Effectiveness and Safety of Pharmacopuncture Therapy for Chronic Low Back Pain: Study protocol

Protocol ID : JS-CT-2021-02

Clinical trials : NCT04833309

Document Date : September 30, 2021

Study Design and Setting

This two-armed, parallel, multi-center RCT will competitively recruit 100 patients in the Jaseng Hospital of Korean Medicine, Daejeon Jaseng Hospital of Korean Medicine, Bucheon Jaseng Hospital of Korean Medicine, and Haeundae Jaseng Hospital of Korean Medicine. The study protocol was approved by the Institutional Review Board (IRB) of Jaseng Hospital of Korean Medicine before participant recruitment (JASENG 2021–02- 012, JASENG 2021–02-013, JASENG 2021–02-014, JASENG 2021–02-032). Additionally, the study protocol will be registered with Clinicaltrials. gov (NCT04833309) and Clinical Research Information Service (KCT0006088) and continuously updated.

Inclusion/Exclusion Criteria

Inclusion Criteria

- LBP onset ≥ 6 months

- Numeric rating scale (NRS) score of LBP ≥ 5

- Age 19–70 years

- Signing of the ICF to participate in the clinical trial

Exclusion Criteria

- Diagnosis of a serious disease that may cause LBP (eg, spinal metastasis of tumor, acute fracture, spinal dislocation)

- Progressive neurological defects or severe neurological symptoms

- Pain is caused by soft tissue disease rather than the spine (eg, tumor, fibromyalgia, rheumatic arthritis, gout)

- Other chronic diseases that may hinder the interpretation of treatment effects or outcomes (eg, stroke, myocardial infarction, renal disease, diabetic neuropathy, dementia, epilepsy)

- Current use of steroids, immunosuppressants, antipsychotic agents, or other drugs that may affect study outcomes

- Contraindications for pharmacopuncture, including hemorrhagic diseases, anticoagulant usage, severe diabetes mellitus with risk of infection

- Use of drugs that may affect pain, including non-steroidal anti-inflammatory drugs, or pharmacopuncture therapy within the previous week

- Pregnant or breastfeeding women, as well as women planning to conceive

- Lumbar surgery in the previous three months

- Less than one month since participating in another clinical trial or planning to participate in another clinical trial during the study period or follow-up period within 6 months upon enrolment

- Declining to sign a consent form to participate

- Other disqualifications as determined by the investigators

Interventions

Experimental Group: Pharmacopuncture Therapy

Pharmacopuncture therapy will be given two times a week for five weeks. With reference to a study on the current trend in pharmacopuncture therapy that used electronic medical records from 12 Korean medical hospitals,11 the treatment will be performed following the physician's clinical judgment. Additionally, all procedure-related matters will be recorded in patients' charts. Pharmacopuncture procedures will be retrospectively reviewed and recorded in a case report form (CRF) for analysis.

Control Group: Physiotherapy

Based on a study on HIRA data, patients with LBP in Korea are treated using a combination of deep heat therapy, superficial heat therapy, transcutaneous electrical nerve stimulation, and intermittent pelvic traction therapy.12 According to this data, a physician will choose the method, site, and duration of physiotherapy based on their clinical judgment with respect to the patients' symptoms, radiological findings, and improvement levels. Physiotherapy will be performed twice a week for five weeks; further, all matters regarding the physiotherapy, including the type, duration, and site of physiotherapy, will be recorded in patients' charts. The treatment method will be retrospectively reviewed and recorded in CRF for comparison.

Criteria for Discontinuation and Withdrawal

A participant may be discontinued from the clinical trial for the following reasons: Discovery of a previously undetected disease that may affect study outcomes Request for discontinuation during the study period by the participant or their legal representative or withdrawal of consent by the participant Confirmation of pregnancy during the study period Problems regarding the administration of medical and Korean medical procedures for LBP to the participant Other reasons that warrant discontinuation from the study as determined by the researcher

Concomitant Treatment

Pharmacological therapy and medical care for LBP from another healthcare facility may be permitted during the treatment or follow-up period in case of severe pain. The treatment details and frequency will be recorded in the CRF for analysis.

Outcome

Primary Outcome

NRS score of LBP

The LBP intensity within the previous week will be assessed using the NRS. Patients will be instructed to choose a number from 0–10 that best represents their current discomfort level (0 for no pain, 10 for the worst imaginable pain).

Secondary outcomes

NRS score of radiating leg pain

The intensity of radiating leg pain in the past week will be assessed using the NRS. Patients will be asked to choose a number from 0–10 that best represents their current discomfort level (0 for no pain, 10 for the worst imaginable pain).

Visual analog scale (VAS) score of low back pain and radiating leg pain

The VAS represents the patient's pain level, where one end of a 100-mm line refers to no pain while the other end indicates the worst imaginable pain. Patients are instructed to indicate their intensity of LBP and radiating leg pain within the previous week by marking a point on the line.

Oswestry disability index (ODI)

The participants' functional status will be assessed using the ODI, which is a 10-item tool developed to assess LBP-caused disability. Each item is divided into six steps; further, it is rated on a scale from 0–5. A higher score indicates a more severe disability. We will use the Korean version of the ODI questionnaire, which has been shown to be reliable and valid.

Korean version of the Roland–Morris disability questionnaire (RMDQ)

The RMDQ is among the most widely used tools for evaluating the functional state of patients with LBP. It comprises 24 items, with the patient marking the specific activities limited by their LBP. A positive response scores 1 point, and the questionnaire is scored from 0 (minimal disability) to 24 (severe disability). We will use the questionnaire of the Korean-adapted version, which has been shown to be reliable and valid.

Patient Global Impression of Change (PGIC)

The PGIC is a self-reported tool for patients' improvement levels: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. A consistent relationship between the change in NRS and the PGIC was demonstrated regardless of study, disease type, age, sex, study result, or treatment group.

Short Form-12 Health Survey (SF-12) version 2

The SF-12 is a questionnaire for evaluating health-related quality of life. It comprises 12 items in 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. It usually takes less than five minutes to complete the questionnaire, with a higher score indicating a better health-related quality of life. We will use the Korean version SF-12, which has been shown to be reliable and valid.

5-level EuroQol-5 dimension (EQ-5D-5L)

The EQ-5D-5L is the most widely used indirect evaluation tool for the health state. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. There are specific weights for the level of each category; moreover, these weights and constant numbers are used to compute the preference score. We

will use the questionnaire of the Korean-adapted version, which has been shown to be reliable and valid.

Credibility and Expectancy

Participants' expectations for the treatment will be assessed using a 9-point Likert scale. At the enrolment visit, the participants will respond to the question, "How much pain relief do you expect from the pharmacopuncture therapy and physiotherapy? (1 = not at all, 5 = somewhat, and 9 = very much)

Cost Analysis

Cost analysis will be performed using a structured questionnaire for official/unofficial medical costs, nonmedical expenses, time costs, and cost of productivity loss. The official medical cost refers to the cost spent utilizing healthcare facility services, while the unofficial medical cost refers to the cost spent on purchasing health supplements and medical equipment. Non-medical expenses refer to the cost incurred while utilizing healthcare, including transportation, patient's time, and caregiver cost. Cost of productivity loss refers to the cost incurred by lost productivity due to absenteeism and presenteeism due to the disease. The work productivity and activity impairment questionnaire will be used to determine productivity loss; additionally, this will be converted to cost for cost-effectiveness analysis.

Drug Consumption

The types and doses of drugs (rescue drugs) taken for LBP during the study period will be surveyed and recorded at each visit. The frequency of other treatment types, including physiotherapy and injections, will be recorded.

Adverse Events

For safety evaluation, hematology tests (white blood cell [WBC], neutrophil, lymphocyte, monocyte, eosinophil, basophil, red blood cell [RBC], hemoglobin [Hgb], hematocrit [Hct], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet, erythrocyte sedimentation rate [ESR]), clinical chemical tests (T-protein, albumin, T-bilirubin, aminotransferase [ALT], aspartate aminotransferase [AST], r-glutamyl transpeptidase [GTP], blood urea nitrogen [BUN], creatinine), and immunologic tests (C-reactive protein [CRP]) will be performed before and after treatment for both groups to compare the incidence of adverse events.

Adverse events refer to undesirable and unintended signs, symptoms, or diseases that occur after the procedure, including events that may not be caused by the procedure. In this study, data regarding adverse events are collected based on patients' reports and investigators' observations. Further, we will analyze the incidence of adverse events, abnormal laboratory parameters, and serious adverse events suspected to be related to the treatment. The causality between the treatment and adverse events will be assessed using a 6-point scale following the World Health Organization-Uppsala Monitoring Centre causality assessment system (1, definitely related; 2. probably related; 3, possibly related; 4, probably not related; 5, definitely not related; and 6, unknown). The severity of all adverse events will be classified into three categories based on the Spilker classification: Mild (1), treatment not required without marked hindrance of normal everyday life (function); Moderate (2); significantly hinders normal

everyday life (function) with possible treatment being required and subsequent treatment; Severe (3): serious adverse event requiring advanced treatment and leaving sequelae.

Sample Size Calculation

A pilot study was conducted to compare the effectiveness of pharmacopuncture and physiotherapy in patients with chronic LBP. The between-group difference in the mean reduction of the NRS score for LBP was 1.37 ± 1.94 at the primary endpoint, which is immediately after the 5-week treatment; further, Cohen's d was calculated as 0.71. The correlation between the baseline and endpoint was 0.53. Given a significance of 95% and power of 90%, the sample size was calculated to be 64. Considering a 30% withdrawal rate and the recruitment of participants from four facilities, we aim to recruit 100 patients.

Recruitment

Participants will be recruited using a press release, advertisement posters at the clinical trial facility, and online recruitment sites.

Randomization and Allocation Concealment

A statistician will randomize patients into two groups at the same ratio (50 persons for each) using a randomization table on R studio 1.1.463 (© 2009–2018 R Studio, Inc.). The random sequence will be performed using block randomization; further, the size of each block will be randomly set to 2 or 4. The randomization results will be placed in a sealed opaque envelope and stored in a double-locked cabinet by a third person not involved in the study. The coordinator at each study facility will open the envelope for group allocation. Only participants who provide an ICF will be randomly assigned. The randomization number assigned to each participant will be recorded in the electronic medical record.

Blinding

Since blinding the practitioner administering the treatment and the participants is impossible due to the nature of the intervention, only the outcome assessors will be blinded. Outcome-assessors not involved in the procedure and blinded from the group allocation will perform the assessment before the procedure in an isolated space.

Data Collection and Management

We will use an e-CRF using the Internet-based Clinical Research and Trial management system (iCReaT). The principal investigator will train the outcome assessors and investigators of each facility on the standard operating procedure (SOP) as a reference for the study procedures, including writing a CRF and entering data. A query will be issued for a range check of data values. Data entered into the e-CRF will be cleaned and locked to prevent access by investigators other than the one in charge of data management.

Statistical Methods

We will perform both intention-to-treat (ITT) and per-protocol (PP) analyses, with ITT as the primary analysis. For the PP analysis, we will include participants who complete at least seven treatment sessions over 5 weeks. Missing data will be handled by multiple imputation (MI) for analysis of covariance (ANCOVA) and comparison of area under the curve (AUC), as well as

the mixed model for repeated measures for the linear mixed model. For survival analysis, outcomes after the missing time point will be censored. For sensitivity analysis, the last observation carried forward (LOCF) will be used for missing data imputation; further, the normality of distribution will be tested. Nonparametric data will be analyzed using the Wilcoxon-rank sum test. Sociodemographic characteristics and treatment expectancy of the participants will be assessed according to the group. Continuous variables will be presented as mean (SD) or median (quartile), with between-group differences being analyzed using Student's t-test or Wilcoxon-rank sum test, depending on their distribution. Categorical variables will be presented as frequency (%) and analyzed with the chi-square test or Fisher's exact test.

The study endpoints are the differences in the extent of changes in continuous outcomes (NRS, VAS, NDI, NPQ, EQ- 5D-5L, SF-12) at each time point from the baseline. As the primary analysis, we will use a linear mixed model with the covariant factors significantly different from the baseline as covariates and the group as the fixed factor. Next, ANCOVA will be performed on sets processed by MI and LOCF.

To compare the total difference in each outcome within a certain period (treatment period and total study period), the AUC will be calculated for each time point after randomization and compared using Student's t-test. Further, the proportion of patients whose NRS and VAS scores dropped by > 50% from the baseline values will be compared at each time point. The time from randomization to lumbar recovery, which was defined as > 50% reduction in the pain indices, will be compared using Kaplan–Meier survival analysis. Further, the curves will be compared using the Log rank test. Additionally, hazard ratios will be compared using the Cox proportional hazard model. The significance level will be set at 0.05 for all analyses. All statistical analyses will be performed using the SAS 9.4 (© SAS Institute, Inc., Cary, NC, USA) or R studio 1.1.463 (© 2009-2018 RStudio, Inc.) software. Statistical significance will be set at $p < 0.05$.

In case the superiority test fails, a non-inferiority test will be performed. The non-inferiority margin will be set to −1 (NRS), which represents half of the minimal clinically important difference. Pharmacopuncture will be considered non-inferior to physiotherapy if the lower bound of the 95% confidence interval (CI) of the between-group difference of the NRS score reduction does not exceed the non-inferiority margin.

Data Monitoring

The monitoring staff will supervise the clinical trial process, as well as periodically review and confirm whether the study is performed and recorded according to the protocol, SOP, clinical trial management standards, and applicable regulations. The clinical trial will be monitored by the monitoring staff of each clinical trial facility and the sponsor institution using periodic visits and phone calls. At the monitoring visits, the monitoring staff will check the original participant records and data storage (study files). Further, they will inspect the clinical trial procedure and discuss any problems with the investigators.

In case of unexpected or unacceptable risks to participants or occurrence of serious adverse events related to pharmacopuncture or physiotherapy in ≥ 25% of the participants, the clinical trial may be paused. The analysis will be only accessed by the statistician and principal investigator; additionally, the final decision to terminate the study will be made by the principal

investigator