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CLINICAL STUDY PROTOCOL

Add-on Effect and Safety of Pharmacopuncture Therapy in the Treatment of Patients with Lumbar Spinal Stenosis

Yoona Oh[1,†], Chang-Hyun Han[2,3,†], Yeonhak Kim[1], Jihun Kim[1], Changsop Yang[2], Young Eun Choi[4], Byoung-Kab Kang[2], Gi Young Yang[1,5], Byung Ryul Lee[1,5], Eunseok Kim[1,5,*]

[1]Department of Acupuncture and Moxibustion Medicine, Pusan National University Korean Medicine Hospital, Yangsan, Korea
[2]KM Science Research Division, Korea Institute of Oriental Medicine, Daejeon, Korea
[3]Korean Convergence Medicine, University of Science & Technology (UST), Campus of Korea Institute of Oriental Medicine, Daejeon, Korea
[4]Clinical Research Coordinating Team, Korea Institute of Oriental Medicine, Daejeon, Korea
[5]Division of Clinical Medicine, School of Korean Medicine, Pusan National University, Yangsan, Korea

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Correspondence to
Eunseok Kim
Division of Clinical Medicine, School of Korean Medicine, Pusan National University, Yangsan, Korea
E-mail eskim@pusan.ac.kr
[†]These authors contributed equally to this work.

Background: Recently, Korean Medicine treatment with pharmacopuncture therapy (PPT) has been increasingly used in clinical practice to improve symptoms in patients with lumbar spinal stenosis (LSS). The aim of this study is to evaluate the effectiveness and safety of PPT in addition to conventional Korean Medicine treatment (CKMT) for the treatment of patients with LSS, compared with CKMT alone.
Methods: This study is designed as a pragmatic, randomized, two-armed, parallel, stratified (by sex), controlled pilot trial. Forty patients diagnosed with LSS will be randomly allocated to the PPT + CKMT group or the CKMT group. Patients in the two groups will receive treatment two times weekly for 5 weeks. The primary outcome will be the mean change in the 100-mm visual analog scale score from the baseline to the end of treatment (week 5). The secondary outcomes will include the clinically important difference, Zurich Claudication Questionnaire score, self-reported walking capacity, Modified–Modified Schober test, EuroQol 5-dimension 5-level questionnaire, and Patients' Global Impression of Change. Adverse events will be assessed at each visit.
Discussion: The results of this study will provide meaningful data to evaluate the add-on effect and safety of PPT in the medical care of patients with LSS.

Keywords: Lumbar spinal stenosis, Pharmacopuncture therapy, Add-on effect, Conventional Korean Medicine treatment, Pragmatic randomized pilot trial

Trial registration: Clinical Research Information Service (CRIS): KCT0007229. Registered on 26 April 2022.

INTRODUCTION

Lumbar spinal stenosis (LSS) is a spinal disorder caused by compression or narrowing of the spinal cord and nerve roots as a result of degenerative changes in the ligament flavum, facet joints, disc, and bone [1]. The major complaints from patients with LSS are back pain and discomfort in the lower extremities, resulting in gait disturbance. Most of the symptoms are aggravated with walking and alleviated during stabilization or lumbar flexion [2,3] LSS causes a more severe disruption on daily life and a greater reduction in the quality of life (QOL) than other degenerative diseases, including knee osteoarthritis and hip arthritis [4]. According to the Korean Health Insurance Review & Assessment Service, the medical expenses associated with LSS in Korea were about 540 million dollars in 2021, and the prevalence of LSS is on the rise, resulting in an economic burden for the older population [5]. Factors affecting the LSS prevalence and symptom severity are related to old-age, diabetes history, and vitamin D deficiency [6,7].

Pharmacopuncture therapy (PPT) includes an injection of a medicinal extract into an acupuncture point using a needle, and is widely used in the treatment of musculoskeletal disorders in Korean medicine clinical practice. PPT is expected to induce the synergistic effect between the medicinal extract and acupuncture stimulation [8,9]. The most common ingredients used in pharmacopuncture in Korea are animal-derived materials, such as bee venom

and Hominis placenta, and herbal extracts, such as Hwangryunheadok-tang and Jinseng [10]. In general, PPT tends to be used in combination with other conventional Korean Medicine treatments (CKMTs), rather than alone in Korean clinical practice. CKMTs include treatments such as acupuncture, electroacupuncture, cupping, and infrared irradiation therapy. Several studies have reported that CKMT is effective for pain relief and functional recovery in patients with musculoskeletal disorders, including LSS [11-15]. However, to the best of our knowledge, no previous pragmatic clinical trial on the effect of PPT in the treatment of patients with LSS has been reported, despite the frequent use of PPT. Therefore, we will evaluate the add-on effect of PPT in clinical practice for the treatment of patients with LSS, with a focus on external validity. This pragmatic clinical trial aimed to evaluate the effectiveness of PPT in addition to CKMT, compared with that of CKMT alone, in relieving pain and functional disability resulting from LSS.

MATERIAL AND METHODS

1. Study design

This study is designed as a pragmatic, randomized, two-armed, parallel, stratified (by sex), controlled pilot trial. The study was approved by the institutional review board (IRB) of the Pusan National University Korean Medicine Hospital (PNUKH) (PNUKHIRB 2022-01-002-003), and registered with the Clinical Research Information Service (KCT0007229).

As this study is a pilot randomized clinical trial (RCT), conducted as the preparatory analysis for large-scale studies, we assumed 40 participants to be an acceptable sample size (20 subjects each in the PPT + CKMT and CKMT groups). From April-December 2022, a total of 40 patients visiting the Spine and Joint Center of PNUKH will be recruited. The researcher will inform the subjects of the details of the study, and participants who voluntarily sign the written consent form will be screened based on the eligibility criteria. At visit 1, eligible participants diagnosed with LSS will undergo baseline assessments, after which they will be allocated to 1 of 2 groups (PPT + CKMT or CKMT group). The participants allocated to the PPT + CKMT group will be treated with additional PPT, while those assigned to the CKMT group will be treated with the usual CKMT only.

Participants will receive ten allocated treatments twice weekly for 5 weeks. Outcomes will be measured before treatment (week 1), after treatment completion (week 5), and 2 weeks (week 7) and 8 weeks (week 13) after treatment completion (Fig. 1). The participants will be recruited through an advertisement on the hospital website, hospital bulletin board, brochure, local advertisement, media, and public institution website. All potential participants will have a preliminary telephone interview conducted by the clinical research coordinator and will be scheduled for a screening visit. In addition, participants will be monitored by a third party (not associated with the study) at the initiation of the site, at first patient enrollment, during the duration of the study, and after trial completion.

2. Participant selection

1) Inclusion criteria

Patients who satisfy the following conditions will be considered eligible: (1) age 40-80 years; (2) diagnosis of LSS by computed tomography (CT) or magnetic resonance imaging (an L-spine CT scan will be provided if there are no existing image data or if necessary); (3) pain or discomfort in the lower extremities or buttocks is over or equal to 40 mm on a visual analog scale (VAS); (4) clinical features of spinal stenosis, such as neurogenic claudication or changes

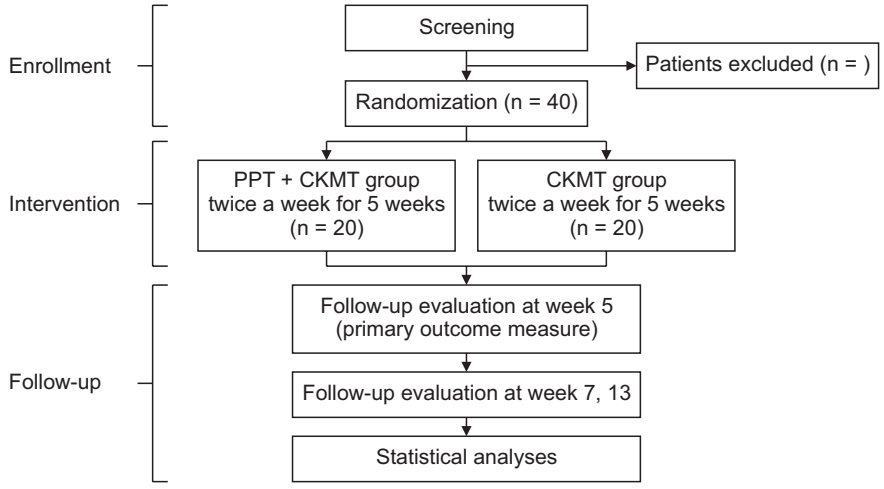

Fig. 1. Flowchart of the study. PPT = Pharmacopuncture Therapy; CKMT = Conventional Korean Medicine Treatment.

in symptoms due to position; (5) comprehensive diagnosis of LSS based on physical examination, history taking, and imaging examination; and (6) voluntary agreement with the research purpose and process, and the signing of informed consent for study participation.

2) Exclusion criteria

Patients with any of the following conditions will be excluded: (1) diagnosis of congenital or developmental spinal stenosis; (2) severe defects, such as spinal segment muscle atrophy, gait disorder, and cauda equina syndrome due to spinal canal problems; (3) moderate to severe spinal malalignment and spinal instability due to spondylolisthesis, spondylolysis, thoracic and lumbar fractures, and other conditions; (4) diagnosis of other spinal diseases, such as vertebral body tumors, spinal infection, and ankylosing spondylosis; (5) history of spinal surgery, such as spinal fusion or laminectomy; (6) factors that may affect hemostasis, such as taking anticoagulants and antiplatelet drugs, and bleeding disorders; (7) history of metal allergy, acupuncture hypersensitivity, severe atopic dermatitis, keloid skin, and other skin hypersensitivities; (8) moderate to severe chronic kidney disease (stage ≥ 4), uncontrolled diabetes mellitus, or severe cardiovascular disease; (9) significant neuropsychiatric history, or current mental or cognitive impairment; (10) history of intemperate alcohol or drug use; (11) comorbidities requiring ongoing treatment, which could prevent participation in the study; (12) current or planned pregnancy, or lactation in women of childbearing years; (13) difficulty in complying with informed consent or a questionnaire on one's own or under the supervision of a guardian or researcher; and (14) difficulty in participating in the trial based on an investigator's decision.

3. Randomization and blinding

An independent statistician who is not involved in the clinical trial evaluation and intervention will generate a random set of numbers in SAS® version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA) to randomly assign 40 people to the two groups. Stratified block randomization, which uses sex as a strata factor, will be used to control biases that may occur in the study. The generated table will be kept in a cabinet under lock by the independent statistician.

In this study, since PPT will be applied only in the experimental group, it is impossible to conceal the group assignment to the PPT practitioner and study subjects. Nevertheless, to minimize bias in favor of the experimental group, the practitioners administering CKMT to the participants in both groups will be blinded to group allocation. The practitioners assigned to administer PPT will not be allowed to provide CKMT. The evaluator, data manager, and statistician will also be blinded to each patient's allocation status.

4. Interventions

This pragmatic study will set up a pool of different types of extracts and needle sizes for PPT, acupuncture points, and needle sizes for CKMT to allow flexibility in the intervention. All details of the treatment will be recorded.

1) Pharmacopuncture therapy

PPT will be administered by clinical experts with over 10 years of experience in Korean medicine, based on clinical features such as lesions on images and pain areas in the lower extremities. Bee venom pharmacopuncture will mainly be applied to the EX-B2 spinal level with the stenosis lesion. In case of hypersensitivity to bee venom, or persistent pain despite the bee venom pharmacopuncture, bamboo-salt or Hominis placenta pharmacopuncture will be selectively applied.

The pool of PPT acupoints will consist of EX-B2 (L1-5), Yaoyangguan (GV3), Shenshu (BL23), Dachangshu (BL25), Guanyuanshu (BL26), Huangmen (BL51), Zhishi (BL52), Ciliao (BL32), Zhibian (BL54), Huantiao (GB30), and Ashi points. Based on clinical judgment, practitioners will choose one pharmacopuncture type, such as the sweet bee venom, Hominis placenta, or bamboo salt, which are commonly used for LSS in clinical practice. Details of PPT intervention, including the type of PPT, dosage, type of needle, and treatment site, will be recorded on the case report form (CRF).

2) Conventional Korean Medicine treatment

The CKMT procedure (Table 1) will be performed as follows: With a patient in the prone position, cupping will be applied to the back and pelvis for 5 min, followed by acupuncture treatment. Compulsory main acupuncture points will include the bilateral EX-B2, corresponding to the level of LSS. Individualized auxiliary acupuncture points will be selected from the following suggested acupoint pool by referring to the clinical features of the patient: Yaoyangguan (GV3), Shenshu (BL23), Dachangshu (BL25), Huangmen (BL51), Zhishi (BL52), Ciliao (BL32), Zhibian (BL54), Huantiao (GB30) and Ashi points in the lumbar and buttock region, and Weizhong (BL40), Chengshan (BL57), Weiyang (BL39), Kunlun (BL60), Yinlingquan (SP9), Yanglingquan (GB34), Xuanzhong (GB39), and Ashi points on the lower extremity. Depending on the patient's physique, fear of invasive treatment, and postoperative pain, different types of acupuncture needles (Dongbang Acupuncture, Dongbang Medical, Seongnam-si, Gyeonggi-do, Republic of Korea) will be inserted for each acupuncture point. De qi sensation will also be induced by manual stimulation with the acupuncture

Table 1. Standards for reporting interventions in clinical trials of acupuncture for CKMT

Item	Detail	Contents
1. Acupuncture rationale	1a) Style of acupuncture	Korean Medicine
	1b) Reasoning for treatment provided	Based on the clinical practice guidelines and a textbook of acupuncture.
	1c) Extent to which treatment was varied	Most treatments were selected individually according to the patient's symptoms and conditions
2. Details of needling	2a) Number of needle insertions per subject per session	4-20 needles were used.
	2b) Names of points used	Essential acupoints: L-spine EX-B2(bilateral) Auxiliary acupoints: GV3, BL23, BL25, BL51, BL52, BL32, BL54, GB30, BL40, BL57, BL39, BL60, SP9, GB34, GB39, and Ashi points.
	2c) Depth of insertion	Between 0.5 cm and 5.0 cm.
	2d) Response sought	De-qi sensation or local muscle twitch response.
	2e) Needle stimulation	Both of manual and 2-100 Hz electrical stimulation were applied within individual pain thresholds.
	2f) Needle retention time	20 min
	2g) Needle type	0.25 mm × 40 mm or 0.35 mm × 60 mm (Dong-bang disposable acupuncture needle).
3. Treatment regimen	3a) Number of treatment sessions	10 sessions
	3b) Frequency and duration of treatment sessions	2 sessions per week for 5 weeks
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group	Cupping and Infrared irradiation.
	4b) Setting and context of treatment	Information on the treatment was provided to the patients.
5. Practitioner background	5) Description of participating acupuncturists	Three resident trainees in Korean Medicine with 3 years of experience, and certified clinical specialist of Korean Medicine with 30 years of experience.
6. Control or comparator interventions	6a) Retionale for the control or comparator in the context of the research question	Not applicable (same acupuncture treatment was applied to the control and experimental groups).
	6b) Precise description of the control or comparator	Not applicable (same acupuncture treatment was applied to the control and experimental groups).

CKMT = Conventional Korean Medicine treatment.

needle. The practitioner will apply electrical stimulation with an alternating frequency of 2-100 Hz to the acupuncture needle inserted in the EX-B2 point, at an intensity that the patient can tolerate for 20 min. During needle retention, infrared irradiation will be applied to the treatment site using an infrared device (Omega-302, ENS tech., Gwangju-si, Gyeonggi-do, Republic of Korea).

3) Cointerventions

Invasive treatment (injection or endoscopic resection) and other Korean Medicine treatments (herbal medicine, pharmacopuncture, acupuncture, cupping, moxibustion, or chuna) except for CKMT provided in the study will not be allowed during this study. Participants will be instructed not to receive any treatment other than the intervention assigned to them during the treatment phase, and to take rescue medication (acetaminophen, up to 3,000 mg per day) only if necessary, during the follow-up period. Drugs typically used for treating an underlying disease that are not expected to affect the results of the trial will be allowed at the discretion of the investigator. Information on all co-interventions will be recorded in the CRF.

5. Primary outcome

The primary outcome is the mean change in the 100 mm VAS value at the primary endpoint (week 5), immediately after the end of treatment, compared with that at baseline (week 1). The 100-mm VAS, where 0 means no pain and 100 means the most severe pain [16], will be used to measure pain or discomfort in the hip, legs, and lower back (Table 2).

Table 2. Schedule for the treatment and outcome measurements

	Study period												
		Treatment phase										Follow-up phase	
Visit	Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Week	0		1W		2W		3W		4W		5W	7W	13W
Informed consent	●												
Inclusion/Exclusion criteria	●												
Vital sign	●	●	●	●	●	●	●	●	●	●	●	●	●
Demographic characteristics	●												
Medical history	●												
Lab test	●										●		
L-spine MRI/CT	●												
Physical examination	●												
Random allocation		●											
Interventions:													
PPT + CKMT		○	○	○	○	○	○	○	○	○	○		
CKMT		◎	◎	◎	◎	◎	◎	◎	◎	◎	◎		
Assessments:													
VAS	●	●									●	●	●
ZCQ		●									●	●	●
Self-reported walking capacity		●									●	●	●
MMST		●									●	●	●
EQ-5D-5L		●									●	●	●
PGIC											●		●
CID											●		●
Safety assessment		●	●	●	●	●	●	●	●	●	●	●	●

CID = clinically important difference; CKMT = conventional Korean Medicine treatment; CT = computed tomography; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; MMST = Modified–Modified Schober test; MRI = magnetic resonance imaging; PGIC = Patients' Global Impression of Change; PPT = pharmacopuncture therapy; VAS = visual analog scale; ZCQ = Zurich Claudication Questionnaire.

6. Secondary outcomes

1) Pain

The mean change in the 100-mm VAS value from baseline to week 7 and week 13 will be measured to evaluate pain in the follow-up phase at 2 and 8 weeks post-treatment, respectively.

2) Clinical relevance

The ratio of decreases of ≥ 15 mm, the minimal clinically important difference, or percentiles ≥ 30% and ≥ 50% on the 100-mm VAS compared to the baseline score will be adopted [17].

3) Zurich Claudication Questionnaire score

The Zurich Claudication Questionnaire (ZCQ) is an evaluation tool for the symptoms and functions of patients with LSS, consisting of the following three domains: symptom severity, physical functional status, and postoperative satisfaction [18]. Since PPT and CKMT are not surgical interventions, only two parts of the ZCQ, i.e., symptom severity and physical functional status, will be adopted. The ZCQ symptom domain has a total of seven questions, including pain, sensory abnormalities, weakness, and balance disorders. The scores range from 1 to 5, and the higher the score is, the more severe the symptoms are. The ZCQ function domain includes questions about the average walking distance, outdoor walking, grocery shopping, walking in the house, and inconvenience in the toilet. The scores range from 1 to 4, and the higher the score is, the more severe the symptoms are. The Korean version of the ZCQ, which has been verified to be transculturally equivalent, will be used in this study [19].

4) Self-reported walking capacity

The self-reported walking capacity is the distance (m) that the patient can walk at a time without rest. This distance will be calculated by multiplying the maximum walking time by the walking speed according to the age in Koreans (15-49 years [66.67 m/min], 50-64 years [56.67 m/min], 65-74 years

[47.00 m/min] and over 75 years [41.83 m/min]) [20].

5) Modified-Modified Schober test

The Modified–Modified Schober test evaluates the lumbar flexion range of motion. After the subject takes a standing position, the examiner will mark points 10 cm above and 5 cm below the point where the center line intersects with that connecting the posterior superior iliac spine on both sides. After the subject flexes their lumbar spine to the maximum extent without experiencing pain, the assessor will record the increased distance between the two marked points [21].

6) EuroQol 5-dimension 5-level questionnaire

The participant's QOL assessment will be performed using the validated Korean version of the EuroQol 5-dimension 5-level questionnaire [22]. Participants will be asked to check the most appropriate sentence for five items related to their condition (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [23].

7) Patients' Global Impression of Change

Patients' Global Impression of Change is a tool to evaluate the global assessment before and after intervention. Participants will choose one of the seven categories for the degree of improvement between the before and after treatment (very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse) [24].

8) Adverse events and safety

All types of adverse events (AEs), including those from PPT, will be recorded at every visit to document the time of occurrence, end time, severity, frequency, causality with intervention, and details on coping. In the case of the sweet bee venom, to minimize AEs such as itching, redness, and swelling, the dose will be gradually increased while examining the post-treatment responses of the patient. The severity of AEs will be classified into five grades according to the World Health Organization (WHO) guidelines. AEs that do not correspond to the WHO guidelines will be evaluated using the Spilker's three-step classification method (mild, does not require additional treatment and does not significantly impair normal activities; moderate, possibly requires additional treatment and significantly impacts daily life, but is recoverable; and severe, requires advanced treatment and leaves aftereffects) [25]. The causal relationship between the intervention and AEs will be evaluated using a six-stage classification (1 = definitely related, 2 = probably related, 3 = possibly related, 4 = probably not related, 5 = definitely not related, 6 = unknown). When a severe AE occurs, the researcher will notify the principal investigator (PI), and the PI will report to the IRB to determine whether the subject should be excluded. At the baseline and end of treatment, all participants will have a blood test.

7. Statistical methods

All analyses will be performed using SAS® version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA) by an independent statistician, and statistical significance will be set to $p < 0.05$ (two-tailed). A full analysis set (FAS) and per-protocol (PP) set will be included in the analyses set. The FAS set will include study subjects assessed at least once after randomization, and will be used for the main analysis. For inclusion in the PP set, patients will have to complete the trial without any major protocol violations, and those in the experimental group will have to receive eight or more (≥ 80%) sessions of treatments. The missing data will be handled by the last observation-carried-forward method.

For both groups, the summary statistics for demographic data and baseline characteristics will be presented as the means and standard deviations for continuous variables and frequencies with percentages for categorical variables. Baseline assessments for the two groups will be performed using either a t-test or the Wilcoxon signed-rank test for continuous variables, and either the chi-squared or Fisher's exact test for categorical variables.

For a confirmatory analysis of the primary outcome, analysis of covariance will be implemented with the baseline score and sex as covariates. In each of the two groups, the paired t-test or Wilcoxon signed-rank test will be performed to compare outcomes before and after treatment. A repeated-measures analysis of variance will be carried out to assess differences between the two groups over time. The safety set will include study subjects who received at least one treatment, and the results will be presented as descriptive statistics. The types and methods of pharmacopuncture therapy will also be presented as descriptive statistics. Subgroup analyses will be performed based on sex, age, morbidity period, level of spinal stenosis, and PP for the primary and secondary endpoints, if necessary. No interim analyses will be conducted.

8. Withdrawal and dropout

The participant may request to withdraw consent for the treatment and decline further participation for any personal reasons or because of unsatisfactory treatment results. The participants will be dropped out of the study based on the decision of the PI when continuation of the clinical trial is deemed inappropriate, such as if they commit a serious violation of the eligibility criteria or the major protocol, or experience an adverse effect that poses a serious threat to their health.

9. Ethics

This trial will be performed in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Korean Good Clinical Practice. The participants will be thoroughly informed on the study objectives and procedures, as well as the potential benefits, risks, and responsibilities regarding the study and must voluntarily submit written consent. In accordance with the personal information protection principles, all documents involved in the study will be recorded and sorted with a unique subject code, rather than the name of the participant, and all source data collected during the study will be securely stored in a locked storage container or facility in the Clinical Trial Center at PNUKH. In addition, the compiling, integrating, and coding of data for statistical analyses will be conducted by a third party.

DISCUSSION

This study is designed to evaluate the add-on effect of PPT on CKMT, while allowing flexibility in clinical practice for patients with LSS. The type of PPT, depth of insertion, acupuncture points, number of needles for one session, and needle size will be selected according to the patient symptoms. This intervention plan will allow the practitioner to provide individualized treatment according to the clinical features of the patient with LSS.

The eligibility criteria are designed to exclude congenital and traumatic stenosis of the lumbar spine that is not responding conservative treatment, and not to limit the anatomical classification of stenosis, including central and lateral stenosis. In screening, research clinicians diagnosed patients with LSS based not only on imaging results, but also on neurological symptoms in the lower extremity and gait disorders caused by LSS.

Although in actual clinical practices, the practitioner selectively administers several appropriate types of pharmacopuncture, depending on the patient symptoms and disease properties, there have been no studies to evaluate PPT as a treatment modality for LSS, except several studies that assessed the effectiveness of a single type of pharmacopuncture [26-28]. In this study, we will adopt the ZCQ as one of the evaluation methods because not only pain and discomfort, but also dysfunction due to gait disturbance affects the QOL for patients with LSS. In a previous study on chronic lower back pain [26], 6 sessions of bee venom pharmacopuncture over a period of 3 weeks led to a significant improvement over the sham control group immediately after and 1 week after treatment; however, the differences between the two groups decreased after 5 weeks. Based on these results, our study will assess the effectiveness of PPT immediately after, and 2 and 8 weeks after treatment.

This study has some limitations. First, participants cannot be blinded due to the nature of the designated treatment. However, to maintain blinding of the group allocation among the researchers, CKMT and PPT practitioners will be separated. Additionally, to avoid guessing for the group assignment based on information from AEs, such as itching, redness, and swelling resulting from PPT, evaluators for outcome measurement will not participate in evaluating the AEs. Second, treatment modalities on pharmacopuncture applied in this study, which have not yet been standardized or optimized, may be based on the practitioner's individual clinical experience. Nevertheless, the details for PPT and its effect size in this study can serve as preliminary data for future large-scale confirmatory research. Third, the sample size (40 participants) is considerably small, and the 8-week follow-up after treatment is short.

As the first pragmatic RCT to evaluate the add-on effect of PPT in patients with LSS, despite the limitations, the results from this study will be used to determine the sample size for a full-scale study. Furthermore, treatment details of the PPT derived from this study and the collected AEs will be used as the basic data and valuable insights for designing future pharmacopuncture-mediated studies.

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AUTHORS' CONTRIBUTIONS

Conceptualization: Chang-Hyun Han, Changsop Yang, Eunseok Kim; Data curation: Byoung-Kab Kang; Formal analysis: Byoung-Kab Kang; Investigation: Yoona Oh, Yeonhak Kim, Jihun Kim, Byung Ryul Lee; Methodology: Yoona Oh, Chang-Hyun Han, Eunseok Kim; Project Administration: Eunseok Kim; Resources: Eunseok Kim; Supervision: Eunseok Kim, Young Eun Choi, Gi Young Yang, Byung Ryul Lee; Validation: Young Eun Choi, Eunseok Kim, Gi Young Yang, Byung Ryul Lee; Visualization: Eunseok Kim; Writing-original draft: Yoona Oh, Chang-Hyun Han; Writing-review and editing: Eunseok Kim.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Yoona Oh, https://orcid.org/0000-0002-6987-0675
Chang-Hyun Han, https://orcid.org/0000-0003-4285-3063
Yeonhak Kim, https://orcid.org/0000-0003-2025-000X
Jihun Kim, https://orcid.org/0000-0001-5333-8628
Changsop Yang, https://orcid.org/0000-0003-1277-3329
Young Eun Choi, https://orcid.org/0000-0001-6915-3716
Byoung-Kab Kang, https://orcid.org/0000-0002-3016-2428
Gi Young Yang, https://orcid.org/0000-0002-9468-8904
Byung Ryul Lee, https://orcid.org/0000-0002-3782-7445
Eunseok Kim, https://orcid.org/0000-0002-9342-3082

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