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Original Article

Individualized Traditional Korean Acupuncture for Knee Osteoarthritis : a Protocol for a Randomized Controlled Trial

Hyuk Byun[1], Seung-Tae Baek[1], In-Shik Park[1], Kap-Sung Kim[1], Sun-Woong Kim[2], Sun-Mi Choi[3], Seung-Deok Lee[1]

Department of Acupuncture & Moxibustion[1]
Graduate School of Oriental Medicine, Dongguk University
Department of Statistics, Dongguk University[2]
Department of Medical Research, Korea Institute of Oriental Medicine[3]

Objective : To test the hypotheses that individualized traditional Korean acupuncture improves pain and disability in patients with osteoarthritis of the knee and that benefits remain after stopping treatment more so than is the case for standardized minimal acupuncture.

Design : Randomized single blind controlled trial with two intervention arms (individualized traditional Korean acupuncture, standardized minimal acupuncture) of six weeks' duration and three months follow-up.

Setting : Acupuncture interventions were applied by two training doctors in the Department of Acupuncture and Moxibustion in a 1000-bed hospital. Assessment of the result was performed in a university-based laboratory.

Participants : 50 patients with symptoms of knee osteoarthritis as diagnosed by an orthopedist.

Intervention : Individualized traditional Korean acupuncture or standardized minimal acupuncture for six weeks.

Main outcome measures: Primary outcome measure was pain as measured by the visual analogue scale. Secondary measures of pain and disability included the Western Ontario and McMaster Universities (WOMAC) index, Short Form-36 (SF-36), Lequesne Functional Index (LFI) score and Korean version of Health Assessment Questionnaire (KHAQ).

Discussion : This paper presents detail on the rationale, design, methods and operational aspects of the trial.

Key Words : Knee Osteoarthritis (OA), Individual Traditional Korean Acupuncture, Standardized Minimal Acupuncture, VAS, WOMAC, Randomized Controlled Trial (RCT)

Introduction

Osteoarthritis (OA) is the most common form of chronic progressive arthritis affecting primarily elderly people[1]. Worldwide, OA is the fifth largest contributor to disability life years[2]. OA most frequently affects the knee joint[3]. OA of the knee is a debilitating disease that affects 52% of adults over the age of 75 years[4]. About 40-60% of subjects with radiological OA changes suffer from clinical symptoms such as pain, joint stiffness and joint deformities. OA of the knee is common and contributes greatly to morbidity in the community[5-6]. There is no cure for OA. Current therapies for OA are largely aimed at providing symptom relief, and include non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 specific inhibitors and mild opioids[7-8]. However, chronic use of these drugs is associated with significant side-effects, for example, NSAID-

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Corresponding author : Lee Seung-Deok.
Department of Acupuncture & Moxibustion, Dongguk University International Hospital 814, Siksa-dong, Ilsandong-gu, Goyang-si, Gyeonggi-do, 411-773, Korea.
Tel : 82-31-961-9122 / Fax : 82-31-961-9009
E-mail : chuckman@dongguk.edu

induced upper gastrointestinal tract complications, which are major iatrogenic disorders[9].

Acupuncture is an integral part of an ancient Chinese system of medicine that has been used for more than 2,500 years to treat diseases and relieve pain. Acupuncture is a multifaceted healing modality that originated in China, and has been gradually gaining in both popularity and credibility in Western countries[10]. There are numerous techniques and approaches to acupuncture, reflecting a variety of medical traditions and schools from China, Korea, Japan, Vietnam and other countries. One of acupuncture's characteristics is a plurality in diagnosis and treatment, which has withstood many attempts to create a singular and uniform system[11-12]. While this lack of standardization is potentially confounding in research trials, the multiplicity inherent in acupuncture is a reality of the practice. Moreover, acupuncture remains more of an art than a science because many factors that can profoundly influence the outcome of the treatment have to be considered. Such variations make it difficult to standardize procedures and hamper acupuncture clinical research. Few comparative studies of acupuncture and NSAIDs for its treatment have been conducted[13]. As a result, the clinical effectiveness of acupuncture in OA of the knee is still a matter of controversy[14]. Each acupuncturist has his/her own individualized treatment styles based on clinical experience and personal belief. Many practitioners believe it is vital to use treatment that is individualized to the patient, involving, for example, choice of points or method of stimulation. The importance of individualization in comparison with formular acupuncture has not been demonstrated in clinical trials. Interventions used in some previous studies have not reflected clinical practice that would be acceptable to many acupuncturists, which seriously limits the conclusions that can be drawn. Another problem associated with acupuncture research is defining an adequate placebo as a control intervention for acupuncture studies. Some trials compare acupuncture to drugs, and others use "sham acupuncture" (acupuncture at random spots on the body surface that are thought to be inactive). There is substantial controversy, however, about the use of sham acupuncture as a control treatment[15]. The aim of this study is to determine whether the effectiveness of individualized traditional Korean acupuncture is better than one of standardized minimal acupuncture for OA of the knee.

Methods / Design

The design of this clinical trial is a randomized, controlled and single blind trial with two parallel treatment groups stratified by whether the patient had OA in one or both knees. (Fig. 1. Scheme)

1. Study population

Potential study subjects must have had a history of symptomatic OA of the knee with chronic pain for at least 6 months. Participants must have been able to read and write Korean, willing to consent to participation and voluntarily signed an IRB-approved informed consent. They must have had the capacity to understand the requirements of the study and complete questionnaires. They must also be available for telephone contact.

2. Inclusion Criteria

Orthopedist diagnoses with OA of the knee based on the American College of Rheumatology definition for OA of the knee and meeting the criteria as follows :

- At least 40 years old

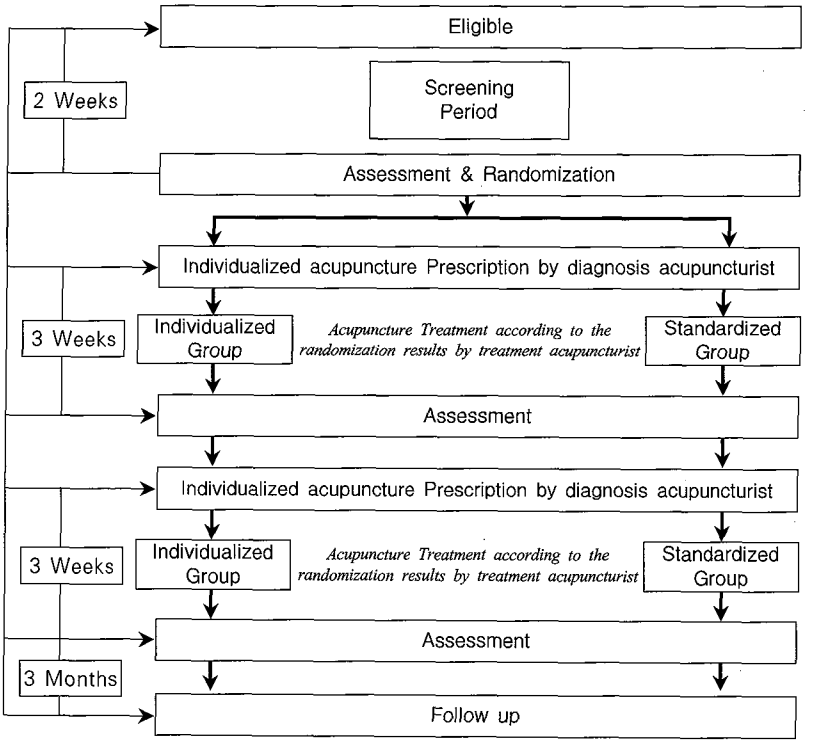

Fig. 1. Scheme

- Current symptoms of chronic (6 months), stable pain and/or stiffness in one or both knees during weight-bearing activities
  - knee pain due to OA rated > 4 cm on a 10 cm VAS in one or both knees
  - morning stiffness of knee for ≤ 30 min
- Mild joint space narrowing (>= 2mm remaining) in knee AP standing or Rosenberg view.

3. Exclusion Criteria

- Inflammatory, metabolic or neuropathic arthropathies
- Trauma or surgery to the knee(s) which is causing pain or functional problems within 6 months prior to the enrollment period
- Suspicious meniscus injury by physical examination
- Pain emanating more from back or hip than from knee interferes with patient knee assessment
- Any condition which severely limits local ambulation, such as amputation or stroke
- History of or evidence of active rheumatologic disease, severe peripheral neuropathy, clinically evident cardiac or respiratory disease that interferes with functional status, or other serious diseases, including psychiatric disorders
- Autoimmune disease, systemic lupus erythematosus (SLE), psoriatic arthritis, active (redness, swelling, fever, etc.) gout or pseudo-gout within 6 months prior to screening
- History of prolotherapy, or injection of hyaluronic acid or cortisone within the last 3 months

- Inability to stop anti-inflammatory medication or NSAID such as acetaminophen for the entire study
- Bleeding disorders that might contraindicate acupuncture
- Pension or disability benefits

3. Informed Consent

Before the first study procedure, every patient signed a written informed consent to study participation and GCP data verification, analysis and processing. The written study information covers all important aspects on study participation and patient rights, especially that participation is completely voluntary and may be revoked at any time without naming reasons. It is a summary of and addition to the comprehensive talk the clinician had with the patient before the first study procedure. Moreover, there was information about the study timetable and treatment, its known risks, benefits and possible treatment alternatives. One copy of the written informed consent signed by the investigator remains with the patient. A copy of the written informed consent form is attached as supplement.

4. Randomization

The patients were stratified by whether the patient has osteoarthritis in one knee or both knees. Randomization was performed only after a patient was deemed eligible and written consent obtained. The treating clinician, or their designate, completed the randomization form. Patient details were recorded and a treatment arm and randomization number allocated to the patient, both recorded in the patient's hospital file. Then the randomization form was completed and returned to the principal investigator.

In order to ensure balance within the two treatment groups we used blocked randomization. This was performed using computer-generated random numbers from Random Allocation Software (version 1.0.0). If there is an important predictor of the outcome, stratified blocked randomization is available. For example, an affecting number may be a strong predictor. Thus we could carry out a blocked randomization within each of the two strata, OA of one knee and both knees.

5. Blinding

All patients, Korean medicine doctors for diagnosis and investigators were blinded. Only Korean medicine doctors for intervention know randomization results. The Korean medicine doctor for diagnosis who does not know the randomization results inserts needles into the subcutaneous layer with the Acugun (neoDr, Korea). The Korean medicine doctor for intervention accomplishes the needling technique according to randomization results and the order from the diagnosing Korean doctor.

6. Study Treatment

Patients were randomly assigned to receive either individualized traditional Korean acupuncture or standardized minimal acupuncture. Acupuncture treatments consist of 12 sessions of 20 minutes duration, each administered over a period of 6 weeks (preferably 2 sessions in each of the 6 weeks). Patients receive the acupuncture on Tuesday ± 1 day and Thursday ±1 day each week. In the case of unilateral osteoarthrosis, the treatment are performed with 6 local points on the affected side and 4 distal points on the opposite side (10 needles altogether). If both knees are affected, both knees have to be acupunctured with 6 local points on each side and 4 distal points acupunctured on the lesser

Table 1. Checklist for Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) items

Intervention	Item	Description
Acupuncture rationale	1	• Style of acupuncture Individualized traditional Korean acupuncture • Rationale for treatment and individualization if used Meridian theory of traditional Korean medicine to treat knee joint pain, known as the "Bi" syndrome • Literature sources to justify rationale An Interview Survey for Developing Clinical Trial Protocol on Individualized Acupuncture Treatment for Knee Osteoarthritis. 2005.16)
Needling details	2	• Points used - 6 local points : *Yanglinquan* [GB 34], *Yinlinquan* [SP 9], *Dubi* [ST 35], *Heding* [Ex-LE 2], *Xiyan* [EX-LE 5] and *Ashi* point in collateral ligament areas on meridians that traverse the area of pain If both knees are affected, 6 needles are inserted in each leg. - 4 distal points : Liver-reinforcing or reducing manipulation acupoints, Kidney-reinforcing or reducing manipulations acupoints on adverse side of pain area If necessary, the other reinforcing or reducing manipulations can be used. If both knees are affected, 4 needles are inserted in the lesser affected side. All patients have to be treated with a selection of permitted local and distant points which must be selected according to the principles of Traditional Korean Medicine by experienced acupuncturists. • Needle type Pre-packed, sterile, disposable 40mm×0.35mm needles • Depths of insertion Korean medicine doctor (KMD) for diagnosis inserts needles into the subcutaneous layer with the Acugun (neoDr, Korea). KMD for intervention accomplishes acupuncture according to the depths order from KMD for diagnosis. • Responses elicited All participants in the treatment group achieved the 'De-Qi' sensation, a local sensation of heaviness, numbness, soreness, or paresthesia that accompanies the insertion and manipulation of needles during acupuncture at acupoints. • Needle stimulation KMD for diagnosis orders a needling technique on the basis of 「On Governing the Needles」 in 『Yellow Emperor's Canon Internal Medicine』 .17) KMD for intervention accomplishes the needling technique according to the order from KMD for diagnosis. The needles in local points are stimulated with method; Mix, frequency; Low 2, High 30 and out-range; L by PG-306 pulse generator (Suzuki Iryoki, Japan). • Needle retention time 20 minutes
Treatment regimen	3	• Number of treatment sessions 12 sessions • Frequency of treatment Twice a week: Tuesday ± 1 day, Thursday ± 1 day
Co-interventions	4	• Other interventions Nothing is done.
Practitioner background	5	• Duration of relevant training More than 2 years in Korean medical hospital. • Length of clinical experience More than 2 years in Korean medical hospital. • Expertise in specific condition Completion of the first-year course in acupuncture and moxibustion clinic

Intervention	Item	Description
Control intervention(s)	6	• Intended effect of control intervention and its appropriateness to research question and, if appropriate, blinding of participants It seems that standardized minimal acupuncture as control intervention also may have positive outcomes although lesser than individualized traditional Korean acupuncture does. Standardized minimal acupuncture is minimally active penetrating. Single blind is intended. • Explanations given to patients of treatment and control interventions Patients are informed in the study as follows: 'In this study, different types of acupuncture will be compared. All types are the acupuncture treatments used in OA of the knee. Each type has been associated with positive outcomes in clinical studies.' • Details of control intervention *Points used, Needle type, Needle retention time* The same as ones of individualized traditional Korean acupuncture *Depths of insertion* KMD for diagnosis inserts needles into the subcutaneous layer with the Acugun. The needles should be placed subcutaneously. *Responses elicited* 'De-Qi' and manual stimulation of the needles should be avoided. All acupuncturists were trained to apply minimal acupuncture and received a videotape and a brochure showing detailed information on minimal acupuncture. *Needle stimulation* The needles in local points are stimulated with method; Mix, frequency; Low 2, High 30 and out-range; L by PG-306 pulse generator (Suzuki Iryoki, Japan). *Sources that justify choice of control* Berman identified the effectiveness of standardized minimal acupuncture for OA of the knee with the same acupoints in 'Effectiveness of Acupuncture as Adjunctive Therapy in Osteoarthritis of the Knee: A Randomized, Controlled Trial'.

affected side (16 needles altogether). (Table 1)

7. Adverse Events

Serious adverse events associated with acupuncture include transmission of infectious disease. Minor adverse events include exacerbation of symptoms, minor bleeding, hematoma, fatigue, sweating, severe nausea, fainting and headache. Adverse events may be associated with practitioner competence and training[18]. Documentation of adverse events will be checked every visit from the first day of study acupuncture application up to 1 week after the last study acupuncture application.

8. Outcome measure

The primary outcome measure is participant pain rating based on a 100 mm VAS. Secondary outcome measures include the WOMAC, a validated, disease-specific questionnaire addressing severity of joint pain, stiffness and limitation of physical function. A higher WOMAC score indicates a worse symptom severity, with 96 representing the worst possible score. General health related quality of life is also assessed using the SF-36 questionnaire, which provides separate summary scores for subjects' quality of mental and physical health. Other outcomes that will be assessed are the LFI score and KHAQ.

9. Data analysis

We will conduct basic analyses of demographic and baseline characteristics of the patients and use chi-square tests and t-test to compare the two

treatment groups on those characteristics. By using a mixed-model approach we will examine mean change from baseline at 3, 6 and 20 weeks. We will also perform a multiple imputation analysis if there is a large drop-out of patients during the clinical study. In addition, an exploratory analysis will be conducted to provide the graphics for univariate and multivariate data.

10. Sample size

The primary outcome measure for this trial is the VAS scale. We have defined overall success as a 20% difference in the VAS between individualized traditional Korean acupuncture and standardized minimal acupuncture. For this comparison, a minimum of 20 participants was needed in each group to reject the null hypothesis with 80% power and at a 5% significance level (two-tailed). As our trial will compare individualized traditional Korean acupuncture and standardized minimal acupuncture we will have two groups and therefore, needed 40 participants. Allowing for a 20% dropout rate in those recruited to the trial, the total number of participants required to be randomized was 50.

11. Monitoring

Every participating investigator or institution will permit trial-related monitoring, audits, IRB review and regulatory inspections, providing direct access to source data/documents. The CRA will perform adequate monitoring visits. The site will be visited at least once before the study start, during subject enrollment and once for site closing at study end.

Conclusions

We have described the protocol and conduct of a randomized controlled trial of knee OA. This study is one of the first to compare two acupuncture methods known to be effective in clinic. The trial is currently successfully over. Trial procedures were well received by both patients and clinicians. Much effort has gone into maintaining the profile of the trial and disseminating trial procedures across all disciplines.

1. Human participation protection

The study protocol and informed consent form were approved by the IRB of the Dongguk University International Hospital.

2. CAST research team

1) Trial Steering Committee

Department of Acupuncture & Moxibustion, Dongguk University International Hospital

2) Data Monitoring Committee

Korea Institute of Oriental Medicine

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