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ORIGINAL RESEARCH

Pharmacopuncture Therapy as an Adjunctive Treatment for Patients with Lumbar Spinal Stenosis: A Pragmatic Randomized Controlled Pilot Trial

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

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

*These authors contributed equally to this work

Correspondence: Eunseok Kim, Division of Clinical Medicine, School of Korean Medicine, Pusan National University, 49, Busandaehak-ro, Mulgeum-eup, Yangsan-si, Gyeongnam, 50612, Republic of Korea, Tel +82 55 360 5950, Fax +82 55 360 5890, Email eskim@pusan.ac.kr

Purpose: Pharmacopuncture therapy (PPT) combines medicinal extracts with acupuncture and is widely used as an adjunct in clinical practice. This study assessed the safety and feasibility of PPT in addition to conventional Korean Medicine treatment (CKMT), including electroacupuncture, cupping and infra-red, for lumbar spinal stenosis (LSS).

Patients and Methods: Forty patients diagnosed with LSS were randomly assigned to undergo PPT with CKMT (experimental group) or CKMT alone (control group) at a 1:1 ratio, receiving 10 sessions of each intervention over five weeks. The primary clinical outcome was measured using the 100-mm Visual Analog Scale (VAS) for buttock and leg pain five weeks post-treatment. Secondary outcomes included clinically important difference (CID), Zurich Claudication Questionnaire, self-reported walking capacity, Modified–Modified Schober test, EuroQol 5-dimension 5-level questionnaire, and the patient's global impression of change. The adverse events were assessed at each visit. The analysis of covariance was conducted to compare between two groups.

Results: Intervention completion rates were 95% and 100% in the experimental and control groups, respectively. No statistically significant differences were found between groups regarding the primary outcome (adjusted mean difference: 8.0; 95% confidence interval: −1.4–17.4). The mean difference in the 100-mm VAS for low back pain at week 5 (adjusted mean difference: 12.9; 95% confidence interval: 2.4–23.4) and the proportion of patients who reached the minimum CID was higher in the experimental group than in the control group. However, no significant differences were observed with other secondary outcomes. One patient in the experimental group experienced a systemic skin rash that resolved the same day, whereas the adverse events in the other group were mild and transient.

Conclusion: This trial demonstrated the feasibility of add-on effects and the safety of pharmacopuncture in patients with LSS. Further studies are warranted to evaluate the add-on effects of PPT in treating LSS.

Trial Registration: Clinical Research Information Service (CRIS), KCT0007229; registered on April 26, 2022.

Keywords: lumbar spinal stenosis, pharmacopuncture therapy, add-on effect, conventional Korean medicine treatment, pragmatic randomized pilot trial

Introduction

Lumbar spinal stenosis (LSS) is a degenerative condition of the lumbar spine that is prevalent among geriatrics.[1] As the population ages and life expectancy increases, the incidence and burden of LSS rise. According to the Health Insurance

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Review and Assessment Service of Korea, the number of patients with LSS is 1.7 million, and the associated medical expenditure was 700 billion won in 2021.[2] It narrows the spinal canal, compressing the neural elements within the lumbar region. This chronic and progressive condition poses significant challenges, such as discomfort in the back and lower extremities, resulting in gait disturbances.[3,4]

Surgical intervention for LSS is carefully considered and individualized, except for cauda equina syndrome and severe nerve deficits, owing to the potential risks of increased instability of adjacent vertebrae and persistent pain, even postoperatively.[5] Various conservative therapies are used for LSS management; however, recent studies revealed that acupuncture has better analgesic effects than nonsteroidal anti-inflammatory drugs or physical therapy.[6,7] Pharmacopuncture therapy (PPT) is a combined technique that involves the infusion of medicinal extracts and acupuncture to achieve a synergistic effect.[8,9] In Korean clinical practice, PPT is selectively incorporated into conventional Korean Medicine treatment (CKMT), including acupuncture, electroacupuncture, and cupping for treating musculoskeletal disorders. Common PPTs include bee venom, blood stasis, Hwangryunhaedok-tang, Jinseng, and Hominis placenta.[10] Several studies have examined the effectiveness and safety of individual types of pharmacopuncture;[11–14] however, no pragmatic clinical trial has evaluated the PPT modality reflecting clinical practice to the best of our knowledge.

This pilot study aimed to assess the feasibility and safety of incorporating PPT with CKMT before conducting a confirmatory clinical trial to validate the add-on effect of PPT in LSS treatment. This study was conducted to determine the possibility of evaluating the addition of PPT to CKMT compared to CKMT alone in improving pain and functional impairment from LSS.

Materials and Methods

Study Design and Participants

Patients diagnosed with LSS identified by the International Classification of Diseases (M48.06) were recruited from the Spine and Joint Center of Pusan National University Korean Medicine Hospital (PNUKH) between April and December 2022. Using a published article's protocol, the study was designed as a pragmatic, randomized, two-parallel, and sex-stratified pilot clinical trial with a 1:1 allocation ratio.[15] This study was approved by the Institutional Review Board of PNUKH (PNUKHIRB 2022-01-002-003) and registered with the Clinical Research Information Service (KCT0007229). We conducted the study in accordance with the Declaration of Helsinki.

Participants were aged 40–80, with LSS signs such as neurogenic claudication and posture-related complaints. The diagnosis was based on a physical examination conducted by certified Korean Medicine doctors, medical history assessment, and imaging evaluation performed by certified radiologists. Individuals with spinal fusion or laminectomy history and those with severe spinal canal defects such as cauda equina syndrome or paralysis were excluded. Before starting the study, all participants voluntarily agreed to the research goals and procedures and signed the informed consent form.

Sample Size Calculation

To ensure robustness in our study design, we conducted a sample size calculation following established guidelines.[16] The recommended pilot trial sample sizes per treatment arm range from 75 to 10, depending on the standardized effect size. Specifically, suggested sample sizes for effect sizes categorized as extra small (≤0.1), small (0.2), medium (0.5), or large (0.8) are 75, 25, 15, and 10, respectively.[16] Considering our expectation that the effect size ranges between small and medium, we determined a sample size of 20 per group.

Randomization and Blinding

Patients were randomized to the control or experimental group. The randomization sequence was generated by an independent statistician who did not participate in the clinical trial interventions or assessments using SAS® version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA). Sex-stratified randomization was used with a block size of four. The block size was concealed from all participants except the statistician until the study ended. The generated randomization table was securely stored in a locked cabinet by the independent statistician.

Considering that PPT was administered exclusively to the experimental group, the researcher performing PPT, and the patients could not be blinded from its allocation information. Therefore, the researchers conducting the CKMT (a common

intervention for both groups) remained blinded to the group information to minimize bias favoring the experimental group. Additionally, an independent researcher performed the PPT. The evaluators were unaware of patient group allocation.

Interventions

Participants assigned to the experimental and control groups were administered PPT in addition to CKMT and CKMT alone, respectively, twice weekly for five weeks.

A professional Korean Medicine doctor with over 10 years of experience administered the PPT (bee venom, Hominis placenta, or bamboo salt) based on clinical features such as spine impairment extent, confirmed via imaging and the pattern of radiating pain in the lower extremities. Each session involved a single pharmacopuncture dose. Pharmacopuncture using 10% sweet bee venom (Kirin Herbal Dispensary, Wonju, Republic of Korea), from which macromolecular substances acting as antigens have been removed, was applied solely to the stenotic lesion level (EX-B2). In cases where participants had hypersensitivity to bee venom, an alternative, such as bamboo salt (Kirin Herbal Dispensary, Wonju, Republic of Korea) or Hominis placenta (Kirin Herbal Dispensary, Wonju, Republic of Korea), was selectively applied. Additional acupoints used in the PPT based on their relevance to symptom management included the GV3, BL23, BL51, BL52, BL32, BL54, GB30, BL39, GB34, BL57, GB39, and Ashi points (Figure 1). The sizes of the pharmacopuncture needles used in the study were: 30 gauge x 12.7 mm, 27 gauge x 38 mm, and 27 gauge x 60 mm. The needle size was selected based on the location of the acupoints. The maximum dose administered per session was 2 mL, which is often used in clinical practice.[8]

CKMT comprised cupping, acupuncture, electroacupuncture, and infrared irradiation. Cupping was applied to the back for 5 min, followed by acupuncture using 0.25 mm x 40 mm or 0.35 mm x 60 mm needles (Dongbang Acupuncture, Dongbang Medical, Seongnam, Republic of Korea). The essential acupoints used was EX-B2 (lumbar region) and other selective acupoints included the GV3, BL23, BL25, BL51, BL52, BL32, BL54, GB30, BL40, BL57, BL39, BL60, SP9, GB34, GB39, and Ashi points. Subsequently, electroacupuncture was applied to EX-B2 using a low-frequency stimulator (ES-160, ITO Co., LTD, Tokyo, Japan) at an alternating frequency of 2–100 Hz for 20 min. An infrared device (Omega-302, ENS Tech., Gwangju, Republic of Korea) was applied during the treatment retention time. Both groups were allowed to take rescue medication (acetaminophen) if necessary.

Outcome Measurements

Feasibility outcomes included intervention completion, follow-up completion, and clinical outcome measurement completion rates for each group. The primary clinical outcome was the mean change in the 100-mm visual analog scale (VAS)[17] score for buttock and leg pain at the primary endpoint (week 5). Secondary outcomes were the clinical relevance,[18] Zurich Claudication Questionnaire (ZCQ),[19,20] self-reported walking capacity,[15] Modified–Modified Schober test,[21] EuroQol

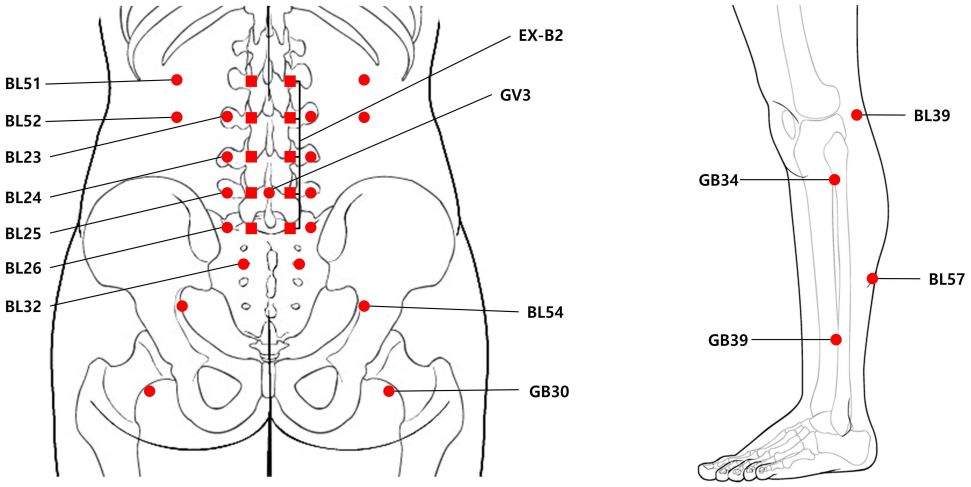

Figure 1 Acupoints Used in Pharmacopuncture Therapy.
Notes: Essential acupoints depending on individual stenotic level; Additional acupoints depending 470 on individual's symptom.

5-dimension 5-level questionnaire (EQ-5D-5L),[22,23] and patients' global impression of change (PGIC).[24] All outcomes except PGIC were measured at weeks 1, 5, 7, and 13, whereas adverse events (AEs) were documented per visit.

Statistical Methods

An independent statistician conducted the statistical analyses using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The significance level was set at $p < 0.05$ for two-tailed tests. The full analysis set (FAS) and per-protocol (PP) were defined as the analysis sets. The FAS included all study participants evaluated at least once after randomization, whereas the PP included those who completed the study without major protocol violations and underwent eight treatment episodes. Missing data in the main outcome analysis were imputed using the multiple imputation method.[25] For confirmatory analysis of the outcomes, analysis of covariance was performed using the baseline values and sex as the covariates. Repeated-measures analysis of variance was conducted to assess trends over time in both groups. Descriptive statistics was used to present the safety analysis, including all study participants who underwent at least one treatment.

Results

Recruitment and Baseline Characteristics

Forty-nine individuals were assessed for eligibility between April and October 2022. Eight patients did not meet the selection criteria, and one patient withdrew consent immediately before the clinical study owing to uncontrolled wrist pain. Ultimately, 40 patients were randomly assigned to the control (n = 20) and experimental groups (n = 20). Figure 2 illustrates the study progression.

Table 1 summarizes the 40 participants' demographic and clinical characteristics. A higher proportion of the study participants were female (75%), with a mean age of 64.7 years (standard deviation (SD): 8.41). The average duration of buttock/leg and low back pain was 60.5 months (SD: 57.19) and 89.7 months (SD: 97.11), respectively. The experimental group had longer durations of buttock/leg and lower back pain than the control group; however, these differences were not significant. No significant differences were observed in other demographic or clinical characteristics between both groups.

Intervention

During the 193 PPT sessions, 59.1% (SD: 2.36), 22.2% (SD: 2.22), and 14.0% (SD: 2.08) of the patients were administered bee venom, Hominis placenta, and bamboo salt, respectively. In the first session, all participants except one with hypersensitivity reactions in the bee venom skin test were administered bee venom pharmacopuncture (Table 2). The initial dose was 0.8–1.0 mL, which was increased to 2.0 mL based on the participant's response. The dose for each bamboo salt and Hominis placenta session was 2.0 mL. The injections were administered intramuscularly in the EX-B2, except for two sessions where subcutaneous injections as weak stimuli were used because of the participant's poor condition. Among intramuscular injections, 93%, 4%, and 3% used 27 gauge x 38 mm, 27 gauge x 60 mm, and 30 gauge x 12.7 mm needles, respectively.

Feasibility Outcomes

Intervention completion rates were 95% and 100% in the experimental and control groups, respectively. Among the three participants who did not complete the follow-up, one withdrew consent during the follow-up, and the remaining participants (one each from the control and experimental groups) were excluded because they underwent invasive treatment to relieve LSS symptoms. One participant in the control group violated the study protocol after the last evaluation owing to treatment disclosure during the follow-up. Therefore, 92.5% and 90% were the clinical outcome measurement and the follow-up completion rates, respectively.

Primary Outcomes

At week 5, the observed mean change in buttock/leg pain, measured using the 100-mm VAS, was −31.5 mm (95% confidence interval (CI): −38.2–−16.4) and −24.3 mm (95% CI: −32.2–−16.4) in the experimental and control groups, respectively. The adjusted mean difference between both groups was 8.0 (95% CI: −1.4–17.4), which was not significant (p =0.094) (Table 3).

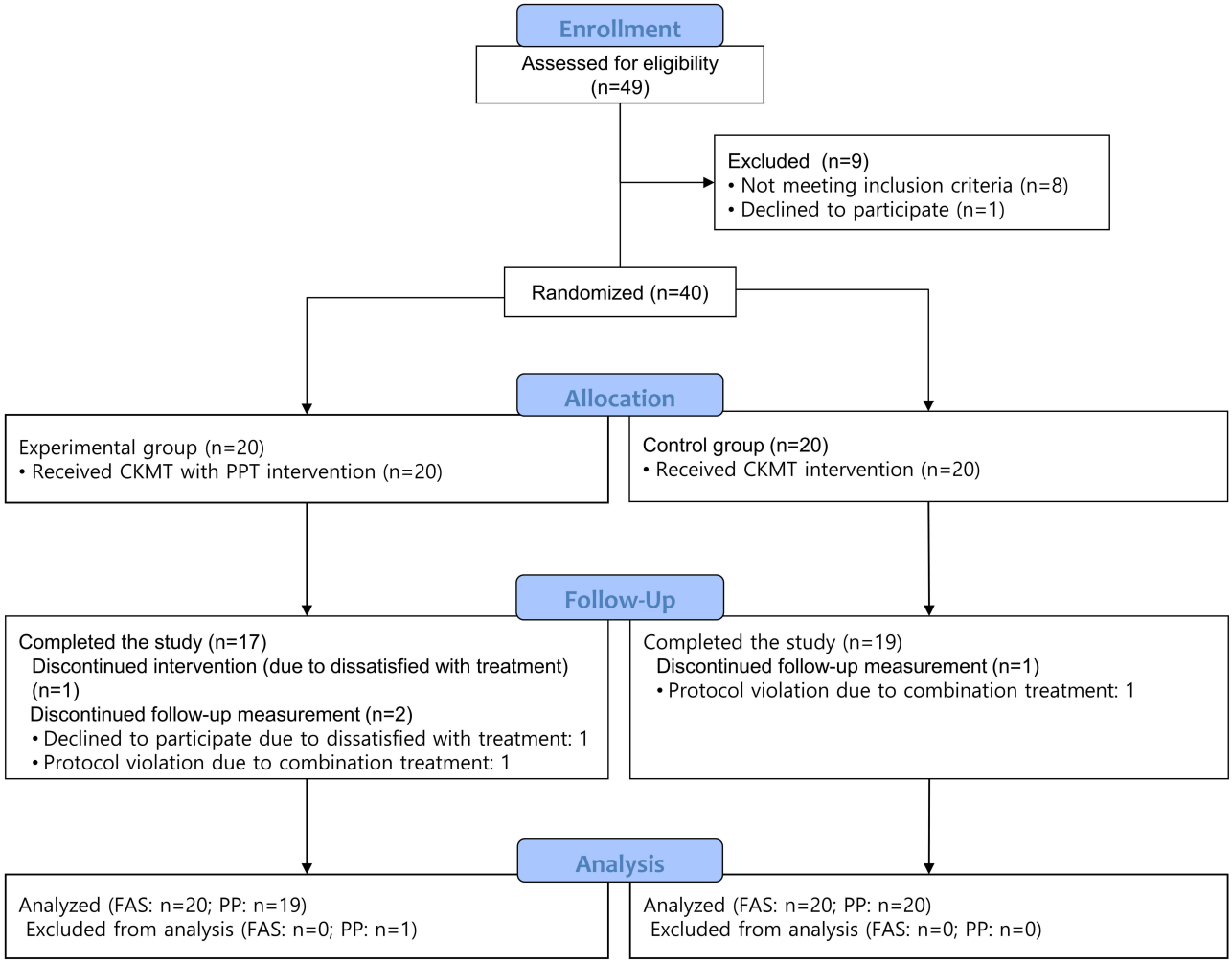

Figure 2 Flow diagram of the study.
Abbreviations: CKMT, conventional Korean Medicine treatment; FAS, full analysis set; PP, per protocol; PPT, pharmacopuncture therapy.

Secondary Outcomes

The mean difference in the 100-mm VAS for low back pain at week 5 (adjusted mean difference: 12.9, 95% CI: 2.4–23.4) revealed a significant difference (Table 3). In addition, the proportion of patients who satisfied the minimum clinically important difference (CID) (Figure 3) was significantly higher in the experimental group (90%) than in the control group (60%). However, no significant differences existed in other secondary outcomes, including ZCQ, self-reported walking

Table 1 Baseline Demographics and Clinical Characteristics

Characteristics	Experimental Group (n=20)	Control Group (n=20)	*p* value
Age, mean (SD), years	65.5 (8.4)	64.0 (8.8)	0.597
Male/Female, n (%)	5 (25) / 15 (75)	5 (25) / 15 (75)	1.000
Body mass index, mean (SD), kg/m^2	24.1 (2.2)	24.0 (3.4)	0.953
Current Smoking, n (%)	1 (5)	1 (5)	1.000
Exercise, mean (SD), hour/week	4.8 (4.6)	6.5 (8.0)	0.665
Work status			
Mostly Sedentary, n (%)	17 (85.5)	18 (90)	1.000
Less Sedentary, n (%)	3 (15.5)	2 (10)	

(*Continued*)

Table 1 (Continued).

Characteristics	Experimental Group (n=20)	Control Group (n=20)	*p* value
Comorbidities			
DM, n (%)	2 (10)	2 (10)	1.000
Knee or hip Osteoarthritis, n (%)	1 (5)	3 (15)	0.605
Osteopenia, n (%)	0 (0)	2 (10)	0.487
LSS Level			
Single-level, n (%)	10 (50)	7 (35)	0.337
Multi-level, n (%)	10 (50)	13 (65)	
LSS Severity			
Mild, n (%)	6 (30)	8 (40)	0.698
Moderate, n (%)	11 (55)	8 (40)	
Severe, n (%)	3 (15)	4 (20)	
LSS Category			
Central stenosis, n (%)	3 (15)	2 (10)	0.796
Lateral stenosis, n (%)	3 (15)	5 (25)	
Both, n (%)	14 (70)	13 (65)	
Other Spinal Problem			
Herniated disc disorder, n (%)	5 (25)	6 (30)	0.723
Spondylolisthesis, n (%)	2 (10)	4 (20)	0.661
Scoliosis, n (%)	1 (5)	1 (5)	1.000
Duration of pain			
Buttock/leg, mean (SD), months	62.2 (61.4)	58.7 (55.8)	0.861
Low back pain, mean (SD), months	103.6 (109.4)	51.0 (88.4)	0.386
Surgery recommendation, n (%)	6 (30)	8 (40)	0.507

Notes: *p* values were calculated using an independent *t*-test, Wilcoxon rank-sum test for continuous variables, or chi-square test and Fisher's exact test for categorical variables.
Abbreviations: DM, diabetes mellitus; LSS, lumbar spinal stenosis; SD, standard deviation.

Table 2 Pharmacopuncture Therapy Status in the Experimental Group

Patient	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										

(*Continued*)

Table 2 (Continued).

Patient	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
13										
14										
15										
16										
17										
18										
19										
20										

Notes: The types of pharmacopuncture administered to patients in each session–bee venom, Hominis placenta, and bamboo salt–are illustrated as light gray, black, and dark gray areas, respectively. The white areas represent unvisited sessions.

capacity, Modified–Modified Schober test, EQ-5D-5L and PGIC (Table 3 and Figure 4). Furthermore, no significant group-time interaction effects on the measured outcomes were observed (Figure 5).

Adverse Events

Table 4 describes AEs that occurred during the trial. During the 193 PPT sessions, five (2.6%) reported AEs due to bee venom pharmacopuncture. Four patients experienced four minor and one moderate AE in 114 bee venom sessions. The

Table 3 Observed Outcomes and Adjusted Group Differences

Variable	Week	Experimental Group (n=19)	Control Group (n=20)	Adjusted Mean Difference (95% CI)	*p* value
VAS					
Buttock/leg	Baseline	60.0 (2.2)	62.0 (3.2)		
	5	28.5 (3.3)	37.7 (3.9)	8.0 (−1.4, 17.4)	0.094
	7	40.0 (4.8)	38.5 (5.4)	−2.5 (−16.5, 11.5)	0.729
	13	33.9 (5.3)	43.1 (5.4)	8.1 (−6.4, 22.7)	0.274
Low back	Baseline	58.0 (4.3)	58.2 (3.7)		
	5	27.2 (4.1)	40.2 (4.7)	12.8 (2.2, 23.3)	0.018*
	7	39.3 (4.8)	42.3 (5.9)	2.9 (−11.5, 17.3)	0.694
	13	33.8 (5.1)	44.5 (5.3)	10.5 (−2.6, 23.6)	0.117
ZCQ					
Symptom	Baseline	21.4 (0.8)	21.3 (0.9)		
	5	15.9 (0.9)	16.3 (0.9)	0.4 (−1.8, 2.7)	0.709
	7	16.6 (1.0)	16.9 (1.2)	0.3 (−2.0, 2.7)	0.779
	13	14.5 (1.3)	17.0 (1.2)	2.5 (−0.9, 5.9)	0.153
Function	Baseline	9.4 (0.4)	9.6 (0.5)		
	5	7.3 (0.4)	7.7 (0.4)	0.2 (−0.9, 1.3)	0.680
	7	7.8 (0.4)	7.8 (0.7)	0 (−1.6, 1.5)	0.954
	13	6.5 (0.4)	7.3 (0.6)	0.7 (−0.7, 2.0)	0.329
Self reported walking capacity (m)	Baseline	1626.6 (219.7)	1718.3 (235.1)		
	5	2086.2 (189.1)	2641.7 (300.8)	507.0 (−112.9, 1126.8)	0.109
	7	2490.7 (332.4)	2479.7 (230.4)	−61.6 (−784.4, 661.2)	0.867
	13	2811.8 (337.5)	2333.7 (247.2)	−501.2 (−1317.1, 314.8)	0.229

(*Continued*)

Table 3 (Continued).

Variable	Week	Experimental Group (n=19)	Control Group (n=20)	Adjusted Mean Difference (95% CI)	*p* value
MMST	Baseline	5.1 (0.3)	4.9 (0.3)		
	5	4.9 (0.2)	4.9 (0.3)	0.14 (−0.47, 0.76)	0.652
	7	5.1 (0.3)	5.0 (0.3)	0 (−0.59, 0.59)	0.995
	13	5.2 (0.2)	4.9 (0.3)	−0.19 (−0.67, 0.28)	0.424
EQ-5D-5L	Baseline	0.68 (0.03)	0.69 (0.02)		
	5	0.77 (0.01)	0.77 (0.02)	0 (−0.04, 0.04)	0.966
	7	0.76 (0.01)	0.77 (0.02)	0.02 (−0.03, 0.06)	0.452
	13	0.79 (0.02)	0.76 (0.02)	−0.03 (−0.09, 0.02)	0.251

Notes: Least squares mean difference and *p* values were analyzed using analysis of covariance (ANCOVA), with the baseline score and sex as covariates and group as the fixed factor. *Significant difference ($p < 0.05$, ANCOVA).
Abbreviations: CI, Confidence interval; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; MMST, Modified-Modified Schober test; VAS, Visual analog scale; ZCQ, Zurich Claudication Questionnaire.

symptoms included itching and pain at the injection site, fatigue, and myalgia, classified as mild AEs that resolved within 10 days. One patient experienced a systemic skin rash within 30 min of the first bee venom pharmacopuncture administration. Ice packs were applied to the affected areas, and the vital signs were continuously monitored to detect abnormalities. After two hours of observation, the rash pattern was alleviated, and the patient reported no symptoms. Out of 200 sessions in the control group, AEs were reported in four (2.0%), including three mild and one moderate. The mild AEs were myalgia, foot numbness, and calf pain, while the moderate AE was fatigue. All reported AEs resolved without complications or additional interventions. Furthermore, no abnormalities were identified when blood tests were compared before and after the intervention.

Discussion

This study determined the feasibility of investigating the add-on effects of PPT on CKMT in patients with LSS. The intervention completion rates, which measure feasibility, were 95% and 100% in the experimental and control groups, respectively. The follow-up and clinical outcome measurement completion rates were 90% and 92.5%, respectively, indicating that the study was feasible. In the experimental group, the rates of improvement in back pain and satisfaction

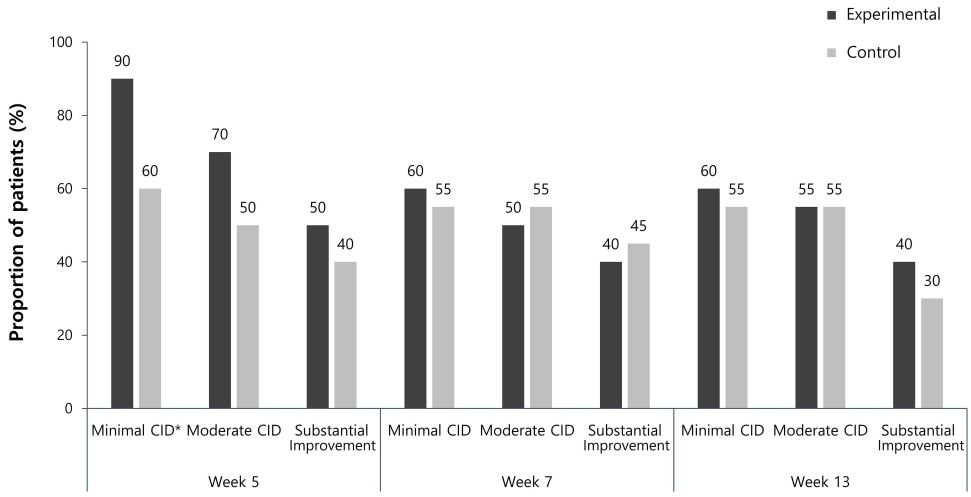

Figure 3 Clinical relevance.
Note: *Significant difference ($p < 0.05$, chi-square test).
Abbreviation: CID, clinically important difference.

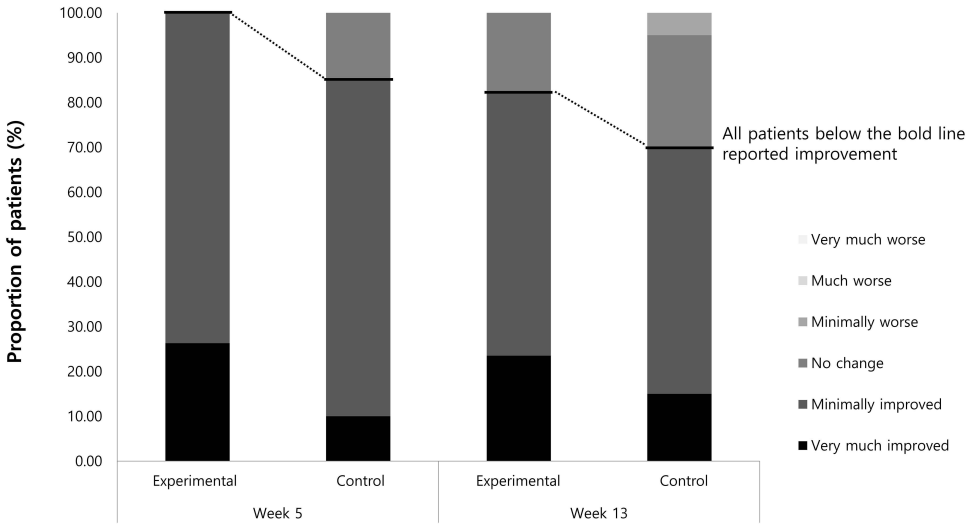

Figure 4 Patient global impression of change.

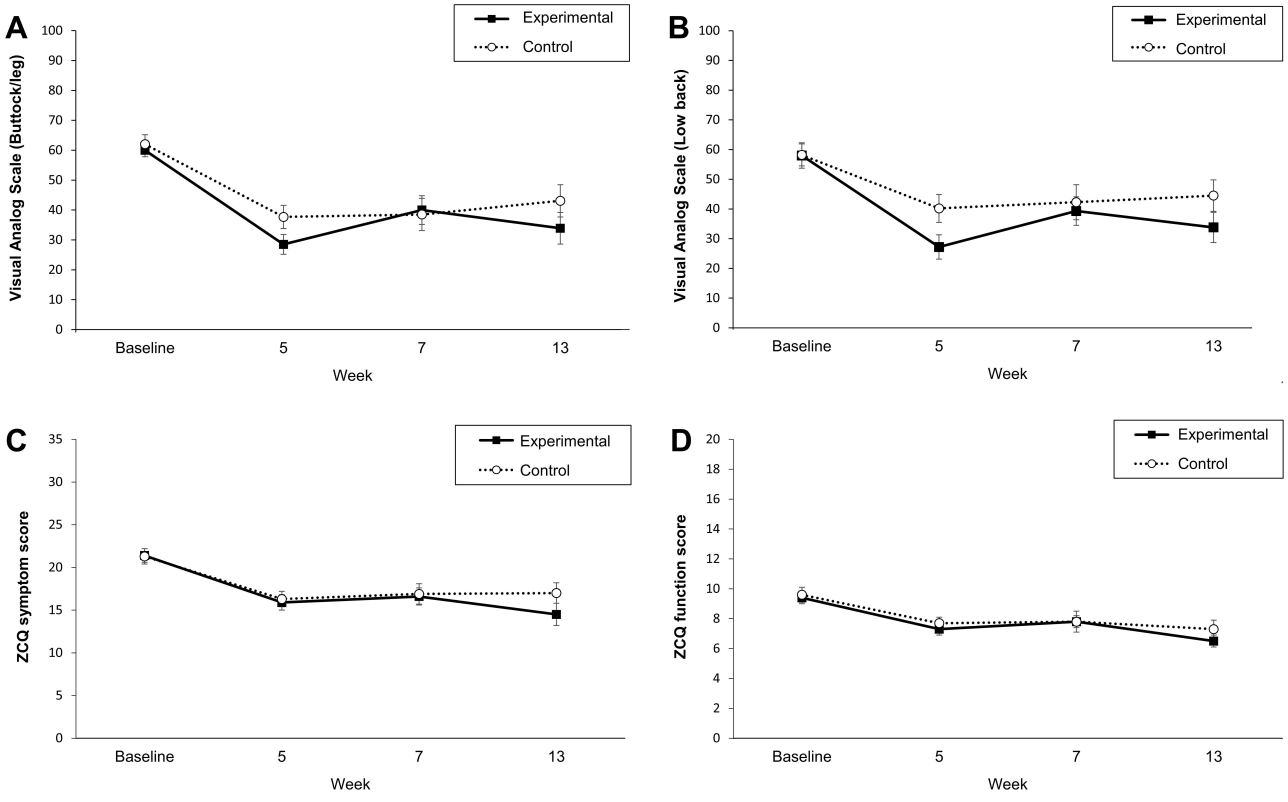

Figure 5 Change over time in the visual analog scale and Zurich claudication questionnaire score. ((**A**) Visual analog scale of buttock/leg pain, (**B**) Visual analog scale of low back pain, (**C**) Zurich claudication questionnaire symptom score, (**D**) Zurich claudication questionnaire function score).
Note: Data are presented as mean ± standard error.
Abbreviation: ZCQ, Zurich Claudication Questionnaire.

with the minimum CID at the end of treatment were significantly different from those of the control group. However, no significant differences existed between both groups in terms of other outcomes.

The difference in the mean change of buttock/leg pain between the groups at five weeks revealed a wide SD range (95% CI: −1.4–17.4), which might necessitate a larger sample size for future studies.[26] This suggests that the treatment

Table 4 Summary of Intervention-Related Adverse Events

Number of sessions with reported adverse events associated with the intervention in the experimental group, n (%)	5 (2.6)†
List of adverse events	
Itching, n (mean duration in days)	1 (3)
Skin rash, n (mean duration in days)	1 (1)
Multiple Myalgia, n (mean duration in days)	1 (2)
Fatigue, n (mean duration in days)	1 (1)
Pain of injection site, n (mean duration in days)	1 (10)
Number of sessions with reported adverse events associated with the intervention in the control group, n (%)	4 (2.0)
List of adverse events	
Myalgia, n (mean duration in days)	1 (3)
Fatigue, n (mean duration in days)	1 (3)
Numbness of foot, n (mean duration in days)	1 (30)
Pain of calf, n (mean duration in days)	1 (5)

Notes: Multiple adverse reports were available. †All adverse events reported in the experimental group were observed subsequent to bee venom pharmacopuncture sessions.

responses may vary significantly among patients. Unmeasured confounding variables such as previous experience with CKMT and expectations of related treatments could influence responses.

In clinical practice, pharmacopuncture is performed based on the patient's symptoms and disease characteristics. Existing studies have primarily assessed the effects of each pharmacopuncture type rather than evaluating them as a comprehensive LSS treatment.[11–14] A randomized controlled study that investigated the effects of bee venom pharmacopuncture on chronic back pain[11] revealed that participants administered twice weekly for three weeks experienced significantly improved pain intensity compared to the sham control group at the end of treatment (mean difference: −0.95, 95% CI: −1.89–-0.01). Another clinical study reported a similar outcome as measured by the VAS in participants who received treatment twice weekly for four weeks compared to the sham control group at the end of treatment (mean difference: −13, 95% CI: −22.81–-3.19).[12] However, no significant differences were observed in pain intensity between the experimental and control groups during the follow-up period in both studies. Here, we applied 10 treatment sessions and observed no significant differences at two and eight weeks, consistent with findings from previous studies. Nevertheless, the differences between both groups increased over time in the ZCQ, EQ-5D-5L, and self-reported walking capacity (Table 3). Considering that LSS treatment duration is longer than that for chronic back pain; therefore, factors such as Hominis placenta and bamboo salt, in addition to bee venom pharmacopuncture, or an increased number of treatments may have influenced the changes in symptoms and function.

Bee venom, Hominis placenta and bamboo salt pharmacopuncture are commonly used for pain relief and functional recovery in patients with musculoskeletal disorders.[9] Bee venom pharmacopuncture is obtained by processing venom extracted from the venom sac of honeybees (*Apis mellifera*). Melittin, a key component of bee venom, has been reported in previous studies to inhibit signaling pathways such as toll-like receptor (TLR) 2, TLR 4, and cluster of differentiation 14, reducing the expression of inflammatory mediators. Additionally, research has suggested that bee venom, through the regulation of iron metabolism, inhibits M1 (pro-inflammatory) differentiation of macrophages while promoting M2 (anti-inflammatory) differentiation, thus suppressing pain induced by LSS.[27,28] Hominis placenta pharmacopuncture has been shown to regulate inflammatory cytokines and reduce the infiltration of inflammatory cells.[29,30] It has also been reported to contribute to the regeneration of damaged nerve cells by regulating protein synthesis.[31] The study on bamboo salt pharmacopuncture is not as extensive compared to studies on bee venom pharmacopuncture and Hominis placenta pharmacopuncture. However, a study has been reported suggesting that when injecting hypertonic saline into the peripheral coccygeal area in chronic low back pain patients, it may affect the decrease in intradiscal pressure within the peripheral coccygeal area, influencing the relief of nerve entrapment.[32] There is also research indicating that injecting

saline solution with concentrations ranging from 1.5% to 7.0% could block C-fibers mediating pain.[33] Although the bamboo salt pharmacopuncture used in this study is at a concentration of 2% NaCl, which might be expected to have similar effects, directly applying the results from preclinical studies to clinical research has limitations. Therefore, further clinical studies are necessary to verify its effects.

Intervention-related AEs were reported in 2.6% and 2.0% of the sessions in the experimental and control groups, respectively. The collection of AEs in this study utilized open-ended questions instead of a standardized checklist, which may have introduced limitations in the completeness of AE reports.[34] However, independent evaluators exhaustively inquired concerning AEs at every visit to ensure a thorough safety assessment. Furthermore, they actively monitored the participants' progress and provided additional treatments to address their symptoms, further enhancing the safety measures implemented in the study. Despite the negative skin tests, one case of moderate systemic skin rash caused by bee venom was reported. Retrospective chart analysis revealed that the incidence of bee venom-related systemic immune responses is 0.02–0.234% in clinical practice.[35,36] A systematic literature review indicated that bee venom pharmacopuncture increased the relative risk of AEs by 2.6 times compared to normal saline injection.[37] Furthermore, this study reaffirmed the potential risk of a systemic hypersensitive immune response despite using sweet bee venom and its application.

Here, stratification by sex was implemented, with the male-to-female ratio being equally assigned based on previous research indicating that females exhibit higher sensitivity to back and lower extremity pain when adjusted for age and intervertebral disc degeneration.[38] Our study revealed no significant differences in the location, severity, and type of stenosis between both groups. However, the correlation between the degree of stenosis observed in magnetic resonance imaging scans and patient-reported symptoms remains debatable.[39] Underlying factors, such as diabetes, low bone density, and high body mass index,[40,41] associated with LSS symptom severity, did not differ significantly between the groups. In cases of LSS accompanied by scoliosis, conservative treatment yielded a limited response and increased complaints.[42] Therefore, imaging tests were used to identify spinal diseases other than LSS, and no significant differences existed between both groups.

This study had several limitations. First, owing to the characteristics of the pharmacopuncture intervention, blinding the patients was impossible, resulting in a bias in favor of the experimental group that underwent additional treatment. Measures were taken to minimize bias, and the evaluator of the study outcomes was unaware of the AE evaluations, further minimizing the potential impact on the study results to mitigate these issues. Secondly, this study adopted a pragmatic approach and did not select a sham control group for the intervention. Moreover, the intervention method might have been influenced by operator preference, resulting in variations in acupoints, insertion method, and pharmacopuncture type selection. Third, the sample size was small, and the follow-up period was short to comprehensively evaluate our findings.

Despite these limitations, this study is profound, as it is the first preliminary investigation to examine the feasibility of using PPT as an additive treatment for patients with LSS. Furthermore, it demonstrated its feasibility by exhibiting a high intervention and completion rate for clinical outcome measurements with low AE incidence.

Conclusions

This randomized, controlled pilot trial demonstrated that PPT could be incorporated as an add-on treatment in patients with LSS. This study provides insights for future investigations to enhance the efficacy and safety of PPT for LSS treatment. Future research with adequate sample sizes, optimal intervention and follow-up periods, well-designed eligibility criteria, and systematic adverse event response protocols are crucial to evaluate the add-on effects of PPT on LSS.

Abbreviations

AE, adverse event; CI, confidence interval; CKMT, conventional Korean medicine treatment; CT, computed tomography; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FAS, full analysis set; LSS, lumbar spinal stenosis; MMST, Modified-Modified Schober test; PNUKH, Pusan National University Korean Medicine Hospital; PP, per-protocol; PPT, pharmacopuncture therapy; SD, standard deviation; VAS, visual analog scale; ZCQ, Zurich Claudication Questionnaire.

Data Sharing Statement

The datasets are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the current manuscript, 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

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