

Non-Pharmacological and Pharmacological Treatments for Non-Acute Lumbar Disc Herniation: A Protocol for a Multicenter Pragmatic Trial

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Purpose: Lower back and radiating leg pain are common worldwide. Most cases are treated with invasive treatments, including injection therapy and nerve blocks; however, their efficacy remains unclear. In the present study, we describe a study protocol for comparing the effectiveness, cost-effectiveness, and safety of non-pharmacological treatment strategies with those of active pharmacological treatment strategies for non-acute lumbar disc herniation (LDH).

Patients and Methods: The primary outcomes of this study are the Oswestry Disability Index and Numerical Rating Scale scores at 13 weeks from baseline. This two-arm, parallel, multicenter, pragmatic, randomized trial will be conducted in four hospitals in South Korea. Two hundred patients with LDH symptoms confirmed via magnetic resonance imaging will be randomly assigned to either a non-pharmacological or pharmacological treatment group. The non-pharmacological group will receive acupuncture and spinal manipulation therapy, whereas the pharmacological group will receive active pharmacological interventions for 8 weeks with a follow-up period of 3 years. Secondary outcomes include the European Quality of Life 5 Dimensions 5 Level Version, Short Form-12 Health Survey Version 2, and Patient Global Impression of Change. A cost survey will be conducted for economic evaluation. The primary analysis will involve the intention-to-treat approach, and differences between the two groups will be analyzed using a linear mixed model. This is the first well-designed, large-scale clinical trial comparing non-pharmacological and pharmacological strategies in patients with non-acute LDH. The findings of this study may provide high-quality evidence on the effectiveness, cost-effectiveness, and safety of non-pharmacological strategies centered on manual therapy.

Ethics and Dissemination: All participants will provide written informed consent. The study protocol, case report form, informed consent form, and all other study-related documents are approved by the IRB of Jaseng Hospital of Korean Medicine. Approval numbers: JASENG 2023-05-001 (Jaseng hospital of Korean Medicine), 2023-05-002 (Daejeon Jaseng hospital of Korean Medicine), 2023-05-003 (Haeundae Jaseng Hospital of Korean Medicine), 2023-05-004 (Bucheon Jaseng hospital of Korean Medicine).

Registration Details: The protocol has been registered on ClinicalTrials.gov (number: NCT06024460; July 20, 2023).

Keywords: intervertebral disc displacement, low back pain, sciatica, drug therapy, pragmatic clinical trial

Introduction

Lumbar disc herniation (LDH) occurs when the annulus fibrosus ruptures and the nucleus pulposus protrudes, leading to compression of the spinal cord or nerve roots and resulting ischemic and inflammatory responses.¹ Depending on the affected neural structures, patients may present with low back pain, radiating leg pain, sensory disturbances, or muscle

weakness.² LDH occurs in approximately 20 cases per 1000 adults annually and most commonly affects individuals in their 30s to 50s.³ Although acute LDH-related LP generally resolves within 2 weeks to 3 months with favorable outcomes,⁴ some patients experience chronic, recurrent pain throughout their lifetime rather than achieving complete recovery.⁵ In the United States, the annual economic burden associated with low back pain exceeds 100 billion dollars, underscoring the substantial socioeconomic impact of LDH.⁶

Pharmacological (PHM) treatment is the standard therapeutic option for LDH; however, its emphasis in major clinical guidelines is declining,⁷ and it is recommended only for patients with an inadequate response to first-line non-PHM treatments.⁸ Furthermore, medication should be used at the lowest effective dose for the shortest duration, considering the potential harm thereof,⁹ and opioids should only be prescribed to select patients for short-term use.^{10,11}

Invasive treatments, including injection therapy and nerve blocks, are widely used; however, their efficacy remains controversial. Recent guidelines^{8,12} advise against epidural or facet joint injections, whereas others^{9,13} strongly recommend epidural injections for managing LP and LDH.

Although conservative non-PHM treatments should be the first-line treatment for LDH, recommended approaches differ across clinical guidelines,⁴ especially for acupuncture and spinal manipulation therapy. The ACP recommends non-PHM treatments, including acupuncture and spinal manipulation therapy, as the first-line approach for both acute and chronic LBP.⁸ Similarly, standard clinical practice guidelines for LDH in Korean medicine strongly recommend acupuncture and spinal manipulation therapy.¹⁴

In contrast, other guidelines^{9,12} oppose acupuncture and adopt a more cautious stance on spinal manipulation therapy. Meanwhile, opioid use continues to increase.^{15,16} Approximately 80% of patients receive non-opioid analgesics, approximately 15% undergo nerve block therapy, and over 10% receive injection therapy.¹⁷

Given the discrepancies between guideline recommendations and actual clinical practice, as well as conflicting opinions among different guidelines, high-quality evidence is needed to clarify the effectiveness and safety of available treatments. In Korea, physicians may administer acupuncture and spinal manipulation therapy as either a complementary or an alternative approach to PHM treatment. Patients can choose treatment based on their preferences and clinical conditions. Therefore, Korea represents an optimal setting for comparing non-PHM and PHM strategies in real-world practice.

Acupuncture is thought to modulate pain through activation of the endogenous opioid system and descending inhibitory pathways, while also exerting anti-inflammatory effects that reduce peripheral and central sensitization.^{18,19} Spinal manipulation may alleviate pain by inducing mechanical stimulation of joint and muscle receptors, leading to neuromodulatory effects that reduce nociceptive input and improve spinal segmental function.^{20,21}

Accordingly, we aimed to compare the effectiveness, cost-effectiveness, and safety of a non-PHM strategy involving acupuncture, electroacupuncture, and spinal manipulation therapy with those of an active PHM strategy involving nerve block therapy and analgesics in real-world clinical practice. Prior to this study, two pilot studies were conducted to assess feasibility.^{22–24} Based on the findings of these pilot studies, we designed a large-scale pragmatic clinical trial involving 200 patients with LDH to compare non-PHM and PHM strategies. This article presents the protocol for this large-scale trial.

Materials and Methods

Design and Setting

This multicenter, pragmatic, randomized, controlled, and parallel-group study will involve 200 patients with non-acute LDH. The participants will be randomly assigned in a 1:1 ratio to receive either non-PHM treatment (n = 100) or active PHM treatment (n = 100), administered twice weekly for 8 weeks. Follow-up assessments will be conducted at weeks 9, 13, 26, and 39, and at 1, 1.5, 2, and 3 years after randomization (Figure 1). At the time of manuscript submission, participant recruitment is ongoing. The recruitment phase is expected to be completed by the end of 2026. Given the planned 3-year follow-up period, data collection is anticipated to conclude by the end of 2029. Final analyses and dissemination of the results are expected to be conducted in 2030.

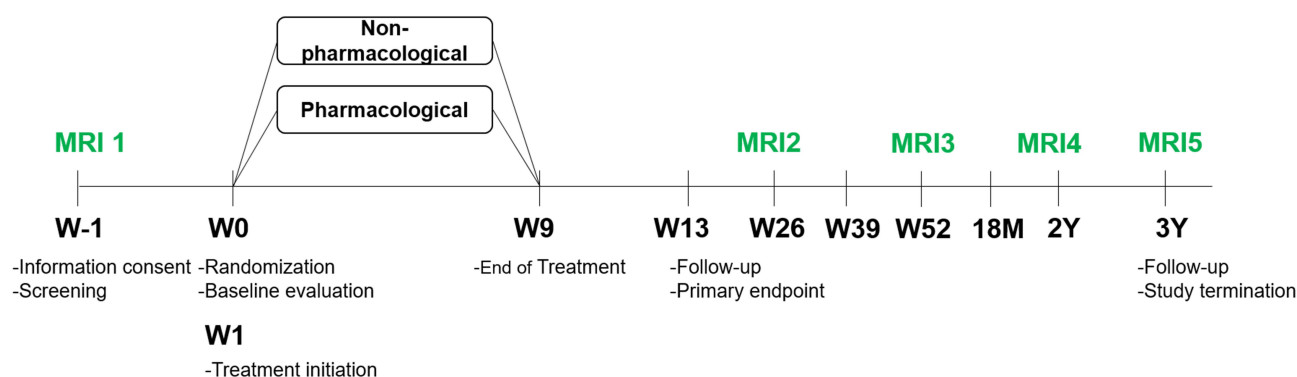


Figure 1 Study protocol flowchart.

Participants

All patients will undergo lumbar magnetic resonance imaging (MRI) screening to determine their study eligibility. We plan to include patients aged 19–69 years who are experiencing LP with symptoms persisting for >1 month, a numeric rating scale (NRS) score for LP/LBP of ≥ 5 over 3 consecutive days, LDH confirmed using MRI that explains their LP and LBP, and who agree to participate in the clinical study by providing written informed consent.

Patients diagnosed with serious diseases that may cause LBP and LP; those with progressive neurological deficits or severe neurological symptoms; patients with pain originating from soft tissue disorders rather than the spine, such as tumors, fibromyalgia, rheumatoid arthritis, or gout; those with other chronic conditions that may interfere with treatment effects or outcome interpretation; are currently taking steroids, immunosuppressants, psychiatric medications, or other drugs that may affect study outcomes; those for whom acupuncture or nerve block treatment is deemed inappropriate or unsafe; those have taken pain-related medications or received acupuncture treatment within the past 5 days; those who are pregnant, planning to conceive, or breastfeeding; patients who have undergone lumbar surgery within the past 3 months; those who have participated in another clinical study within the past month or plan to participate in another clinical study within 6 months or during the follow-up period; patients who have difficulty providing informed consent; or those determined by the investigator to be unsuitable for participation in the study for any reason will be excluded.

Interventions

Patients assigned to each group will receive education and be encouraged to follow the assigned treatment strategy, which will be implemented in real-world clinical practice without restrictions on specific institutions. Treatment will be administered at the clinician's discretion based on the assigned strategy.

Non-PHM treatment will be administered for 8 weeks, with a recommended frequency of twice per week for 16 sessions. However, the number of treatments may be adjusted based on the patient's condition and clinician's judgment. Non-PHM treatment will primarily involve manual therapies, including acupuncture, electroacupuncture, and spinal manipulation therapy. The clinician will determine the selection of acupoints, needle insertion depth, electroacupuncture frequency and intensity, and type of spinal manipulation therapy. Details of the treatments will be recorded in a case report form (CRF).

PHM treatments will involve nerve blocks, epidural steroid injections, and active medications. Patients may receive treatment at their medical institution of choice. During the 8-week treatment period, three nerve block procedures will be recommended, although the actual number of procedures will be determined by the clinician. Medication prescriptions will be provided twice a week; however, the actual number of visits, prescriptions, duration of medication use, and dosage will be left to the clinician's discretion. Depending on their condition, patients may also receive adjunctive physical therapy, such as transcutaneous electrical nerve stimulation or interferential current therapy. After each treatment, patients will receive a statement detailing the procedures and prescriptions, which will also be recorded in a CRF.

All participants will receive education from the study team regarding the treatment strategy corresponding to their assigned group, and they will be encouraged to adhere to that strategy throughout the study period. For participants in the pharmacological treatment group, treatment-related costs incurred at external medical institutions will be reimbursed, and

the study team will maintain regular contact to support adherence to the assigned treatment strategy. In both groups, detailed treatment information will be documented using Korea's standardized medical claim, which include comprehensive descriptions of all procedures and services provided; these records, as well as all study processes, will be monitored regularly by a researcher. As this is a pragmatic clinical trial designed to reflect real-world medical practice, each group is assigned a treatment strategy rather than a fixed treatment protocol, and specific rescue medications or mandatory restrictions are not imposed.

Outcomes

The primary outcomes are the Oswestry Disability Index and Numerical Rating Scale scores at 13 weeks from baseline. Functional status will be assessed using a validated Korean version of the Oswestry Disability Index (ODI),²⁵ a 10-item questionnaire developed to evaluate the degree of functional disability due to LBP. Each item is rated on a 6-point scale ranging from 0 to 5, with higher scores indicating greater disability. The ODI will be measured at baseline, week 5, and week 8; follow-up visits at weeks 9, 13, 26, 39, and 52; and at months 18, 24, and 36.

LBP and LP intensities over the past week will be assessed using an NRS, in which patients select a number from 0 to 10 that best represents their current discomfort level (0 = no pain; 10 = worst imaginable discomfort).^{26–28} The measure with the greatest change from baseline to the primary endpoint (week 13) will be defined as the NRS for dominant change (NRS for DC) for each individual. After week 13, the NRS score for DC will be recorded as the NRS score for either LBP or LP, depending on which was identified as the dominant change.

Secondary outcomes include the European Quality of Life 5 Dimensions 5 Level Version, Short Form-12 Health Survey Version 2, and Patient Global Impression of Change. Recurrence will be evaluated to assess treatment stability and is defined as either a worsening of symptoms after improvement or a failure to improve. Using the ODI as a criterion, a score of ≥ 30 is considered indicative of recurrence,²⁹ and will be assessed at the end of the intervention period (week 9) and at each follow-up visit.

LBP and LP intensities over the past week will be assessed using an NRS. Scores will be recorded at baseline, weekly during the intervention period, and at each follow-up visit.

The Patient Global Impression of Change is a self-reported outcome measure that evaluates a patient's perception of improvement on a 7-point Likert scale as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.³⁰

A validated Korean version of the Fear-Avoidance Beliefs Questionnaire (FABQ), a self-reported 16-item instrument designed to assess fear-avoidance beliefs regarding physical and occupational activities in patients with LBP, will be used.³¹ The questionnaire includes five items evaluating fear-avoidance beliefs about physical activity and 11 items assessing fear-avoidance beliefs about work. Among the 16 items, five (items 2, 8, 13, 14, and 16) are excluded from the total score calculation. Each item is rated on a 7-point scale from 0 (completely disagree) to 6 (completely agree), with total scores ranging from 0 to 66. Higher scores indicate stronger fear-avoidance beliefs.

The Short Form-12 Health Survey (SF-12) version 2 is a 12-item questionnaire designed to assess health-related quality of life (HRQoL) encompassing eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Higher scores indicate better HRQoL. A validated Korean version of the SF-12 will be used in this study.³²

The EuroQol-5 Dimension (EQ-5D-5L) is a widely used instrument for evaluating health status from multiple perspectives and measuring quality of life. It comprises five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each rated on a 5-point Likert scale, with total scores ranging from 0 to 1. Higher scores indicate a better quality of life.³³ A validated Korean version of the EQ-5D-5L will be used in this study.

To assess participant expectations regarding treatment, a 9-point Likert scale will be used. During the screening visit, potential study participants will respond to the question: "How much do you think non-PHM treatment and PHM treatment in conventional medicine will relieve your symptoms?" Responses will be recorded on a scale from 1 (not at all) to 9 (very much).

Intention-to-treat (ITT) refers to the preferred treatment strategy between non-PHM and PHM interventions. Participants will respond to the question, "If you were to receive treatment again in the future, which treatment would

you prefer?” Using a 9-point Likert scale for each intervention (1 = no intention to use; 9 = strong intention to use). This assessment will be conducted twice: after the end of the intervention (week 9) and at the final follow-up.

Productivity loss will be assessed using the Work Productivity and Activity Impairment–Specific Health Problem questionnaire. Among its components, employment status and overall work productivity (a combined measure of absenteeism and presenteeism) will be used as outcome measures.³⁴

The degree of lumbar intervertebral disc degeneration observed on MRI will be classified into grades I–V based on differences in signal intensity.³⁵ If multiple levels exhibit disc degeneration, the classification will be based on the most severely affected level. The degree of disc herniation observed on MRI will be classified as bulging, protrusion, extrusion, sequestration, or migration. If multiple levels exhibit disc herniation, classification will be based on the most severely affected level. The herniated disc area (mm²) will be evaluated based on the largest cross-sectional area observed in the transverse plane on MRI. Changes from baseline will be measured.

To assess costs, a structured questionnaire developed for this study will be used to measure formal and informal medical costs, non-medical costs, time-related costs, and productivity loss. Formal medical costs refer to expenses incurred for services provided by medical institutions, whereas informal medical costs include out-of-pocket expenses, such as health supplements and medical devices. Non-medical costs include transportation, patient time, and caregiver costs associated with medical utilization.

The type and dosage of medications taken during the study period, including those prescribed for existing conditions and rescue medications, will be confirmed through surveys at each visit. Additionally, the frequency of other treatments, such as physical therapy and injection therapy, will be recorded.

Sample Size Estimation

The sample size was calculated based on results from a previous pilot study.²³ Using the outcome values at week 9 (primary endpoint), the required sample size was estimated assuming a significance level of 5% and a statistical power of 80%. The effect size of the ODI was 0.36. After adjusting for the correlation coefficient with baseline, 78 participants were required per group. Considering a 20% dropout rate, the final required number of participants was calculated to be 97 per group, totaling 194 participants.

The effect sizes for the NRS for LBP and LP were calculated as 1.16 and 0.87, respectively. Based on these values, the required sample sizes, assuming a 20% dropout rate, were estimated to be 16 per group (32 participants) for the LBP NRS and 26 per group (52 participants) for the LP NRS. A conservative approach was adopted for the main study, and the final sample size was determined based on calculations using the ODI, resulting in the recruitment of 200 participants.

Recruitment and Timeline

Participants will be recruited through various methods, including press releases, posting promotional materials inside and outside clinical research institutions, and advertisements on online recruitment websites. The timeline for the trial is shown in [Table 1](#).

Randomization and Blinding

Participants who voluntarily sign the informed consent form will be screened to determine eligibility based on the inclusion and exclusion criteria. Eligible participants will then be randomly assigned to one of the two groups in a 1:1 ratio (100 participants per group) using a randomization table generated by a statistician in RStudio 1.1.463 (RStudio, Inc., PBC, Boston, MA, USA). The randomization sequence will be generated using permuted block randomization, with block sizes randomly set to two, four, or six. Randomization envelopes will be allocated in a stratified manner, with 60 envelopes per study site, and recruitment will proceed competitively. The generated randomization results will be sealed in opaque envelopes and stored in a double-locked cabinet. Each research site's designated personnel will open the envelopes for individual participants to assign them to their respective groups. Randomization will only be conducted for participants who have voluntarily signed an informed consent form after receiving sufficient explanation about the study. Each participant's assigned randomization number will be recorded in their electronic medical record.

Table I Timeline of the Trial

Time Point	Screening Week	Enrollment, Allocation Week	Active Treatment Post-Allocation, Week				Follow-Up, Week								Unscheduled Visit
	−1	0	1	2, 3, 4	5	6, 7, 8	9	13	26	39	52	18	24	36	
Window period	−10–0	Control point	±3	±3	±3	±3	±7	±14	±14	±14	±14	±14	±14	±28	
Enrollment															
Written informed consent	○														
Eligibility screening	○														
Vital signs	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Sociodemographic characteristics	○														
Medical history	○	○													
Review of system	○														
L-spine MRI	○														
Blood analysis	○						○				○		○	○	
Randomized allocation		○													
Interventions (data collection only)															
Non-pharmacological group (experimental)				○	○	○	○								
Pharmacological group (control)				○	○	○	○								
Assessments															
Education for strategy		○													
Drug consumption	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Adverse events			○	○	○	○	○	○	○	○	○	○	○	○	○
NRS score for LBP	○		○	○	○	○	○	○	○	○	○	○	○	○	○
NRS score for leg pain	○		○	○	○	○	○	○	○	○	○	○	○	○	○
ODI			○		○		○	○	○	○	○	○	○	○	○
Recurrence								○	○	○	○	○	○	○	○
PGIC							○	○	○	○	○	○	○	○	○
SF-12			○		○		○	○	○	○	○	○	○	○	○
EQ-5D-5L			○		○		○	○	○	○	○	○	○	○	○
FABQ			○		○		○	○	○	○	○	○	○	○	○
Physical/sensorineural examination			○		○		○	○	○	○	○	○	○	○	○
Credibility and Expectancy	○														
Intention-to-treat							○							○	
WPAI-SHP			○	○	○	○	○	○	○	○	○	○	○	○	○
Classification of disc degeneration			○						○		○		○	○	○
Stages of disc herniation			○						○		○		○	○	○
Herniated disc areas			○						○		○		○	○	○
Costs for medical use			○	○	○	○	○	○	○	○	○	○	○	○	○
Cost for time			○	○	○	○	○	○	○	○	○	○	○	○	○

Notes: “○” indicates that the corresponding assessment or procedure was performed at that time point. Weeks −1, 0, 1 can be performed on the same day. Blood test results can be used if performed within the last 2 weeks (including our hospital and other hospitals). L-Spine MRI test results can be used for screening if performed within the last 3 months after the onset of the disease and within 2 weeks from the date of visit for follow-up thereafter (including our hospital and other hospitals). Time–cost surveys for interventions may be conducted from week 2, and for non-drug groups, surveys are only conducted in week 2.

Abbreviations: NRS, numeric rating scale; MRI, magnetic resonance imaging; LBP, low back pain; ODI, Oswestry Disability Index; SF-12, Short Form-12 Health Survey; EQ-5D-5L, EuroQol-5 Dimension; FABQ, Fear-Avoidance Beliefs Questionnaire.

As blinding of participants and clinicians is not feasible, the study will be conducted as an open-label clinical trial. However, to minimize potential bias arising from this design, outcome assessors will remain blinded to group allocation. Before each assessment, participants will be instructed not to discuss their assigned treatment strategy with the assessors. All outcome evaluations will be performed in a separate room without the presence of other study personnel, and the assessment forms will contain no information that could reveal group assignment.

This study will use an electronic CRF (e-CRF). Double data-entry verification will be performed to ensure data accuracy and reliability. Data entered into the e-CRF will be locked and concealed from all researchers except for the data management supervisor.

Statistical Analysis

This study will conduct ITT and per-protocol analyses, with ITT serving as the primary analysis. For the per-protocol analysis, a complier average causal effect analysis will be performed. Missing data will be handled using a mixed model for repeated measures within the primary analysis, specifically a linear mixed model (LMM) approach. Additionally, multiple imputation (MI) and last observation carried forward (LOCF) methods will be applied in the supplementary analyses.

The basic characteristics and treatment expectancy of participants will be evaluated separately for each group. Continuous variables will be expressed as mean and standard deviation or median and interquartile range, and compared between the two groups using Student's *t*-test or the Wilcoxon rank-sum test, depending on the distribution. Categorical variables will be presented as frequency (%) and analyzed using chi-square tests or Fisher's exact test, as appropriate.

Among the efficacy evaluation outcomes in this clinical trial, continuous outcomes (NRS, ODI, FABQ, EQ-5D-5L, SF-12, and herniated disc area) will be analyzed by comparing the change from baseline to each follow-up time point between the two groups. The primary analysis will use an LMM, including baseline values of each variable, clinically meaningful covariates that statistically differ between treatment groups at baseline, and the treatment group (as a fixed factor) as a covariate. For additional analyses, an analysis of covariance (ANCOVA) will be performed on datasets where missing values were imputed using MI and LOCF.

To examine the relationship between structural abnormalities and clinical symptoms, Pearson or Spearman correlation coefficients will be calculated between MRI-derived measures (eg, herniation area, degeneration grade) and pain/function outcomes (NRS for leg pain, NRS for low back pain, and ODI) at each follow-up time point. Longitudinal associations between MRI changes and clinical outcomes will be evaluated using linear mixed-effects models, with NRS or ODI as the dependent variable and MRI parameters as time-varying covariates, adjusting for age, sex, baseline symptom severity, and treatment group. The number and proportion of patients who experienced recurrence at each assessment time point will be reported. A generalized LMM will be used to statistically compare recurrence rates between the two groups. ANCOVA will be applied to datasets processed using MI and LOCF.

To compare the total change in each outcome over time (during both the treatment and follow-up periods) between the two groups, the area under the curve (AUC) will be calculated and compared using an LMM. A survival analysis will be conducted to assess the time to efficacy acquisition between the two groups. The efficacy acquisition time is defined as follows: for NRS for DC, when the score is reduced to less than half of the baseline value; and for ODI, when the score is reduced to $\leq 70\%$ of the baseline value.

The median survival time will be analyzed using Kaplan–Meier survival analysis; for intermittent censoring due to missing data, those periods will be assumed event-free. Statistical significance will be determined using the Log rank test. A Cox proportional hazards model will be used to compare hazard ratios between groups, with missing data handled using MI. The significance level for all analyses will be set at 0.05. Statistical analyses will be conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) or RStudio 1.1.463 (RStudio, Inc).

A midterm analysis may be performed after the primary endpoint. If the superiority test fails, a non-inferiority test will be conducted. The non-inferiority margin will be set at half of the minimal clinically important difference for the LDH: ODI criterion, -6.4 ; pain criterion, -0.85 .

Adverse Events (AEs)

All AEs occurring during this clinical trial will be identified and recorded. AEs will be recorded through patient reports or direct observation, and their frequency will be compared between groups. The investigators will assess the causal relationship between each treatment method and the reported AEs using a six-point scale: 1 = definitely related; 2 = probably related; 3 = possibly related; 4 = probably not related; 5 = definitely not related; and 6 = unknown. AE severity will be classified into three levels: mild, did not impair participants' normal activities of daily living (ADLs), caused minimal discomfort, or required no additional treatment; moderate, significantly impaired ADLs, may require treatment but resolved after treatment; and severe, severely impaired ADLs, requiring intensive treatment and resulting in sequelae. A serious AE is defined as any event that results in death or is life-threatening, requires hospitalization or prolongation of hospitalization, causes persistent or significant disability or functional impairment, leads to congenital anomalies or birth defects, or represents other medically significant conditions.

The researcher will thoroughly explain all potential AEs that may occur after the procedure to the participants (or their guardians). Participants will be instructed to report any post-procedural symptoms. All AEs will be recorded in the CRF. In the event of a serious AE related to treatment, the Institutional Review Board (IRB) will be notified to determine whether the study should continue or be terminated.

Ethics and Dissemination

All participants will be required to provide written informed consent voluntarily after receiving a full explanation of the study's purpose and procedures from the research personnel prior to study initiation. The study protocol, CRF, informed consent form, and all other study-related documents are approved by the IRB of Jaseng Hospital of Korean Medicine (approval numbers: JASENG 2023-05-001/2023-05-002/2023-05-003/2023-05-004). The protocol has been registered on ClinicalTrials.gov (registration number: NCT06024460; July 20, 2023). This trial will be conducted in accordance with the principles of the Declaration of Helsinki and all relevant ethical guidelines.

Discussion

This large-scale, multicenter, pragmatic clinical trial is designed to compare and evaluate non-pharmacological and active pharmacological treatment strategies for patients with non-acute LDH in real-world clinical settings. The non-PHM treatment strategy group will receive manual therapy consisting primarily of acupuncture, electroacupuncture, and spinal manipulation.

Acupuncture and electroacupuncture are widely used to treat LDH, and their efficacy has been extensively investigated. Acupuncture demonstrates superior efficacy rates and pain reduction effects over ibuprofen, diclofenac sodium, and meloxicam.³⁶ Additionally, acupuncture significantly improves pain and functional scores in patients with LDH compared to sham acupuncture.³⁷

In this study, Chuna manual therapy will serve as the primary spinal manipulation strategy. This is a type of manual treatment involving the application of manipulative techniques using the practitioner's hands or auxiliary tools to adjust regions of the patient's body, thereby modulating physiological and pathological conditions to achieve therapeutic effects. Chuna manual therapy, highly recognized in Korea and internationally, is predominantly used for musculoskeletal disorders.³⁸ Notably, in the Korean clinical practice guidelines for LDH, meta-analytic evidence demonstrated that Chuna manual therapy produced statistically significant improvements in pain and functional outcomes compared with active controls, including Western medicine or injections.¹⁴ However, current evidence remains still insufficient.^{38,39}

Based on existing studies, non-PHM treatments, such as acupuncture, electroacupuncture, and spinal manipulation therapy, may offer a safer and more effective therapeutic approach than PHM treatments, particularly in the contexts where PHM treatments are widely prevalent despite clinical guidelines recommendations. Consequently, we aimed to generate high-quality evidence to substantiate this potential. Our pilot clinical trials compared and evaluated the effectiveness of PHM and non-PHM treatment strategies in patients with non-acute LDH. The first pilot study, conducted at a single institution, involved the random allocation of 30 patients with LDH to either a non-PHM or PHM treatment group in a 1:1 ratio, with all treatments provided at a Korean medical hospital.²² At the 13-week follow-up, following an 8-week treatment period, the participants in the non-PHM treatment group showed significantly greater improvements in

NRS scores for LP and ODI scores compared to those in the PHM treatment group. An analysis of treatment records confirmed that the non-PHM group received acupuncture, electroacupuncture, and spinal manipulation therapy. Notably, 70% of patients in the PHM group underwent nerve block procedures, and 100% received medication prescriptions, indicating adherence to the respective treatment protocols in both groups. However, because patients in the PHM treatment group received treatment within a Korean medicine hospital, the study was limited in its ability to fully reflect the diversity of prescriptions encountered in real-world clinical settings. Regarding PHM treatments, all patients received aceclofenac, paracetamol, pregabalin, and almagate, and only one patient received celecoxib, naproxen, or eperisone. To enhance the external validity of the main study, we removed restrictions on treatment institutions for the PHM treatment group, allowing patients to receive treatment at their institution of choice. However, unfamiliar with such a pragmatic study design, assessing whether participants would adhere to their assigned treatment strategies and whether detailed treatment records from these settings could be reliably collected and documented was necessary. Therefore, a second pilot study was conducted to evaluate the feasibility of the revised design.

In the second study,^{22,23} 36 patients were recruited from four Korean medical hospitals nationwide. Patients assigned to the PHM treatment group were permitted to receive care at their chosen medical institution without restrictions. After an 8-week treatment period, the non-PHM treatment group demonstrated greater improvements than the PHM group in NRS scores for LBP, NRS scores for LP, and ODI. Furthermore, non-PHM treatment was associated with higher quality-adjusted life years and lower costs than PHM treatment. Patients in the PHM treatment group demonstrated relatively high adherence to their assigned treatment strategies, and treatment records from external institutions were successfully collected and documented. An analysis of these records revealed a greater diversity of treatment modalities than in the first pilot study, including injection therapies and nerve blocks, as well as PHM treatments with eperisone, aceclofenac, and tramadol, suggesting that the study more accurately reflected real-world clinical practice.

These two pilot clinical trials confirmed the feasibility of the main study. Based on these findings, we designed a large-scale pragmatic clinical trial aimed at generating high-quality evidence of the comparative effectiveness of non-PHM and PHM treatment strategies in patients with non-acute LDH in real-world clinical settings. We also conducted various preliminary studies that served as a basis for designing the main study. One study aimed to determine a more appropriate substantial clinical benefit (SCB) threshold for patients with LDH by calculating and comparing SCB values based solely on NRS scores for LP, NRS scores for LBP, and a composite measure that considered both scores together.⁴⁰ NRS scores for the dominant change between the two measures resulted in a higher AUC for SCB than using individual scores for LBP or LP, suggesting that the dominant change approach better reflected patients' perceived improvement. Accordingly, the primary outcome of this study was defined based on the NRS score for the dominant change, rather than specifying either LBP or LP.

Furthermore, a nationwide survey was conducted to identify patient-centered outcomes in patients with LDH.⁴¹ Approximately 55% of respondents prioritized functional recovery over pain reduction, indicating a nearly equal distribution of patients who valued either pain relief or functional improvement. Therefore, both pain and function were designated as primary outcomes in the present study. Additionally, patients expressed a preference for stable, long-term treatment effects without recurrence or exacerbation, rather than rapid effects, and they prioritized treatment safety over efficacy. To account for these preferences, the follow-up period was extended to 3 years with periodic MRI assessments to enhance the accuracy and reliability of follow-up evaluations. Recurrence and AEs were designated as key components of the outcome analysis. Finally, while many clinical studies on LDH have primarily considered radiating leg pain as the main outcome measure,⁴² the survey indicated that patients regarded both LBP and LP as the most critical symptoms requiring improvement. Consequently, the primary objective of this study was to comprehensively evaluate both types of pain.

An ODI score of 30 represents the threshold for discharge in patients who are satisfied with their symptom improvement.²⁹ Based on these findings, an ODI score of 30 was used as the criterion for recurrence in this study.

For this study, all participants will undergo lumbar MRI screening at baseline, and only those with imaging findings consistent with disc herniation that explain their symptoms will be enrolled. Moreover, during the 3-year follow-up period, five MRI scans will be performed to enable continuous monitoring of imaging changes. Various MRI-based indicators will be analyzed as outcomes. Using MRI data from 200 participants collected at five time points over 3 years,

this study is expected to generate a highly valuable database, facilitating analysis of treatment-induced imaging changes, their correlation with patient outcomes, and the prognostic implications of MRI findings.

The strength of our study lies in being the first large-scale, multicenter, pragmatic randomized controlled trial directly comparing non-pharmacological and pharmacological treatment strategies for non-acute lumbar disc herniation. Its pragmatic design, allowing treatments to be delivered in real-world clinical settings at the discretion of clinicians, enhances external validity and generalizability. Especially, its unusually long three-year follow-up combined with five serial MRI assessments, allowing the construction of a large MRI-based cohort that is rare in LDH research worldwide. This dataset will provide valuable insights into the natural course of LDH and the relationship between symptomatic trajectories and radiologic changes. Furthermore, it may serve as a foundation for developing machine-learning-based prognostic models, including those predicting recurrence or clinical deterioration. Moreover, most landmark LDH trials, including the SPORT⁴³ and Hague studies,⁴³ primarily enrolled patients with acute-to-subacute symptoms (typically 6–12 weeks), whereas evidence focusing specifically on non-acute or persistent LDH remains limited. Therefore, the findings of this trial may offer insights that complement and extend the existing literature. Lastly, comprehensive outcome measures, including pain, function, quality of life, recurrence, and cost-effectiveness, will allow for a multidimensional evaluation of treatment strategies.

Nevertheless, given the long follow-up duration and the allowance of treatment at external institutions, ensuring patient adherence could be the most critical factor in the successful execution of this study. To maintain research quality, ongoing training for research teams, particularly study coordinators, and appropriate compensation for participants will be implemented. However, as a pragmatic trial conducted in real-world clinical settings, variability in treatment delivery across clinicians and institutions may introduce heterogeneity that could limit internal validity. Despite the fact that all MRI readings were performed by a radiologist with extensive clinical experience, the lack of a predefined strategy to ensure inter-reader reliability remains a notable limitation. Furthermore, as blinding of participants and clinicians is not feasible, there remains a potential risk of performance and expectation bias despite the use of blinded assessors.

This study may provide high-quality evidence on the effectiveness, cost-effectiveness, and safety of a non-PHM treatment strategy centered on acupuncture, electroacupuncture, and spinal manipulation therapy. The findings of this study also have the potential to inform future clinical practice guidelines and health policy decisions by providing robust comparative effectiveness evidence for non-pharmacological and pharmacological strategies in non-acute LDH.

Conclusion

This is the first well-designed, large-scale clinical study to compare non-PHM and PHM treatment strategies in patients with non-acute LDH. In particular, establishing a large MRI cohort will enable detailed investigation of disease progression and support the development of prognostic models. Considering major LDH trials have largely examined acute-to-subacute presentations, this study may fill an important gap by providing evidence specific to patients with persistent, non-acute symptoms. This study may generate high-quality comparative effectiveness evidence on non-pharmacological and pharmacological strategies for non-acute LDH, thereby informing future clinical practice guidelines and health policy decisions.

Abbreviations

AE, adverse events; ANCOVA, analysis of covariance; AUC, area under the curve; CRF, case report form; DC, dominant change; EQ-5D-5L, EuroQol-5 Dimension; FABQ, Fear-Avoidance Beliefs Questionnaire; HRQoL, health-related quality of life; IRB, institutional review board; ITT, intention-to-treat; LBP, Low back pain; LDH, lumbar disc herniation; LMM, linear mixed model; LOCF, last observation carried forward; LP, leg pain; MI, multiple imputation; MRI, magnetic resonance imaging; NRS, numeric rating scale; ODI, Oswestry Disability Index; PHM, pharmacological; SCB, substantial clinical benefit; SF-12, Short Form-12 Health Survey.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. (I.H.H).

Ethics Approval and Informed Consent

All participants will be required to provide written informed consent voluntarily after receiving a full explanation of the study's purpose and procedures from the research personnel prior to study initiation. The study protocol, CRF, informed consent form, and all other study-related documents are approved by the IRB of Jaseng Hospital of Korean Medicine (approval numbers: JASENG 2023-05-001/2023-05-002/2023-05-003/2023-05-004). The protocol has been registered on ClinicalTrials.gov (registration number: NCT06024460; July 20, 2023).

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Disclosure

The authors declare no conflicts of interest.

References

- Schoenfeld AJ, Weiner BK. Treatment of lumbar disc herniation: evidence-based practice. *Int J Gene Med.* 2010;3:209. doi:10.2147/ijgm.s12270
- Will JS, Bury DC, Miller JA. Mechanical low back pain. *Am Family Phys.* 2018;98(7):421–428.
- Al Qaraghlhi MI, De Jesus O. Lumbar Disc Herniation. In: *StatPearls*. StatPearls Publishing; 2021.
- Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: a systematic review. *Clin Spine Surg.* 2000;13(6):463–469.
- Axén I, Leboeuf-Yde C. Trajectories of low back pain. *Best Pract Res.* 2013;27(5):601–612. doi:10.1016/j.berh.2013.10.004
- Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *JbJs.* 2006;88(suppl_2):21–24.
- Foster NE, Anema JR, Cherklin D, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet.* 2018;391(10137):2368–2383. doi:10.1016/S0140-6736(18)30489-6
- Qaseem A, Wilt TJ, McLean RM, Forciea MA, Physicians* CGCotACo. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Internal Med.* 2017;166(7):514–530. doi:10.7326/M16-2367
- Bernstein IA, Malik Q, Carville S, Ward S. Low back pain and sciatica: summary of NICE guidance. *BMJ.* 2017;356.
- Chou R, Deyo R, Friedly J. Noninvasive treatments for low back pain. Comparative effectiveness review. prepared by the Pacific Northwest evidence-based practice center under contract. 2016.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA.* 2016;315(15):1624–1645. doi:10.1001/jama.2016.1464
- Stochkendahl MJ, Kjaer P, Hartvigsen J, et al. National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. *Eur Spine J.* 2018;27(1):60–75. doi:10.1007/s00586-017-5099-2
- Manchikanti L, Knezevic NN, Navani A, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician.* 2021;24(S1):27.
- Goo B, M-g J, Kim E-J, et al. Korean medicine clinical practice guidelines for lumbar herniated intervertebral disc in adults: based on Grading Of Recommendations Assessment, Development And Evaluation (GRADE). In: *Healthcare*. MDPI. 2022:246.
- Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ.* 2015;350.
- Martell BA, o'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Internal Med.* 2007;146(2):116–127. doi:10.7326/0003-4819-146-2-200701160-00006
- Ahn Y-J, Shin J-S, Lee J, et al. Evaluation of use and cost of medical care of common lumbar disorders in Korea: cross-sectional study of Korean health insurance review and assessment service national patient sample data. *BMJ open.* 2016;6(9):e012432. doi:10.1136/bmjopen-2016-012432
- Han J-S. Acupuncture and endorphins. *Neurosci lett.* 2004;361(1–3):258–261. doi:10.1016/j.neulet.2003.12.019
- Zhao Z-Q. Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol.* 2008;85(4):355–375. doi:10.1016/j.pneurobio.2008.05.004
- Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *J Pain.* 2014;15(2):136–148. doi:10.1016/j.jpain.2013.10.005
- Pickar JG. Neurophysiological effects of spinal manipulation. *Spine J.* 2002;2(5):357–371. doi:10.1016/S1529-9430(02)00400-X
- Kim D, Kim E-S, Lee YJ, et al. A pilot study for effectiveness of non-pharmacological versus pharmacological treatment strategies for lumbar disc herniation: a pragmatic randomized controlled trial. *J Pain Res.* 2023;16:3197–3216. doi:10.2147/JPR.S421148
- Kim D, Lee JY, Lee YJ, Yang CS, Han C-H, Ha I-H. Comparative effectiveness of non-pharmacological and pharmacological treatments for non-acute lumbar disc herniation: a multicenter, pragmatic, randomized controlled, parallel-grouped pilot study. *J Clin Med.* 2025;14(4):1204. doi:10.3390/jcm14041204
- Zhao HY, Jun P, Lee C, Ha I-H, Han C-H. A study protocol for a multicenter, pragmatic, randomized controlled, parallel-grouped pilot clinical trial: effectiveness of non-pharmacological versus pharmacological treatments for non-acute lumbar disc herniation. *Perspect Integr Med.* 2023;2(1):59–64. doi:10.56986/pim.2023.02.009
- Jeon C-H, Kim D-J, Kim D-J, Lee H-M, Park H-J. Cross-cultural adaptation of the Korean version of the Oswestry Disability Index (ODI). *J Korean Soc Spine Surg.* 2005;12(2):146–152. doi:10.4184/jkss.2005.12.2.146
- Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: which to use? *Am J Emergency Med.* 2018;36(4):707–714. doi:10.1016/j.ajem.2018.01.008

27. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). *Arthritis Care Res.* 2011;63(S11):S240–S252.
28. Solodiuk JC, Scott-Sutherland J, Meyers M, et al. Validation of the Individualized Numeric Rating Scale (INRS): a pain assessment tool for nonverbal children with intellectual disability. *Pain.* 2010;150(2):231–236. doi:10.1016/j.pain.2010.03.016
29. Park S-W, Shin Y-S, Kim H-J, Lee J-H, Shin J-S, Ha I-H. The dischargeable cut-off score of Oswestry Disability Index (ODI) in the inpatient care for low back pain with disability. *Eur Spine J.* 2014;23:2090–2096. doi:10.1007/s00586-014-3503-8
30. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113(1):9–19. doi:10.1016/j.pain.2004.09.012
31. Joo M-K, Kim T-Y, Kim J-T, Kim S-Y. Reliability and validity of the Korean version of the fear-avoidance beliefs questionnaire. *Phys Ther Korea.* 2009;16(2):24–30.
32. Kim S-H, Jo M-W, Ahn J, Ock M, Shin S, Park J. Assessment of psychometric properties of the Korean SF-12 v2 in the general population. *BMC Public Health.* 2014;14:1–7. doi:10.1186/1471-2458-14-1086
33. Kim S-H, Ahn J, Ock M, et al. The EQ-5D-5L valuation study in Korea. *Qual Life Res.* 2016;25(7):1845–1852. doi:10.1007/s11136-015-1205-2
34. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire-general health version in patients with rheumatoid arthritis. *Arthritis Res Ther.* 2010;12(5):R177. doi:10.1186/ar3141
35. Pfirrmann CW, Metzendorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine.* 2001;26(17):1873–1878. doi:10.1097/00007632-200109010-00011
36. Tang S, Mo Z, Zhang R. Acupuncture for lumbar disc herniation: a systematic review and meta-analysis. *Acupuncture Med.* 2018;36(2):62–70. doi:10.1136/acupmed-2016-011332
37. Tu J-F, Shi G-X, Yan S-Y, et al. Acupuncture vs sham acupuncture for chronic sciatica from herniated disk: a randomized clinical trial. *JAMA Intern Med.* 2024;184(12):1417–1424. doi:10.1001/jamainternmed.2024.5463
38. Kim D, Baek GG, Shin B-C. An umbrella review of systematic reviews for Chuna (or Tuina) manual therapy on musculoskeletal disorders. *Perspect Integr Med.* 2023;2(3):142–154. doi:10.56986/pim.2023.10.002
39. Lee N-W, Kim G-H, Heo I, et al. Chuna (or Tuina) manual therapy for musculoskeletal disorders: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med.* 2017;2017(1):8218139. doi:10.1155/2017/8218139
40. Jeon SH, Yang Y-M, Lee YJ, Kim M-R, Kim E-J, Ha I-H. The substantial clinical benefit of comprehensively considering low back pain and radiating pain caused by lumbar intervertebral disc herniation. *J Back Musculoskelet Rehabil.* 2022;35(2):323–329. doi:10.3233/BMR-200244
41. Kim D, Kim S-J, Lee YJ, Yang CS, Han C-H, Ha I-H. Are Primary Outcomes Really Primary? An Exploratory Cross-Sectional Nationwide Web-Based Survey Study for Outcomes Reflecting Real Symptoms and Needs of Patients with Lumbar Disc Herniation. In: Healthcare. MDPI. 2023:2598.
42. Peul WC, van den Hout WB, Brand R, Thomeer RT, Koes BW, Group L-THSIPS. Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: two year results of a randomised controlled trial. *BMJ.* 2008;336(7657):1355–1358. doi:10.1136/bmj.a143
43. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *JAMA.* 2006;296(20):2441–2450. doi:10.1001/jama.296.20.2441