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Effectiveness and Safety of Pharmacopuncture Therapy for Chronic Low Back Pain: A Study Protocol for a Pragmatic Randomized Controlled Trial

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Background: Low back pain (LBP) is a common musculoskeletal disorder worldwide, with a lifetime prevalence of up to 80%. Among nonsurgical treatments for chronic LBP, Korean medicine treatments are highly preferred, and pharmacopuncture therapy combining acupuncture and herbal medicine is widely used. However, no evidence-based study has focused on the use of various types of pharmacopuncture.

Methods: The pragmatic randomized controlled clinical trial will include 44 participants; recruitment will start in July 2023. All participants will receive integrated Korean medicine treatment including acupuncture, cupping, and infrared therapy, and the intervention group will also receive pharmacopuncture. After 16 treatment sessions, twice a week for 8 weeks, follow-up assessments will be performed at week 9. As a pragmatic randomized controlled clinical protocol, the type, dose, and acupoints of acupuncture and pharmacopuncture are not determined in advance but are selected and recorded according to the clinical judgment of the Korean medicine doctor.

Results: The primary outcome will be measured using a visual analog scale score, and the secondary outcomes include the Oswestry disability index, patient global impression of change, no worse than mild pain, and range of motion. Safety will be assessed by examining participants' self-reported adverse events and vital signs and conducting blood tests before and after the test.

Conclusion: This study aims to provide clinical evidence of the effectiveness and safety of pharmacopuncture for chronic LBP.

Keywords: Chronic low back pain; Integrated Korean medicine; Pharmacopuncture; Pragmatic randomized controlled trial

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INTRODUCTION

Low back pain (LBP) is a very common musculoskeletal disorder worldwide across all age groups, with a predominance in middle-aged people aged 40–69 years and is more common in women [1-3]. Chronic LBP is defined as LBP that lasts for > 3 months [2,4] and is used to describe a symptom, not disease related, to pain between the 12th rib and the lower gluteal folds [1,4]. LBP can have many causes, including trauma or repetitive motion damage, degenerative changes due to aging, or structural degeneration of the lumbar spine. However, up to 85% of patients with chronic LBP are diagnosed with nonspecific LBP, and determining a definitive cause is challenging [1,4,5]. Chronic LBP is a personal, social, and economic burden that accounts for a large portion of healthcare costs related to musculoskeletal pain [6]. It refers to not only the pain itself but also to a series of symptoms, such as depression, anxiety, and sleep disorders [1,6]. LBP is the most common disease encountered in Korean medical institutions in South Korea [7,8]. Methods for treating chronic LBP include medication, physical therapy, acupuncture, pharmacopuncture, moxibustion, cupping, Chuna therapy, and manual therapy [6,7]. Not one of these treatments is effective for all patients [5].

Pharmacopuncture combines acupuncture and herbal medicine. Injecting herbal medicine extracts into acupoints causes physical stimulation and chemical reactions, increasing the treatment effect [9-11]. Effects of pharmacopuncture include immune system regulation and anti-inflammatory, microcirculatory, and pain relief effects [7,9]. Its advantages include rapid therapeutic effect, synergistic effect between acupuncture and herbal medicine, simple procedure, easy administration, and various indications [9]. Pharmacopuncture is used in various diseases, including the musculoskeletal, nervous, circulatory, dermatology, and autonomic nervous systems, and is most frequently used in musculoskeletal diseases [7,11].

Although the use of pharmacopuncture in treating LBP is thought to contribute greatly to public health, no studies have examined the safety and effectiveness of pharmacopuncture for chronic LBP. Therefore, this study protocol will serve as a guide for a practical randomized controlled study to determine the safety and effectiveness of pharmacopuncture used clinically for such frequently occurring chronic LBP.

MATERIALS AND METHODS

1. Study design

This is a prospective, single-center, pragmatic randomized controlled trial (PRCT). Protocol version 1.1 was approved by the Institutional Review Board (IRB) on June 19, 2023. Recruitment first began on July 27, 2023. The recruitment for this study is ongoing. We anticipate that this trial will take 2 years to complete. The participants will be recruited through placards on outdoor banners in Daejeon University Cheonan Korean Medicine Hospital (DUCKMH) and will receive written explanations and informed consent forms for the clinical trial protocol from a Korean medicine doctor (KMD).

Blood tests for liver function, inflammation-related cells, and complete blood count will be performed to check for adverse events (AEs). Urine human chorionic gonadotropin test and lumbar X-ray imaging will be performed to confirm exclusion.

A total of 44 participants who will meet the eligibility criteria for this study will be randomly assigned in a 1:1 ratio to the intervention group or the control group. The intervention will begin within 1 week of the screening visit. Both groups will receive 16 sessions of the intervention twice a week for 8 weeks, and a follow-up evaluation will be conducted at week 9. The flowchart of the study is shown in Tables 1, 2. This trial complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [12].

2. Inclusion and exclusion criteria

1) Inclusion criteria
   (1) Age 19–64 years.
   (2) LBP ≥ 6 months.
   (3) Visual analog scale (VAS) of back pain score ≥ 50 mm.
   (4) Voluntary participation in this trial and provision of written informed consent.

2) Exclusion criteria
   (1) Diagnosis of spinal metastases of tumors, acute fracture, and/or spinal dislocations.
   (2) LBP caused by tumor, fibromyalgia, rheumatoid arthritis, and/or gout.
   (3) Past history of other chroni.c diseases, such as stroke, myocardial infarction, kidney disease, and/or diabetic neuropathy.
   (4) Currently taking medications such as steroids, immunosuppressants, and/or psychiatric drugs.

Table 1. Study schedule and outcome measurements

	Study period																		
	Screening	Enrollment, allocation	Intervention period																Follow-up
	Visit																		
	Week -1	Week 0 (baseline)	Weeks 1–8																Week 9 (V17)
			V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	
Enrollment																			
Checking the selection/exclusion criteria	•	•																	
Obtain consent form	•																		
Vital signs	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Demographic surveys and body measurements	•																		
Medical history of lumbar and other body organs	•																		
Clinical laboratory test	•		•																•
L-spine X-ray imaging	•																		
Randomized allocation		•																	
Interventions																			
Pharmacopuncture therapy with IKM			◆	—	—	—	—	—	—	—	—	—	—	—	—	—	—	◆	
IKM			◆	—	—	—	—	—	—	—	—	—	—	—	—	—	—	◆	
Assessments																			
Visual analog scale	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Patient global impression of change							•				•				•				•
No worse than mild pain					•		•		•		•		•		•		•		•
Range of motion			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Oswestry disability index			•				•				•				•				•
Checking for adverse events			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Confirmation of study stopping and dropout criteria			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Visit schedule training			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	

IKM, integrated Korean medicine.

Table 2. SPIRIT checklist showing the study schedule

	Study period									
	Enrollment	Baseline	Treatment period							Follow-up
Timepoint	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	...	t_{16}	t_{17}
Enrollment										
Eligibility screening	X									
Informed consent	X									
X-ray imaging of the lumbar spine	X									
Allocation		X								
Interventions										
Pharmacopuncture with IKM			◆	—	—	—	—	—	◆	
IKM			◆	—	—	—	—	—	◆	
Assessments										
Visual analog scale			◆	—	—	—	—	—	◆	X
Patient global impression of change							X			X
Oswestry disability index			X				X			X
No worse than mild pain					X		X			X
Range of motion			◆	—	—	—	—	—	◆	X

The "X" refers to what is done in the given period.
During the omitted period, the same evaluation items are repeated in t_2–t_5, t_6–t_9, t_{10}–t_{13}, and t_{14}–t_{17}.
SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; IKM, integrated Korean medicine.

(5) Pain in other parts worse than LBP.
(6) Pregnancy or breastfeeding.
(7) Lumbar surgery within the last 3 months.
(8) Participation in other clinical trials within 4 weeks.
(9) Spinal surgery scheduled during the test period.

3. Sample size calculation

This clinical trial will explore the effect and safety of pharmacopuncture on chronic LBP. The evidence for the effect size in this study is based on that by Park et al. (2021) [13]. The effect size for the evaluation variables (VAS and numerical rating scale for chronic neck pain) is between 0.16 and 0.51. When the power is set to 80% and the effect size of the clinical study is conservatively considered 0.1–0.3, a total of 40 participants are planned to be recruited, with 20 people per group according to the suggestion of Whitehead et al. (2016) [14]. The dropout rate reported by Park et al. (2021) [13] was 3%, and considering a dropout rate of 5% in this clinical study, the final sample size to be recruited is set to 44 people, with 22 for each group.

4. Randomization procedures

Using the block randomization method, randomization in the treatment and control groups will be performed at a ratio of 1:1. An independent statistician will randomly assign 22 individuals per group, with the same probability of each object being selected using balanced block randomization without stratification. The generated randomization table will be held by a statistician independent of this trial, and the file will be protected from disclosure. The participants who will meet all the registration criteria will be randomly assigned a randomization identification code in the order generated by a computer-randomized program. The randomization code will be placed in an opaque envelope and stored in a locked cabinet. After the researcher has sufficiently explained the clinical research to the participants and the latter have filled out the consent form for trial participation. After the participants' screening for the inclusion and exclusion criteria, the researcher will open the random assignment envelope with the same number as the randomization number in front of the participants and assign the group. The characteristics of the treatments used in this trial precluded blinding of participants and researchers. All evaluations and analyses will be conducted independently.

5. Interventions

In this study, the integrated Korean medicine (IKM) treatment discussed will include acupuncture, cupping, and infrared therapy. Acupuncture will be performed for 15 minutes. Simultaneously, infrared irradiation will be applied to the patient's acupuncture point. Cupping will

be performed on the lumbar region for 5 minutes before or after acupuncture. As a PRCT protocol, the type, dose, acupoints of acupuncture, and the pharmacopuncture type to use are not determined in advance but are selected and recorded according to the clinical judgment of the KMD. A licensed KMD with at least 2 years of clinical experience in acupuncture and phamacopuncture will perform the therapy.

All eligible participants will receive treatment according to their allocated group (combination of pharmacopuncture and IKM treatment or IKM treatment) for 16 sessions during the treatment period. In principle, the procedure will be performed twice a week for 8 weeks. However, depending on the patient's condition, this may increase or decrease to once a week. Treatment may be performed up to three times and at least once a week.

6. Outcome measures

The primary outcome will be the VAS score, which will be used to assess LBP at each visit. The secondary outcomes will be the average changes in the Oswestry disability index (ODI) score, patient global impression of change (PGIC) on treatment, range of motion (ROM), and no worse than mild pain after treatment (V17) compared with the baseline (V1). The VAS scores and ROM will be measured at each visit. The ODI will be measured at V1, V5, V9, V13, and V17. The PGIC will be evaluated at V5, V9, V13, and V17. No worse than mild pain will be assessed at V3, V5, V7 until V17. To ensure the participant's safety, laboratory tests will be conducted at screening and at the end of the procedure (V17), such as that for liver function, complete blood count, and inflammation-related indicators, and vital signs will be evaluated at every visit. Adverse reactions will be checked at each visit.

1) Visual analog scale

VAS will be used to evaluate the intensity and frequency of pain on a line given to the participant. In general, a horizontal line on a non-marking line of 10 cm indicates "no pain" at the left end and "maximum pain imaginable" at the right end. The participant will mark a point on the line [8].

2) Oswestry disability index

ODI will be used to evaluate LBP-related functional disability. It comprises 10 items, each of which comprising six responses scored 0–5 points. The higher the score, the more severe the disability [15].

3) Patient global impression of change

PGIC is a self-reported scale that compares a respondent's improvement before and after treatment. It comprises seven responses: very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse [16].

4) Range of motion

ROM measures the angle of maximum active joint motion in which a participant can move without pain. Flexion, extension, bilateral rotation, and bilateral flexion angles will be measured while the participant is standing upright.

5) No worse than mild pain

For this outcome, the participant subjectively responds to treatment. This index expresses that a minimum clinically significant effect is achieved. We plan to qualitatively evaluate whether the pain level at the time of evaluation has decreased compared with the level before treatment. It reflects improvement and satisfaction with treatment [11,17].

7. Data collection

At screening, the participants will complete a questionnaire regarding their sociodemographic characteristics and provide their lumbar spine medical history within the past 6 months and their drug history within the past 4 weeks. The participants will undergo L-spine X-ray imaging and the aforementioned laboratory tests. Personal information and data will be managed by the investigators. DUCKMH researchers will monitor the data and research activities. The final trial dataset will be accessible to statisticians and the principal investigator. All information regarding the participants and interventions will be kept confidential. All documents related to the clinical trial will be recorded and classified using an identification code instead of the participant's name.

8. Statistical analysis

Statistical analysis will be primarily based on the principle of the full-analysis set group, and secondary analysis will be performed on the per-protocol group. Demographic differences between groups at baseline will be included as covariates, and analysis of covariance will be performed using the baseline value of the evaluation variable as a covariate to test the mean difference in the change in V17 compared with the baseline. Missing values will be analyzed via the last observation carried forward method, a type of multiple imputation method.

The primary outcome measure will be the changes in the VAS scores between baseline and V17. Secondary outcomes will be analyzed according to the primary protocol.

Descriptive statistics will be presented as mean, standard deviation, median, and minimum and maximum values. Continuous data will be tested using t-tests or Wilcoxon's rank-sum tests. Categorical data will be analyzed using the chi-square test or Fisher's exact test. The significance level will be set at a p-value of < 0.05 and confidence interval at 95%. Statistical analyses will be performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp.). Subgroup analysis of demographic variables (e.g., sex, age, and duration of illness) will be performed as needed.

9. Withdrawal and dropout

If the participant does not meet the inclusion or exclusion criteria, withdraws consent, or continued participation is judged as inappropriate, he/she will be excluded from the study. In addition, all participants who become pregnant during the study period will immediately discontinue the clinical trial. The researchers will record the reason for any interruption in the intervention and whether each participant completed the study.

10. Concomitant treatment

If LBP is severe during the clinical research period, noninvasive treatments such as physical therapy, manual therapy, and drugs are allowed under the judgment of the researcher; however, invasive treatments such as surgery and injection are prohibited. The details of the concomitant treatment will be recorded in the case report form for analysis. However, Korean medicine treatment for LBP is prohibited outside of this study.

11. Safety

AEs will be assessed at each visit. The participants will be monitored for undesirable, unintended symptoms, signs, illnesses, and duration of adverse and serious AEs (SAEs) at pre- and post-treatment clinical examinations. All AEs and SAEs will be recorded, with a detailed description of patient symptom reporting and researcher observation. The number and percentage of participants who experience at least one AE will be calculated.

12. Ethics

This study is designed based on the Declaration of Helsinki and the Korean Clinical Practice Guidelines. It was approved by the Korean IRB of DUCKMH (approval no.: DJUMC-2023-BM-06). The IRB is an independent institution without competing interests. This study protocol is registered with the Korean National Clinical Research Information Service (CRIS) (CRIS-KCT0008620). The participants will receive a fully written explanation of the study protocol and an informed consent form. The participants may be required to quit the study and advised to receive appropriate treatment in the case of SAEs or AEs, upon which they will be reported to the IRB of the hospital. They will be allowed to withdraw their consent at any time for any reason or discontinue their participation voluntarily.

DISCUSSION

The prevalence of LBP is > 80% in a person's lifetime [4,5]. Its high prevalence, high recurrence rate, and great functional disability facilitate chronic pain [1,4]. The more common causes in women are pain related to osteoporosis, menstruation, and pregnancy [2]. It is accompanied by numerous problems such as high incidence and recurrence rate, economic and social burden, and various treatment methods for chronic LBP are recommended. However, the clear cause and standard treatment are currently unclear [4,5].

Schwartz and Lellouch [18,19] first used the term in 1967 while comparing explanatory and pragmatic trials. An explanatory trial aims to verify and understand the causal relationship of a clinical hypothesis, and a pragmatic trial aims to determine the choice of the treatment method. In PRCTs, the study design simulates the actual clinical situation as much as possible and often does not use patient or doctor blinding. In many cases, both the treatment and control groups receive usual care; the treatment group receives the intervention for which the effect is to be evaluated. Because PRCT evaluates multidimensional results by complex treatment, it is suitable for clinical research in IKM [20]. In this PRCT, the effects of pharmacopuncture therapy for chronic LBP will be evaluated. The depth, type, concentration, and amount of pharmacopuncture should be selected according to the clinical judgment of the KMD. All acupoints and pharmacopuncture points at the time of the procedure, type of pharmacopuncture used, and total dose (mL) will be recorded.

Pharmacopuncture is a treatment method that combines acupuncture and herbal medicine and maximizes the effect of treatment through the injection of purified herbal extracts into acupoints [9-11,21]. The physical ef-

fect of stimulating acupoints and the chemical effect of herbal extracts are expected to create a synergistic effect [22]. Although pharmacopuncture is highly useful in clinical practice, its therapeutic efficacy in chronic LBP has not been elucidated yet.

The RCT on the effectiveness of bee venom pharmacopuncture reported significant pain relief and functional improvement compared with the sham bee venom pharmacopuncture group [21,23]. In addition, a PRCT reported that pharmacopuncture significantly reduced pain and improved functional outcomes and quality of life compared with physical therapy [24]. However, unlike the cited studies, this research protocol sets the control group as the Korean medicine treatment group; thus, it is thought to be valuable in evaluating the effectiveness and safety of pharmacopuncture in the clinical setting of Korean medicine. Therefore, this study may provide insights into the evidence of Korean medicine treatment on the therapeutic effect of pharmacopuncture for chronic LBP.

AUTHOR CONTRIBUTIONS

Conceptualization: JHK, HL. Funding acquisition: HL. Investigation: YYC. Methodology: YYC, HYR. Project administration: JHK, HL. Supervision: JHK, HYR. Writing – original draft: YYC. Writing – review & editing: HYR, JHK.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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ETHICAL STATEMENT

This study protocol is designed according to the Helsinki Declaration and the Korean Clinical Practice Guidelines. This clinical trial protocol was reviewed and approved by the institutional review board of the Daejeon University Cheonan Korean Medicine Hospital (IRB no. DJUMC-2023-BM-06). All participants will provide voluntary written informed consent after fully discussing potential benefits and risks before participating.

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