

The Effectiveness of Pharmacopuncture in Patients with Lumbar Spinal Stenosis: A Protocol for a Multi-Centered, Pragmatic, Randomized, Controlled, Parallel Group Study

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Purpose: Lumbar spinal stenosis (LSS) is a chronic degenerative disease. Non-surgical intervention is recommended, considering the risks and benefits for the affected age group, as well as the characteristics of the disease. However, to date, no studies have compared various non-surgical interventions to ascertain the appropriate first-line non-surgical treatment for LSS. Therefore, the objective of this study will be to assess the efficacy of pharmacopuncture as a non-surgical, conservative treatment for LSS.

Patients and Methods: A multi-centered, pragmatic, parallel-group study will be conducted. In total, 98 patients will be recruited at seven institutes; recruitment began in May 2022. After two treatment sessions per week over a period of 12 weeks, follow-up assessments will be held at weeks 13, 25, and 53.

Results: The efficacy of pharmacopuncture and conservative care will be pragmatically compared in patients radiologically diagnosed with LSS. Pain severity will be measured using the numeric rating scale and visual analog scale. Walking distance will also be evaluated. Patient-centered evaluations will include the Zurich Claudication Questionnaire, Short-Form 12 for Health-Related Quality of Life, EuroQoL 5 Dimension 5 Levels, and Patient Global Impression of Change.

Conclusion: The results of this study will confirm the efficacy of pharmacopuncture in comparison to conventional non-surgical treatment and will thus facilitate the prioritization of patient-centered interventions for LSS.

Trial registration: This study was registered at Clinicaltrials.gov (registration identifier: NCT05242497) and CRiS (registration identifier: KCT0007145).

Keywords: LSS, constriction, non-surgical intervention, acupuncture, pragmatic clinical trial, protocol

Introduction

Lumbar spinal stenosis (LSS) is a disease that involves narrowing of the spinal cavity due to hyperplasia of the spine and adjacent tissues. LSS is primarily an acquired degenerative stenosis associated with diminished space in the lumbar spinal canal or neural foramen causing neural or vascular compression. It affects over 100 million patients.^{1,2} Degenerative LSS can cause neurogenic claudication and other neurological symptoms, with or without pain, in the lower back and lower extremities.³ The symptoms of LSS are posture-dependent, exacerbated by walking, and are relieved by rest.

Although the underlying mechanism of LSS remains unclear, the main symptoms affecting the lower extremities include neurogenic claudication, radiating pain, paresthesia, and hypotonia.⁴ This chronic degenerative illness is newly diagnosed in

five out of 100,000 people each year, and its prevalence increases with age.⁵ The anatomical deterioration of LSS and the symptoms experienced by patients are often inconsistent.^{6,7} Although its clinical symptoms improve through conservative care, the difference in efficacy in terms of symptom improvement between surgical and non-surgical treatments is not evident.⁸ In addition, considering the economic utility of surgical intervention and the risk of adverse reactions, conservative care is recommended first for the treatment of LSS, and surgery is only conducted if pain persists or neurogenic claudication occurs after conservative care.⁹ Despite this, LSS remains one of the most common indications for spinal surgery.¹⁰

The major treatment goals of non-surgical care of LSS include pain improvement, increased walking distance, and alleviated LSS-specific symptoms, such as neurological symptoms. Rehabilitation, including physiotherapy and kinesiotherapy, is currently considered as the most effective intervention.¹¹ Various other interventions often focus on pharmacotherapy, including massage, exercise, thermotherapy, and acupuncture.¹² Although effective non-surgical conservative care is recommended for the clinical improvement of LSS, no particular treatment has been established as a superior intervention.

Pharmacopuncture is a traditional integrative intervention used in East Asian countries, including the Republic of Korea and China. Pharmacopuncture aims to maximize treatment effects by injecting pharmacopuncture solutions extracted, purified, diluted or mixed from herbal medicines at various acupuncture points, including Ah-shi points and cutaneous and muscle meridians using a solution injection syringe. The most representative pharmacopuncture solutions are bee-venom, placenta, and plant extract. In a previous study conducted among Korean medicine clinics, 98.6% of 33,145 inpatients and 77.6% of 373,755 outpatients received pharmacopuncture over a 4-year period, thus indicating that it is a commonly used medical procedure.¹³ It is recommended by the Korean Medicine Clinical Practice Guidelines for alleviating pain and promoting functional recovery in patients with lumbar herniated intervertebral discs.

Several clinical studies have reported on the active use of various pharmacopuncture treatments for medical ailments and paralytic diseases. Major diseases treated with pharmacopuncture include musculoskeletal pain disorders, such as neck pain, degenerative knee arthritis, and lumbar pain. According to a survey conducted with the aim of clinical practice guideline development, 94.3% of Korean medicine doctors reportedly use pharmacopuncture to manage LSS.¹⁴ Pharmacopuncture is a safe intervention that rarely produces adverse reactions, which are at most mildly severe and do not develop sequelae or require rescue interventions.¹⁵ Therefore, we plan to conduct a clinical study to compare the efficacy of pharmacopuncture and conventional non-surgical treatment for lumbar spinal pain.

Patients and Methods

Study Design and Ethics

This study is a multi-centered, pragmatic, randomized, controlled clinical trial involving seven hospitals (Jaseng Hospital of Korean Medicine, Daejeon Jaseng Hospital of Korean Medicine, Bucheon Jaseng Hospital of Korean Medicine, Haeundae Jaseng Hospital of Korean Medicine, Kyung Hee University Korean Medicine Hospital at Gangdong, Kyung Hee University Korean Medicine Hospital, and Dongguk University Bundang Oriental Hospital) distributed across the Republic of Korea. Pragmaticity was determined prior to study initiation, according to the Pragmatic Explanatory Continuum Indicator Summary tool, version 2 (PRECIS-2).¹⁶ Eligibility and recruitment are explanatory, but settings, delivery of intervention, and adherence are more pragmatic. Ninety-eight patients with LSS who voluntarily consent to participate will be randomly assigned to the pharmacopuncture group or the conservative care group, in a 1:1 ratio.

This study is an investigator-initiated clinical trial and has been approved by the institutional review board of each site (JASENG 2021-12-019, JASENG 2021-12-008, JASENG 2021-12-003, JASENG 2021-12-017, KHNMCOH 2022-01-001, KOMCIRB 2021-12-002, DOBUH 2022-001) prior to patient enrollment. All study procedures will be carried out by the investigators according to the Declaration of Helsinki and the Korean Good Clinical Practice Guidelines. Version 2.0 of the study protocol has been registered and will be updated at Clinicaltrials.gov (NCT05242497) and the Clinical Research Information Service, the South Korean registration service for clinical trials (KCT0007145). The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and checklist and partially follows the Consolidated Standards of Reporting Trials (CONSORT) extension for pragmatic clinical trials. While the assessor will be blinded to group allocation and patient information throughout the study period, researchers and patients will not be blinded.

Eligibility and Setting

Inclusion criteria comprise the following: 1) diagnosis of LSS (L1-S1) using radiology (computed tomography or magnetic resonance imaging) by radiologist, 2) neurogenic claudication, 3) symptoms (lumbar back pain or radiating pain) with severity of the dominant pain rated at 5 or more on the numeric rating scale (NRS), and 4) age 19–69 years. Every participant will have to understand and agree to the study protocol. Written informed consent will be obtained; no alternative consent process will be allowed.

Patients with the following conditions or situations will be ineligible: vascular claudication; pathologies of non-spinal origin; soft tissue pathologies or other systemic illnesses that may cause lumbar back pain or radiating leg pain, such as spinal tumors and fractures; any other chronic comorbidity that may interfere with interpretation of the results, such as dementia or stroke; prescribed medicine that may interfere with interpretation of the results, such as corticosteroids, immunosuppressants, or psychotropic drugs; treatment in the past 7 days involving any medication that may influence pain, such as non-steroidal anti-inflammatory drugs (NSAIDs), pharmacopuncture, or physical therapy; pregnant or planning to become pregnant during the study period; spinal surgery within the past 3 months; previous participation in other clinical trials within 1 month of enrollment; plans to participate in other clinical trials during the study; inability to fill out the informed consent form; and being deemed unsuitable for participation as assessed by the researchers.

Randomization and Allocation

Eligible participants who have signed the informed consent form will be randomly assigned to the pharmacopuncture group or the conservative care group in a 1:1 ratio. A random sequence has been generated by an independent statistician prior to the first enrollment. Random sequence generation was based on permuted block randomization with a random number table, which was generated using R 4.1.1 software (the R Foundation for Statistical Computing, Vienna, Austria). Block sizes of 2, 4, and 6 were randomly selected. The generated random sequence has been sealed in an opaque envelope and stored in a double-locked locker. Only the statistician is aware of the full randomization sequence. The delegated research coordinator in each institution will open a randomization envelope for each patient and assign the patient to the appropriate group.

Interventions

Both the pharmacopuncture and control interventions will be performed biweekly for 12 weeks to account for the chronic nature of LSS. The roles of the physician and the researcher are distinct. The researcher did not act as a physician and did not get involved in the treatment process. In the pharmacopuncture group, the Korean medicine doctor served as a physician, whereas in the conservative treatment group, the conservative medicine doctor served as a physician in order to provide the most effective treatment. The physicians will decide on the prescribed medication, treatment, and perform the procedure according to the medical strategy for each intervention group. The researchers will record treatment details on the electronic case report form in a timely manner. In the pharmacopuncture group, the physicians will decide on the details related to the depth, location, and the inserted pharmacopuncture content according to their medical decisions. In the conservative care group, the physicians will decide on the details of conservative care, including physiotherapy, and will prescribe medications according to their medical decisions. Any medications or physiotherapy procedures that relieve symptoms in the lower back and lower extremities, or that improve LSS, will be recorded in the electronic case report form in a timely manner. Follow-up surveys and assessments will be performed at weeks 25 and 53, respectively.

Concomitant Treatment and Patient Drop-Out

Patients will be allowed to receive rescue medicine (including analgesics) for reasonable conditions, based on medical decisions by the physicians. The adherence rate will be calculated after excluding those who meet the dropout criteria. We set our benchmark rate at 70% to encourage participation; however, patients who fail to meet an adherence rate of 70% will not be excluded from the study. Specific details on the use of rescue medicine and the adherence rate of each patient will be recorded in an electronic case report form in a timely fashion.

Patients will be excluded from the study due to the following: (1) a significant disease develops during the study period that may interfere with the interpretation of the results; (2) request for discontinuation or withdrawal of consent;

(3) pregnancy occurs during the study period; (4) performance status is too poor to allow administration of an intervention; and (5) any other reason for which discontinuation is deemed to be better for the patient based on medical decisions.

Assessment and Safety

Both the NRS and visual analog scale (VAS) will be used to assess the severity of lower back pain and radiating pain in the lower extremities. The NRS is a pain scale on which the patients express their subjective perception of pain as a whole number from 0 to 10, where 0 denotes “no pain or discomfort” and 10 indicates “the most severe pain and discomfort imaginable.” The VAS score, in terms of lower back pain and radiating leg pain, will be reported. In the VAS, the patient indicates the pain severity on a line, ranging from a minimum of 0 mm to a maximum of 100 mm, where a higher score suggests worse severity.

The claudication-free walking distance and maximal walking distance will be assessed to evaluate functional impairment. The Zurich Claudication Questionnaire (ZCQ), an LSS-specific questionnaire, will also be used to evaluate patient-centered improvements. The ZCQ is a patient-reported outcome measure that evaluates disease severity, function, and satisfaction with treatment in patients with LSS. The ZCQ was translated into Korean and validated in 2018.¹⁷ The Oswestry Disability Index is a validated, functional disability questionnaire for assessing lower back pain.¹⁸ The possible range of each item score is 0 to 5. The total score range is 0 (a better outcome) to 100 (a worse outcome). Short-Form 12 for Health-Related Quality of Life (SF-12 v2) consists of 12 questions across 8 domains, with higher scores indicating better health-related quality of life.¹⁹ Cost analysis will be performed using a structured questionnaire covering the following areas: official/unofficial medical costs, non-medical expenses, and time and productivity loss.

The Patient Global Impression of Change will be used to assess a patient’s impression of their improvements. Patients will rate improvement after treatment on a 7-point Likert scale, ranging from “very much improved” to “very much worse.” The EuroQoL 5 Dimensions 5 Levels will be used to assess effects on patients’ quality of life. The questionnaire consists of questions in five areas (mobility, self-care, usual activities, pain, and anxiety/depression) that ask about the patient’s current state of health. Answers are provided on a 5-point Likert scale.

Any adverse events will be recorded using the Medical Dictionary for Regulatory Activities. Causality will be evaluated using the World Health Organization–Uppsala Monitoring Center causality assessment system. Treatment-related adverse events will be recorded independently. The severity of adverse events will be assessed using the Spilker method.

Recruitment

Patients will be recruited nationwide through social media and flyers that will be handed out locally. Broadcast notifications will also be posted on hospital boards and electronic posts on the online webpage. Recruitment began in May 2022.

Data Management and Monitoring

The researchers designed a data dictionary according to the protocol prior to establishing the database for the study. Data will be recorded in a web-based electronic database (MyTrials, Bethesda software, Seoul, Republic of Korea). The authorized clinical research coordinator will record data, and the data safety monitoring committee will be able to access the database to monitor, audit, and lock or release data. Automatic queries are generated in a timely manner in response to recorded data according to predefined algorithms. Initial and interim meetings will be held periodically to monitor integrity and consistency, to coordinate data collection and address concerns, and to determine whether the study should be continued or halted. Independent data monitoring will occur at a minimum of three timepoints: prior to enrollment of the first patient, after a third of the planned dataset is collected, and after every piece of data is recorded and determined to be locked. Although the interim monitoring interval is planned to occur bimonthly, it can be changed according to the risk of each study site.

Statistical Considerations

The total planned sample size is 98 patients. This sample size was determined to provide 80% power, assuming a significance rate of 0.05, an optimal difference between the two groups of 1.75, with a mean standard deviation of 2.75.^{20,21} Based on this equation, there were 38.8 participants in each group, and the sample size was calculated to be 98 people, since the study was done in seven hospitals and 20% of the participants dropped out.

The primary analysis will be intention-to-treat analysis. A per-protocol analysis will also be performed for patients who adhere to more than 70% of the intended treatment schedule. Missing values will be analyzed with a mixed model for repeated measures. Sensitivity analysis will be carried out based on multiple imputations and the last-observation-carried-forward method. For survival analysis, patients who dropped out during the treatment period will be right-censored, and if intermittent censoring occurs, the event will not occur within the intermittent censored period. Sociodemographic characteristics and treatment expectancy will be described per group using descriptive statistics. Each continuous variable will be presented as a mean and standard deviation, or a median and interquartile range. The differences between the two groups will be assessed using Student's *t*-test or Wilcoxon's rank-sum test, according to their distribution. Categorical variables will be presented as the frequency and percentile (%) and will be assessed using the chi-square test or Fisher's exact test.

The primary outcome will be the change in the severity of the dominant lower back pain and radiating pain in the lower extremities at the end of treatment. This severity will be compared with that at baseline. A linear mixed model will be used, mainly the random intercept model. The random effects of the patients will be included in the random intercept model, and the baseline outcomes and covariant factors will be addressed using covariates as fixed effects. Changes over time between groups will be analyzed using this method by including time, group, and the interaction in the model. Sensitivity analysis will be assessed through analysis of covariance (ANCOVA), considering the group as a fixed factor.

The area under the curve (AUC) will also be analyzed to determine cumulative effectiveness. The AUC will be cumulatively evaluated using ANCOVA with multiple imputations. The minimal clinically important difference (MCID) achieved will be determined according to the NRS score for severity of lower back pain. MCID achievement will be estimated using Kaplan–Meier survival analysis, and statistical significance will be assessed using the log rank test. Hazard ratios will be assessed using Cox proportional hazard ratio models.

All analyses will be performed using SAS[®] v.9.4 (SAS Institute, Inc., Cary, NC, USA) or R[®] v.4.1.1 (the R Foundation for Statistical Computing, Vienna, Austria). Differences will be considered statistically significant at a *p*-value < 0.05.

If we fail to achieve a statistical difference of superiority regarding the hypothesis of intervention, non-inferiority analysis will be conducted as an alternative. A pre-specified, non-inferiority margin will be set at 50% of the MCID for lower back pain (0.9). If the difference in the change in pain severity between the two groups does not exceed the lower limit of the 95% confidence interval, pharmacopuncture will be considered non-inferior to conventional care, including physiotherapy and medication.

Discussion

Although surgery is considered the gold standard for LSS patients, non-surgical interventions are recommended as the first line of treatment.²² Surgical intervention, including laminectomy for patients with symptomatic and progressive LSS, spinal instability, and other conditions can lead to re-operation within the first year.²³ Since LSS is a degenerative disorder and aging patients tend to have more comorbidities, the risk of major complications associated with surgery is also considerable.²⁴ Known major complications within a month after surgery include a 0.4% mortality rate, which increases with age. The rate of adverse events, including perioperative and post-operative complications, is 10%–24%.^{25,26}

Non-surgical interventions are non-inferior to surgical interventions, are patient-centered, and lead to fewer complications. The Spine Patient Outcome Research Trial (SPORT) has compared surgical and non-surgical interventions pragmatically, and sheds light on their effectiveness and cost-effectiveness based on real-world data.^{27,28} The SPORT did not identify specific non-surgical interventions, but rather non-operative interventions as per usual recommended care, including physiotherapy, education, and instructions regarding home exercise and use of NSAIDs.

Conservative treatment methods for LSS are not yet standardized.²² Several options have been suggested, including pharmacotherapy (both oral medication and injection) and physiotherapy. The Finnish lumbar spinal research group used non-operative interventions, including assessment for individual treatment, prescribed analgesics, individualized physiotherapy, and active back exercises. It also provided education with a paper brochure that included the principles of activation and physical training, maintaining pain-relieving body postures, and basic ergonomics.^{29,30} Another study described conservative treatment as involving an orthosis and a rehabilitation department program that included daily physiotherapy; however, regular physiotherapy was not provided.³¹

Comprehensive conservative care for LSS typically includes physiotherapy and analgesics.^{20,22,27} Specific methods are yet to be identified, but physiotherapy includes physical exercises and manual therapy.³² Pharmacotherapy is recommended only to a limited extent. Acetaminophen and NSAIDs are effective, but neither are significantly more effective than the other.⁷ Analgesics, including opioids and muscle relaxants, are not more effective than acetaminophen or NSAIDs.³³ Prostaglandins, pregabalin, and other medications have shown positive outcomes, with or without statistical significance, but none have been predominantly recommended.^{34–37} Since no specific intervention is currently recommended as the first-line treatment, conservative approaches should be multi-modal and patient-centered on an individual basis, and specific decisions should be made by physicians.

Pharmacopuncture is officially accepted and practiced in South Korea and is commonly used in patients with LSS.^{10,11} Pharmacopuncture for stenosis tends to be combined with acupuncture and Chuna manual therapy. In one study, when integrated Korean medical treatment was administered to patients with LSS, 93.6% of patients admitted to the clinic received pharmacopuncture and 14.0% received bee venom acupuncture,³⁸ illustrating the active practice of pharmacopuncture for stenosis. Another retrospective chart review with a follow-up survey also reported the efficacy of multimodal Korean medicine therapy, including Hwangryunhaedoktang pharmacopuncture in patients with LSS.³⁹ However, specific forms of pharmacopuncture cannot be prioritized for patients with LSS, since the effect of acupuncture cannot be understood solely based on the ingredients of the subcutaneously injected drug. Pharmacopuncture is a far-reaching treatment when considering the local effect of acupuncture; the distant effect of stimulating acupoints and the composition of herbal medicine are comprehensively understood.

Thus, to collect real-world data for investigating optimal non-surgical interventions for stenosis, we have designed this clinical study to compare the effectiveness of pharmacopuncture with optimal conservative care, including physiotherapy and pharmacotherapy (the control group), as determined by physicians. Due to the pragmatic nature of the research design, it may not be sufficient to validate the experimental efficacy of the pharmacopuncture. However, in clinical settings, the efficacy identified in a fully controlled experimental design does not always appear. By structuring the study to resemble a clinical setting, we were able to compare the effectiveness of the use of pharmacopuncture with that of conservative treatment approaches and demonstrate the effectiveness in real world. In assessing the domains of the PRECIS-2, our clinical study will adopt an approach that allows pragmaticity for delivery, while taking a somewhat conservative explanatory approach to collection, to evaluate the overall effectiveness in a real-world setting. We will allow for combinatory interventions with a pragmatic perspective and will analyze the therapeutic interventions and strategies used for stenosis in the actual clinical environment with immediacy.

However, our study is limited by the fact that neither the physician nor the patient could be blinded. To compensate for these limitations, however, we employed a blinded assessor when evaluating the outcome.

Our study outcomes reflect the treatment goals for patients with stenosis, which include alleviating symptom intensity, decreasing claudication, increasing walking distance, temporarily delaying the onset of neurological defects, reducing the need for surgery, and ensuring post-operative treatment satisfaction. The primary outcome is the change in the severity of the dominant pain, between lower back pain or pain in the lower extremities. The blinded assessor evaluated walking distance and physical examination as outcomes. Patient-reported outcomes include the ZCQ, SF-12 v2, and other questionnaire scores.

Conclusion

This pragmatic, randomized, controlled, parallel-group clinical study will compare the effectiveness of pharmacopuncture to that of conservative care, including physiotherapy and pharmacotherapy. The study results will inform treatment planning and the selection of appropriate non-surgical treatment for individual patients with LSS.

Abbreviations

ANCOVA, analysis of covariance; AUC, area under the curve; CONSORT, Consolidated Standards of Reporting Trials; LSS, lumbar spinal stenosis; MCID, minimal clinically important difference; NRS, numeric rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; PRECIS-2, Pragmatic Explanatory Continuum Indicator Summary tool, version 2; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SF-12 v2, Short-Form 12 for Health-Related Quality of Life; SPORT, Spine Patient Outcome Research Trial; VAS, visual analog scale; ZCQ, Zurich Claudication Questionnaire.

Data Sharing Statement

Availability of data and materials: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the institutional review board of each site (JASENG 2021-12-019, JASENG 2021-12-008, JASENG 2021-12-003, JASENG 2021-12-017, KHNMCOH 2022-01-001, KOMCIRB 2021-12-002, DOBUH 2022-001) prior to patient enrollment. All patients will provide written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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