes chondrocyte repair and regulate cartilage metabolism^[39].

The clinical research confirmed acupotomy effect of knee osteoarthritis^[9-10]. However, the study designs of the trials are both inadequate. They both selected acupuncture as a comparison, which fail to demonstrate acupotomy efficacy powerfully. One used inappropriate randomization procedures and didn't use blinding. While another had a small sample size and used scale as outcome only. Thus, we had designed a stricter study to explore the efficacy and safety of acupotomy in knee osteoarthritis. We had selected sham acupotomy as a comparison. Besides, as we know, this program is the first single-blinding design in acupotomy research. Moreover, we will use clinical outcomes (the WOMAC index, the visual

analog scale, and joint mobility) and surrogate outcomes (musculoskeletal ultrasound, X-ray examination, plantar pressure distribution test, maximum knee circumference) at the same time.

This study has some limitation. Firstly, we will enroll the early and mid-term patients only, thus we cannot observe the effect of acupotomy in the late-period patients. Secondly, the long-term effect cannot be monitored owing to 6 months follow-up. Lastly, this study will be performed in China so the conclusion may not suitable for other races.

To summary, we will perform a parallel, block randomized, single-blinding, sham acupotomy controlled trial to scrutinize the efficacy and safety of acupotomy in knee osteoarthritis patients.

Abbreviations

KOA, Knee Osteoarthritis

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

VAS, Visual Analog Scale

CRF, Case Report Form

Declarations

Trial status

This study had be performed since June 2020. The study protocol is vision 3.0 (2020.4.27). We are recruiting participants from June 1, 2020, to June 30, 2022.

Ethics approval and consent to participate

This trial had been approved by the ethical committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. ZYYECK [2020]015). All the participants must provide informed consent before they attend to the study.

Consent for publication

All the authors had read and agreed to the final version manuscript. The figures for this paper are approved for publication by individuals.

Availability of data and materials

Not applicable. We have no datasets included in this study protocol. In this research, volunteers will provide informed consent to ensure that blood indicators can be used in this study, and are not applicable

to other channels. The result of this study will communicate with others via a peer-review journal. The full protocol can be accessed by contacting to us after the trial finish.

Competing interests

There is no a conflict of interest.

Funding

This study was supported by the Innovative Clinical Research Project of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. 2019IIT31) and Yang Wen Hui Guangdong Traditional Chinese Medicine Inheritance Studio (No. GDTCMO201905). The funding body approved our research design and will monitor our progress during the research, and review our research conclusions after the trial.

Authors' contributions

LZ carried out the conceptualization. DHX designed the study and drafted the manuscript. JH helped to design the study. MHL, CHH and JW will perform this study. MXZ will perform statistical analysis. TTY, WJZ, JLL, RNH and NX helped to revise the manuscript.

Acknowledgements

We would like to thank all the staff in this study.

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Tables

Table 1. the location of point set

Point name	Location
The upper point of the medial collateral ligament	A lateral tubercle located at the medial condyle of the femur
The lower point of the medial collateral ligament	the posterior part of the liri dendron area located at the medial condyle of the tibia
The upper point of the lateral collateral ligament	A lateral tubercle locating at the lateral condyle of the femur
The lower point of the lateral collateral ligament	The apex of the Capitula fibula
The subpatellar ligament points	The lower part of the patellar ligament
The upper point of patella	Directly above the patellar bottom and located in the deep surface of the quadriceps tendon
The insertion of popliteal muscle	Located behind the upper part of the medial tibia
The medial popliteal fossa stimulation points	Located at the medial wall of the popliteal triangle, between the semitendinosus and semimembranosus' muscles.

Table 2. Study schedules. T1-T3: from the first treatment period to the third treatment period. W7: one week after the whole treatment period; M3: the 3th month; M6: the 6th month

STUDY SCHEDULE						
Period	Screening	Baseline	Treatment	End	Follow-up	
Time	W-1	W0	W1-W6	W7	M3	M6
Basic						
Eligibility	√					
Demography	√					
Physical examination	√					
Medical history	√					
Informed consent	√					
Outcomes						
WOMAC		√		√	√	√
VAS		√		√	√	√
X-ray examination		√		√		
Musculoskeletal ultrasound imaging		√		√		
plantar pressure measurement		√		√		
Maximum knee circumference		√		√		
Joint mobility		√		√		
Trial evaluation						
informed consent	√					
Adverse event			√	√		
Safety evaluation			√	√		

Figures

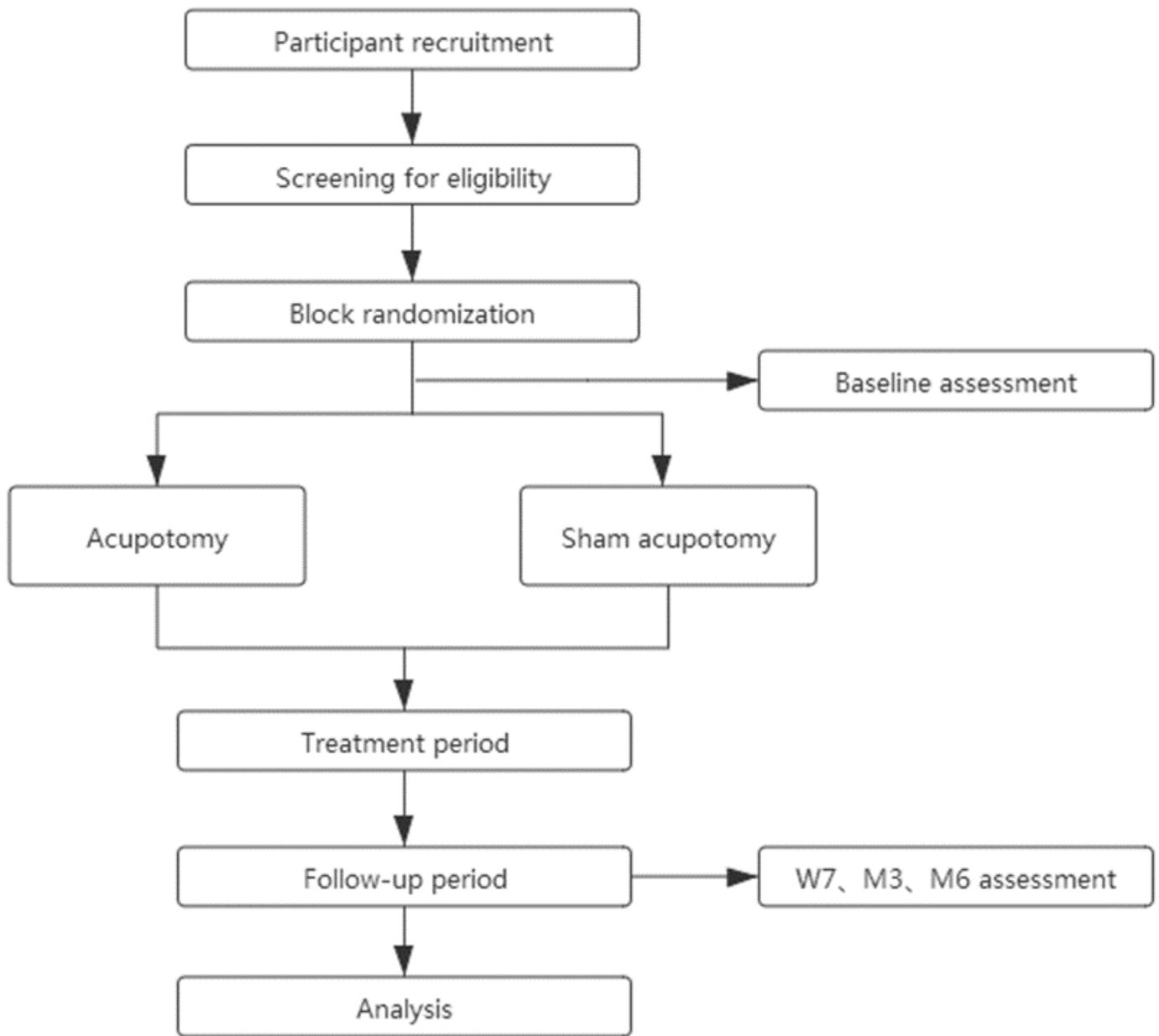


Figure 1

Flowchart of the study design.

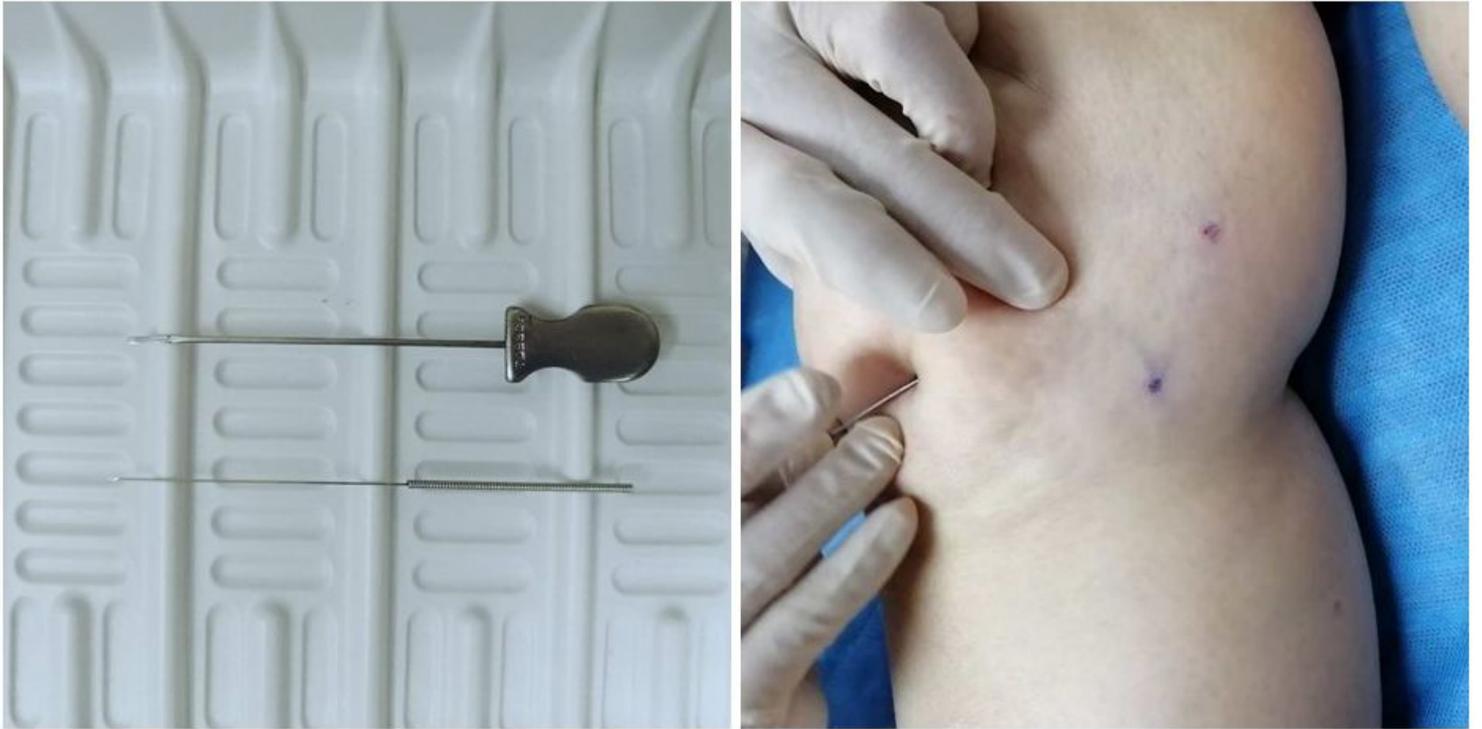


Figure 2

the needle-knife

Supplementary Files

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- [SPIRITchecklist2013.doc](#)