Clinical Study Protocol

Official Title: Pragmatic randomized controlled trial of pharmacopuncture therapy for chronic knee pain: A pilot study

Daejeon Jaseng Hospital of Korean Medicine

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Pragmatic randomized controlled trial of pharmacopuncture therapy for chronic knee pain: A pilot study

Indication: Chronic Knee Pain

Development Stage: NA (Investigator-Initiated Trial)

Protocol Version: 1.0

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▣ Definitions and Abbreviations of Terms

CRF	Case report form
EQ-5D-5L	5-level EuroQol-5 Dimension
PGIC	Patient Global Impression of Change
NRS	Numeric Rating Scale
VAS	Visual Analogue Scale
SF-12	Short Form-12 Health Survey
WHO-UMC	World health organization-Uppsala Monitoring Centre
IRB	Institutional Review Board
HIRA-NPS	Health Insurance Review and Assessment Service-National Patients Sample
RCT	Randomized Controlled Trial
ITT	Intention to treat
PP	Per Protocol
K-WOMAC	Korean Western Ontario & McMaster
AE	Adverse event
SAE	Serious adverse event

▣ Protocol Synopsis

Study Title	Pragmatic randomized controlled trial of pharmacopuncture therapy for chronic knee pain: A pilot study
Sponsor	None (Investigator-Initiated Trial)
Monitoring Representative	Hyun-hee Gil, Jaseng Spine and Joint Research Institute
Clinical Trial Site & Principal Investigator	Soon-ah Kim, Daejeon Jaseng Hospital of Korean Medicine
Study Period	From the date of initial IRB approval to December 31, 2023
Study Population	Patients with chronic knee pain requiring medical management
Study Objectives	This is a pragmatic clinical trial designed to evaluate the comparative effectiveness of a treatment strategy utilizing pharmacopuncture therapy versus a conventional care strategy using physical therapy in patients with chronic knee pain.
Study Design	Pragmatic randomized controlled trial
Study Methodology	This study aims to evaluate the comparative effectiveness of pharmacopuncture by conducting a pragmatic randomized controlled trial in 40 patients presenting with chronic knee pain. Participants will be randomly allocated to either the pharmacopuncture strategy group ($n = 20$) or the standard Western medical physical therapy strategy group ($n = 20$). As this is a pragmatic clinical trial, participants are randomized solely to either the pharmacopuncture or physical therapy strategy. The specific methods of physical therapy and pharmacopuncture procedures are not predetermined. Instead, interventions will be administered based on the clinical judgment of the attending physicians and doctors of Korean medicine according to each patient's condition. All administered procedures will be retrospectively verified via chart review and documented in the Case Report Form (CRF) for subsequent comparison.

1. Pharmacopuncture Therapy

1) Treatment Methods

- **Acupoints:** Because this is a pragmatic clinical trial evaluating the effectiveness of a pharmacopuncture treatment strategy for chronic knee pain, the selection of acupoints, needle insertion depth, and other procedural details will be determined based on the clinical judgment of the practitioner of Korean medicine, taking into account the patient's symptoms, imaging results, and degree of improvement. All acupoints utilized during each session must be documented.
- **Pharmacopuncture Solution:** The type of pharmacopuncture solution and the injection volume will be chosen based on the clinical judgment of the performing practitioner. A retrospective chart review will be conducted to record the specific types of solutions used and the total administered dosage (in mL).

2) Frequency of Treatment

- **Pharmacopuncture:** Treatment will be administered twice a week for a total duration of 3 weeks. All sessions must be fully documented to ensure accurate evaluation.

2. Standard Care: Physical Therapy

1) Treatment Methods

- **Physical Therapy:** As a pragmatic trial comparing the therapeutic effectiveness between pharmacopuncture and physical therapy, the selection of specific physical therapy modalities, application sites, and duration will be determined by the conventional physician's clinical judgment based on the patient's symptoms, imaging findings, and clinical progress. The specific type, frequency, and anatomical location of the prescribed and administered physical therapy will be recorded.

2) Frequency of Treatment

	• **Physical Therapy:** Treatment will be administered twice a week for a total duration of 3 weeks. All sessions must be fully documented to ensure accurate evaluation.
Subject Eligibility Criteria	1. Inclusion Criteria 1. Patients with a knee pain score of 5 or higher on the Numeric Rating Scale (NRS). 2. Patients whose symptoms have persisted for at least 3 months. 3. Adults aged $₩ge 19$ and < 70 years. 4. Individuals who have received a detailed explanation of the clinical study, fully understand its contents, voluntarily choose to participate, and provide written informed consent agreeing to comply with all study instructions. 2. Exclusion Criteria 1. Diagnosis of a specific, severe underlying disease that could be the primary cause of knee pain (e.g., acute fracture, dislocation, or traumatic ligament/cartilage injury). 2. Knee pain attributable to conditions other than localized knee pathology (e.g., malignancy, fibromyalgia, rheumatoid arthritis, gout, or lumbar disc herniation). 3. Cases where the pain onset is secondary to a traumatic event, and surgical intervention is required due to suspected acute fracture, dislocation, or ligament/cartilage injury. 4. Presence of other chronic medical conditions that could interfere with treatment effects or data interpretation (e.g., stroke, myocardial infarction, severe renal disease, diabetic neuropathy, dementia, or epilepsy). 5. Current use of corticosteroids, immunosuppressants, psychotropic medications, or any other drugs that could confound the study outcomes. 6. Cases where pharmacopuncture is deemed inappropriate or unsafe, including individuals with hemorrhagic diseases, those receiving anticoagulant therapy, or patients with severe diabetes presenting a high risk of infection.

	7. Use of medications that could alter pain perception, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), or receipt of pharmacopuncture or physical therapy within the past week. 8. Pregnant women, women planning a pregnancy during the study period, or lactating mothers. 9. Patients within 3 months post-knee surgery, or those who have undergone total knee arthroplasty (TKA). 10. Individuals for whom less than 1 month has elapsed since completing participation in another clinical trial, or those planning to enroll in another clinical trial during the study or follow-up period (within 6 months from the screening date). 11. Individuals who face difficulties providing written informed consent. 12. Any other cases where the investigator deems participation inappropriate. 3. Discontinuation and Drop-out Criteria • A subject may voluntarily withdraw from the clinical study at any time, or may be discontinued at the discretion of the investigator. If a subject drops out, the investigator must evaluate and document the primary reason for withdrawal. Subjects who discontinue treatment may continue follow-up assessments subject to their explicit consent. • Subjects who withdraw prior to randomization will be classified as screening failures. Unless medically necessary, completing all evaluations required at the time of discontinuation is not mandatory for screening failures. • Participants who drop out early due to adverse events (AEs) will receive appropriate medical treatment for the AE if necessary. In cases of discontinuation due to an AE causally related to this study, the investigator must continuously monitor and evaluate the subject until the AE resolves or is deemed permanent. • Criteria for mandatory study discontinuation are as follows: 1. Discovery of a pre-existing medical condition during the study that was undetected during screening and could confound the evaluation of study results. 2. Request for discontinuation by the subject or their legal representative, or withdrawal of informed consent. 3. Confirmation of pregnancy during the course of the study.

	4. Technical or clinical barriers preventing the performance of medical or Korean medical interventions for knee pain. 5. Identification of an inclusion/exclusion criteria violation after enrollment. 6. Occurrence of intolerable adverse events or serious adverse events (SAEs). 7. Major protocol violations that could significantly distort the study outcomes. 8. Loss to follow-up. 9. Any other circumstances where the investigator determines that continuing the study is clinically inappropriate.
Outcome Measures and Clinical Assessments	1. Primary Outcome Measure • **Knee Pain Numeric Rating Scale (NRS):** The mean intensity of knee pain over the past week will be assessed using the NRS. Patients will select a single integer from 0 to 10 that best represents their current level of discomfort, where 0 indicates "no pain" and 10 indicates "the most severe pain imaginable." 2. Secondary Outcome Measures • **Knee Pain Visual Analogue Scale (VAS):** This scale utilizes a 100 mm horizontal line, where the left anchor represents "no pain" and the right anchor represents "the most severe pain imaginable." Patients will mark a point on the line indicating their average knee pain intensity over the past week. • **Range of Motion (ROM) of the Knee Joint:** Passive ROM will be measured before and after treatment to evaluate functional changes. Passive ROM is assessed by measuring the angle between a hypothetical line perpendicular to the ground and the subject's lower extremity at the maximum limits of knee flexion, extension, left lateral flexion, and right lateral flexion. If measurement is impossible due to severe pain, it will be documented as "UC" (Unmeasurable Condition). • **Korean Western Ontario & McMaster Universities Osteoarthritis Index (K-WOMAC):** Functional status will be evaluated using the K-WOMAC questionnaire. The WOMAC is a 24-item instrument validated to assess disability associated with knee pathology. Items are scored on a 5-point scale across three subscales: pain (5 items), stiffness (2

	items), and physical function (17 items). Higher scores reflect greater disability. A validated Korean version will be administered. • **Short Form-12 Health Survey version 2 (SF-12 v2):** The SF-12 v2 is a generic instrument used to assess health-related quality of life (HRQoL), comprising 12 items across 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Completion typically requires less than 5 minutes, with higher scores indicating superior HRQoL. The reliability and validity of the Korean version of the SF-12 were previously established in a representative Korean population ($N = 1,000$) by Kim et al. • **EuroQol-5 Dimension (EQ-5D-5L):** The EQ-5D-5L evaluates multi-dimensional health states to indirectly calculate utility weights based on a predefined preference-based scoring algorithm. It consists of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Preferences and utility scores are derived using a validated Korean tariff. • **Patient Global Impression of Change (PGIC):** The PGIC is a 7-point single-item scale where patients subjectively rate their overall clinical improvement: 1, Very Much Improved; 2, Much Improved; 3, Minimally Improved; 4, No Change; 5, Minimally Worse; 6, Much Worse; or 7, Very Much Worse. • **Credibility and Expectancy Scale:** To measure treatment expectations, a 9-point Likert scale will be used. At the baseline visit, participants will answer the question, *"How much do you expect pharmacopuncture therapy or physical therapy to relieve your symptoms?"* on a scale from 1 (not at all) to 5 (somewhat) and 9 (very much). • **Healthcare Utilization and Cost Data Survey:** A structured questionnaire will be used to assess direct/indirect medical costs, non-medical costs, time costs, and productivity losses. Direct medical costs include expenses incurred for formal healthcare services. Indirect medical costs cover informal expenditures such as health supplements or medical device purchases. Non-medical costs include transportation, patient time, and caregiving expenses. To quantify productivity losses resulting from illness or absenteeism, the Work Productivity and Activity Impairment (WPAI) questionnaire will be

	administered, and converted into monetary values for cost-utility analysis. • **Concomitant Drug Consumption:** Concomitant medications (either prescribed for underlying diseases or taken as rescue medication) and their respective dosages will be monitored via questionnaires at each visit. Other interventions, including concomitant physical therapy or injections, will be recorded by frequency. • **Adverse Events (AEs):** An AE is defined as any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease that occurs during the clinical trial, regardless of a causal relationship with the intervention. Safety analysis will focus on the incidence of AEs suspected to be related to treatment, laboratory abnormalities, and serious adverse events (SAEs). Safety data will be appropriately summarized, and all SAEs will be reported descriptively. AEs will be captured through patient self-reporting and clinical observation. o Casual relationships will be categorized using the 6-point WHO-UMC causality assessment system: 1) Certain, 2) Probable/likely, 3) Possible, 4) Unlikely, 5) Conditional/unclassified, and 6) Unassessable/unclassifiable. Severity will be graded into three levels based on the Spilker classification: ▪ **Mild (1):** No intervention required; does not significantly impair normal daily activities. ▪ **Moderate (2):** Significantly impairs normal daily activities; may require intervention, with recovery expected post-treatment. ▪ **Severe (3):** Severe adverse event requiring intensive medical intervention; may result in sequelae.
Statistical Analysis Plan (SAP)	- In this study, both intent-to-treat (ITT) and per-protocol (PP) analysis will be performed, and ITT will be the primary analysis. PP analysis will separately analyze study subjects who received more than 5 treatments during the 3-week treatment period. Missing values will be processed through Mixed Model (MMRMR) in the case of the linear mixed model, which is the main analysis, and multiple impressions (MI) and last observation delivered forward (LOCF) will be performed for further analysis. - The socio-demographic characteristics and treatment expectation of the study participants were evaluated for each group. Continuous variables are expressed as mean (standard deviation) or median (quartile), and the

	difference between the two groups will be compared by Student's T-test or Wilcoxon-rank summer test depending on the distribution. Categorical variables are expressed as frequency (%) and chi-square test or Fisher's actual test will be performed. - The effectiveness evaluation variables of this clinical study are the difference between the baseline between the two groups and the amount of change in continuous outcomes (NRS, VAS, K-WOMAC, ROM, EQ-5D-5L, SF-12) by time point. As the main analysis, we will perform a linear mixed model with the covariate factor, which has statistical differences between the pre-treatment value (baseline) of each variable and the treatment group at baseline as a covariate, and the group as a fixed factor. As an additional analysis, ANCOVA will be performed on the set treated with missing values with MI and LOCF. - In order to compare the total amount of the difference value of each outcome within the period (the treatment period and the entire study period) in the two groups, we will calculate the area under the curve at each time point after randomization and compare it with a linear mixed model. - We will compare and analyze the proportion of patients at each point in time when NRS and VAS, which are indicators of knee pain, fell by less than half on a baseline basis. Kaplan–Meier survival analysis will be used to compare the time after randomization until knee pain recovery occurs with less than half the pain, and the curve will be compared by log-rank test. Additionally, we will compare the Hazard Ratio using the Cox Proportional Hazard Model. - The significance level of all analyses is set to 0.05. All statistical analyses are conducted by SAS 9.4 (© SAS Institute, Inc., Cary, NC, USA) or Rstudio 1.1.463 (© 2009-2018 RStudio, Inc.) and significance judgment is set to $p<0.05$. - You want to conduct an interim analysis after the primary endpoint for validity analysis. - If the superiority test fails, a non-inferiority test will be performed. Non-inferiority margin (non-inferiority margin) will be considered as -1 (based on NRS), which is half of the minimum clinically important difference (MCID) for chronic knee pain. If the lower bound of the 95% confidence interval of the difference in the amount of reduction in the VAS between the two groups does

	not exceed the corresponding margin, acupuncture is considered not inferior to physical therapy.