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Original Article

Pharmacopuncture therapy for adhesive capsulitis: A pragmatic randomized controlled pilot study

Doori Kim [a], Kyoung Sun Park [b], Sun-A Kim [c], Ji Yeon Seo [d], Hyun-Woo Cho [e], Yoon Jae Lee [a], Changsop Yang [f], In-Hyuk Ha [a,*], Chang-Hyun Han [f,g,*]

[a] Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, Seoul, Republic of Korea
[b] Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea
[c] Daejeon Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea
[d] Bucheon Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea
[e] Haeundae Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea
[f] KM Science Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea
[g] Korean Convergence Medical Science, Korea Institute of Oriental Medicine School, University of Science & Technology, Daejeon, Republic of Korea

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ABSTRACT

Background: Although several studies have reported the effectiveness of acupuncture treatment for adhesive capsulitis (AC), research on pharmacopuncture therapy for AC remains limited. We compared the effectiveness and safety of pharmacopuncture and physiotherapy for AC.

Methods: This pragmatic, randomized, controlled, parallel-group pilot study enrolled patients with limitations of shoulder movement and a numeric rating scale (NRS) score for shoulder pain ≥5 randomized (1:1) to the pharmacopuncture therapy (PPT) and physiotherapy (PT) groups. Treatment sessions were administered twice weekly for 6 weeks, and the participants were followed up for 13 weeks after randomization. The primary outcome was the NRS score for shoulder pain, and the secondary outcomes were the visual analog scale (VAS), Shoulder Pain and Disability Index (SPADI), range of motion (ROM), patient global impression of change (PGIC), EuroQol 5-Dimension 5-Level (EQ-5D-5L), and Short Form 12 Health Survey (SF-12) scores. The intention-to-treat (ITT) analysis was set as the primary analysis.

Results: Among 50 participants, for the primary endpoint (week 7) the PPT group showed a significantly superior improvement in NRS, VAS, SPADI, ROM for flexion, ROM for abduction, and EQ-5D-5L scores. The ROM for extension, ROM for adduction, physical component summary, and patient global impression of change were significantly better in the PPT than in the PT group, and these effects were sustained until week 13.

Conclusion: In this pilot study, PPT showed better effects than PT, confirming the feasibility of a follow-up main study.

Trial registration: Clinicaltrials.gov (NCT05292482) and cris.nih.go.kr (KCT0007198).

1. Introduction

Shoulder pain is a common musculoskeletal problem and it confers substantial burdens in terms of the severity of pain and cost.[1] Shoulder joint pain is related not only to pain but also to quality of life, including functional disabilities and emotional problems.[2,3] Adhesive capsulitis (AC) is one of the most common cause of shoulder pain, and AC incurs the highest medical treatment cost.[4] AC (also known as "frozen shoulder") involves adhesions within the glenohumeral joint, including the synovium and joint capsule, and is mainly characterized by scapulohumeral pain, stiffness, and reduced range of motion (ROM) in the affected shoulder.[5] AC occurs in 2 %–5 % of the general population and more frequently in women aged 40–60 years.[5,6] In general, AC progresses through three phases, starting from a painful phase through stiffness to a recovery phase that typically requires 1–2 years for complete resolution of the symptoms.[7] Nonetheless, AC may induce persistent pain and functional loss.[8,9]

Conservative treatments that are commonly used to manage AC include pain relief with nonsteroidal anti-inflammatory drugs (NSAIDS), oral corticosteroids,[10,11] intra-articular injections,[12,13] physiotherapy or exercise therapy,[14,15] hydrodilatation,[16,17] and nerve blocks.[18,19] In Korean clinical practice, patients with AC may receive various injectable

* Corresponding authors at: Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, 2F Vision Tower, 540 Gangnam-daero, Gangnam-gu, Seoul, Republic of Korea (I.-H. Ha); Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea (C.-H. Han)
E-mail addresses: hanihata@gmail.com (I.-H. Ha), chhan@kiom.re.kr (C.-H. Han).

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treatments, including prolotherapy, wherein small amounts of concentrated glucose (hypertonic dextrose),[20] polydeoxyribonucleotide injections,[21] and injectable collagen[22] are administered. In some cases, surgical intervention, such as arthroscopic capsule release,[23,24] is a treatment option.

Physiotherapy is a representative non-invasive treatment that has been traditionally used for AC.[7] There are a variety of physiotherapy methods, including manual therapy, electrotherapy, and laser therapy, and a lot of research has been done on them.[14,25] In Korea, AC patients also frequently use physical therapy, especially electrotherapy and heat therapy.[26] In addition, in Korea, many patients avail traditional Korean medicine (KM) for the treatment of AC. In 2021, shoulder lesions (Korean Standard Classification of Diseases diagnosis code M75) ranked ninth among diseases treated with KM, and approximately 580,000 patients received KM treatment for shoulder pain.[27] Among the various KM modalities, pharmacopuncture remains one of the most commonly used treatments and constitutes a combination therapy that encompasses traditional acupuncture and herbal medicine.[28] In pharmacopuncture, herbal medicine extracts are injected with a syringe into acupoints, and the physical stimulation of acupuncture and the chemical and pharmacological actions of the pharmacopuncture solution are combined for maximal therapeutic effect.[29,30] Although several studies have reported the effectiveness of acupuncture treatment for AC,[31,32] research on pharmacopuncture therapy for AC remains limited.

A randomized controlled trial (RCT) that evaluated the clinical effectiveness of bee venom (BV) acupuncture for AC[33] and a literature review of various types of pharmacopuncture therapies, such as Ai-Tong-Shu, Danxiang injection, and Fufang-Danggui injection, reported the effectiveness of these therapies for alleviating pain and functional disability in patients with AC.[34] However, no studies have investigated the effectiveness of the pharmacopuncture therapy strategy for the treatment of AC, rather than a specific type of pharmacopuncture. The previous studies conducted to date had a low level of quality in terms of research methodology and limitations, such as small sample sizes.

Therefore, in this study, physiotherapy was used as a comparison group to evaluate the pharmacopuncture strategy in real-world clinical settings for patients with AC. This study was a pilot study for the above purpose and was conducted to confirm the feasibility of a follow-up main study.

2. Methods

2.1. Study protocol

This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines, and all study-related documents, including the protocol, were approved by the Institutional Review Board (IRB) of the Jaseng Hospital of Korean Medicine prior to patient recruitment (JASENG 2022-02-013, JASENG 2022-02-014, JASENG 2022-02-015, and JASENG 2022-02-016). The protocol was registered at Clinicaltrials.gov (NCT05292482) and cris.nih.go.kr (KCT0007198).[35]

2.2. Study design

In this pragmatic randomized controlled parallel-group pilot study, 50 patients with complaints of AC were randomly assigned (1:1) to a pharmacopuncture therapy (PPT) or a physiotherapy (PT) group at four Korean Medicine Hospitals in Korea. Treatment sessions were administered twice weekly for a total of 6 weeks, and the participants were followed up for 13 weeks after randomization (Supplement 1).

2.3. Participants

The participants were recruited from four KM hospitals.The investigators fully explained fully explain the study-related information (effects, adverse events [AEs], and safety) to the participants one-on-one, and obtained written informed consent from the participants.

2.3.1. Inclusion criteria

The inclusion criteria to determine eligibility for study participation were as follows: (1) measurable limitations in shoulder movement (active or passive); (2) a numeric rating scale (NRS) score of shoulder pain ≥5; (3) persistence of the above-described symptoms for more than 1 month; (4) individuals with no special findings in various physical examinations (Drop arm test, Neer test, Empty can test, Hawkins test, O'Brien test, Bicepts load test) and X-ray examinations; (5) age 19–69 years; and (6) patients who received a detailed explanation about the study, fully understood the content, voluntarily decided to participate in the study, and signed an informed consent form, confirming their consent to comply with the study-related instructions. X-ray reading was performed by radiologists, and along with the above findings, the AC diagnosis of all patients was judged by an expert, Korean medicine doctor (KMD).

2.3.2. Exclusion criteria

The exclusion criteria were as follows: (1) diagnosis with a specific, serious disease that may cause shoulder pain (e.g., acute fracture and shoulder dislocation); (2) pain caused by other diseases and unrelated to shoulder lesions (e.g., tumor, fibromyalgia, rheumatoid arthritis, gout, and cervical herniated nucleus pulposus); (3) diagnosis with other chronic diseases (e.g., stroke, myocardial infarction, kidney disease, diabetic neuropathy, dementia, and epilepsy) that may interfere with the interpretation of therapeutic effects or outcomes; (4) patients receiving steroids, immunosuppressants, psychotropic medication, or other medications that may affect the clinical outcomes; (5) cases where the administration of pharmacopuncture therapy may be inappropriate or unsafe, such as in those with hemorrhagic disease, taking anticoagulant drugs, or patients with severe diabetes mellitus having an increased risk of infection; (6) patients who took medications, such as NSAIDs, that may affect pain or received pharmacopuncture therapy or physiotherapy within 1 week; (7) pregnant or lactating women and those who planned to conceive; (8) patients who had undergone shoulder surgery within 3 months; (9) patients who had completed an interventional schedule of another clinical study within 1 month, had participated in another study within 6 months from the date of screening, or planned to participate in other trials during the follow-up period of this study; (10) patients who did not sign the informed consent form; and (11) individuals whose participation in the study was deemed inappropriate according to the judgment of the investigators.

2.4. Randomization and blinding

Participants who were screened using the inclusion/exclusion criteria and signed the informed consent form were allocated to either of the two groups using a randomization table (1:1 allocation) that was generated in advance by a statistician using R Studio 1.1.463 (© 2009–2018 RStudio, Inc.). Block randomization was performed to generate random sequences, and the size of each block was randomly set to two or four. The randomization results were sealed in opaque envelopes and stored in a double-locked cabinet. An investigator at each study institution opened the envelope, including the randomization information, in front of each patient to assign the patient to one of the two groups. The randomization number assigned to each participant was recorded using an electronic chart.

Since the study design did not permit blinding, we implemented assessor blinding only. Assessors who did not participate in the intervention remained unaware of group assignments and conducted the pre-intervention assessments in a separate area.

2.5. Interventions

2.5.1. Pharmacopuncture

Pharmacopuncture therapy was administered twice per week for a total of 6 weeks. The type of pharmacopuncture solution was not determined in advance but was selected based on the clinical judgment of the KMD, depending on the conditions of the individual patients. The intervention was administered by a KMD with more than 5 years of clinical experience, and all detailed information, such as the pharmacopuncture solution used and acupoints selected, was recorded in the chart.

2.5.2. Physiotherapy

Physiotherapy was administered twice per week for a total of 6 weeks. The method of physiotherapy, area of application, and duration of treatment were selected based on the physician's clinical judgment, depending on the patient's symptoms, radiological findings, and degree of improvement. Detailed information, including the type, frequency, and applied area of physiotherapy, was recorded in the chart.

2.6. Outcome measures

2.6.1. Primary outcome

The NRS score for shoulder pain was the primary outcome measure. The NRS is a numeric scale that facilitates objective assessment of pain, which is a subjective sensation felt by individual patients. The NRS was used to assess the severity of pain experienced by the patient since the last visit. Patients chose a number from 0 to 10 (0 for no pain and 10 for the worst pain imaginable), which best represented the level of discomfort felt at the time of assessment.[36-38] The NRS scores were measured at every visit (twice a week for Week1-Week6, Week7, and Week13), for a total of 14 assessments.

2.6.2. Secondary outcomes

2.6.2.1. Shoulder pain visual analog scale (VAS). The VAS uses a 100-mm line, with one end indicating no pain and the other end indicating the worst imaginable pain. The patients choose a point on the line to indicate the intensity of the pain that they experience. The participants selected one point on the line to indicate the intensity of their shoulder pain since their last visit. The VAS assessment was performed eight times in total at the following timepoints: every week during the intervention period (Week1-Week6), Week7, and Week13. Outcomes measure once a week from Week1 to Week6 were measured at the first visit.

2.6.2.2. ROM. Passive ROM was assessed by measuring the angle between the patients' upper limbs and an imaginary line drawn perpendicular to the ground at the maximum range of passive movement. ROM was measured eight times in total at baseline, every week during the intervention period (Week1-Week6), Week7, and Week13.

2.6.2.3. Shoulder pain and disability index (SPADI). The SPADI is a 13-item questionnaire developed to assess shoulder pain and dysfunction. Each item is rated at 10 levels, and the scale consists of pain and disability subscales of five and eight items, respectively. Higher scores indicate a greater degree of disability. This study used a validated Korean version of the SPADI questionnaire.[39] It was measured three times in total at Week1, Week 7, and Week 13.

2.6.2.4. Patient global impression of change (PGIC). The PGIC is a method for the subjective assessment of the level of improvement. A 7-point Likert scale is used to rate the post-treatment improvement in functional limitations (1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse).[40] The PGIC was measured twice at Week 7 and Week 13.

2.6.2.5. Short form-12 health survey version 2 (SF-12 v2). The SF-12 v2 consists of 12 items for the assessment of health-related quality of life (HRQoL) based on eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Higher scores indicate higher HRQoL.[41] The reliability and validity of the Korean version of the SF-12 were assessed. The SF-12 v2 was administered three times in total at Week1, Week7, and Week 13.

2.6.2.6. 5-Level EuroQoL -5 dimension (EQ-5D-5L). The EQ-5D-5L is a method for the indirect estimation of the quality weight of a specific health state that uses pre-assigned scores based on preference weights for each functional level after the assessment of the health state in multiple dimensions. It is commonly used to assess quality of life in five dimensions: mobility, self-care, usual activities, pain, and anxiety/depression. Each item is rated on a 5-point Likert scale, and the overall score runs from 0 to 1, with higher scores indicating a better quality of life. The Korean version of the EQ-5D-5L, which has been validated in a previous study,[42] was used in this study. The EQ-5D-5L was administered three times in total at Week1, Week7, and Week 13.

2.6.2.7. Drug consumption. Information on the types and doses of drugs (medications prescribed for the present illness or rescue medications) administered during the study period was collected using a questionnaire at each visit. Besides drugs that were administered orally, other therapies such as injections were recorded in terms of the number of administrations. The drug-consumption status was assessed at each visit.

2.7. Sample-size calculation

No previous study has compared the effectiveness of pharmacopuncture and physiotherapy in patients with AC that could have been used as a basis for estimating the target sample size in this study. This pilot study aimed to determine the feasibility of follow-up studies. Accordingly, 15 participants, the minimum sample size required for a pilot study, were assigned to each group.[43] Assuming a dropout rate of 25 % and considering subgroup analyses, 50 participants (25 in each group) were recruited.

2.8. AEs

For safety assessment, the following tests were performed, before and after treatment, in both the PPT and PT groups, and the results were used for intergroup comparisons of AE occurrence: hematology (WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBC, Hgb, Hct, MCV, MCH, MCHC, platelets, and ESR), clinical chemistry (T-protein, albumin, T-bilirubin, ALP, AST, ALT, r-GTP, BUN, and creatinine), and C-reactive protein (CRP).

AEs refer to any unfavorable and untoward signs (e.g., abnormality in the results of laboratory tests), symptoms, or diseases that manifest after interventional procedures during the study period. The definition of AEs includes events that have no causal relationship with the intervention. In this study, all AEs were collected at each visit and recorded in the case report forms (CRFs). According to Spilker's criteria[44] and internal meetings of investigators, the severity of all AEs was classified under three levels as follows: Mild (1): symptoms requiring no additional treatment without disruption to the participant's normal activities of daily living (ADL; or functions), causing minimal discomfort; Moderate (2): symptoms causing a significant disruption to the participant's normal ADLs (or functions), which may require treatments and disappear over time when additional treatment is applied; and Severe (3): symptoms causing a serious disruption to the participant's normal ADLs (or functions), requiring advanced treatment due to severity of the symptoms and resulting in sequelae even after treatment. For the assessment of causality between the intervention and the AEs, the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality scale[45] was

used for classification as follows: (1) definitely related, (2) probably related, (3) possibly related, (4) probably not related, (5) definitely not related, and (6) unknown.

2.9. Statistical analysis

In this study, the intention-to-treat (ITT) analysis was set as the primary analysis. The sociodemographic characteristics and treatment expectations of the participants were evaluated for each group. Continuous variables were expressed as mean (standard deviation) or median (quartile), and intergroup differences were compared using the independent *t*-test or Wilcoxon rank-sum test, depending on the distribution. Categorical variables were expressed as frequencies (%), and intergroup differences were compared using the chi-square or Fisher's exact test.

Regarding the outcome measures in this clinical study, the difference in change in continuous outcomes from baseline levels for each time point between the two groups was evaluated. For the primary analysis, analysis of covariance was used with adjustments for baseline values of each outcome. Missing values were imputed with multiple imputation. Three sensitivity analyzes were conducted. First, the per-protocol (PP) analysis was performed that included only participants who underwent treatment sessions at least nine times during the 6-week intervention period. Missing values were imputed with multiple imputation. Second, a linear mixed model was performed with the baseline of each outcome as a covariate and the group as a fixed factor. Missing values were handled with the Mixed Models for Repeated Measures. Third, the last observation carried forward was used to impute missing values. Furthermore, AUCs were calculated from randomization to the last follow-up period, and the cumulative outcome values of the two groups were compared using the Student's *t*-test.

In addition, the number of patients (%) was compared between the two groups at each timepoint where the NRS and VAS scores and shoulder pain outcomes decreased to not more than half of the baseline values. Kaplan–Meier curve was used for survival analysis to compare the time until shoulder pain "recovery" was achieved, with the values of pain outcomes decreasing to less than half of the baseline after randomization, and the curves were compared using the log-rank test. Hazard ratios were compared between the two groups using the Cox proportional hazards model. In this study, the significance level was set at 0.05, and SAS 9.4 (© #SAS Institute, Inc., Cary, NC, USA) and R Studio 1.1.463 (©2009–2018 RStudio, Inc.) were used for the analyses.

2.10. Data management and monitoring

This study used an electronic case report form (e-CRF) based on the online clinical research management systems operated by the Korea Centers for Disease Control and Prevention. Prior to the commencement of the study, training was provided to the investigators at each study institution on the developed standard operating procedures and e-CRF data recording guidelines. Data entered into the e-CRF were locked and concealed from all investigators, except for the personnel who were in charge of data management. In addition, monitoring was conducted five times to ensure the safety of the participants and the completeness of the study data.

3. Results

3.1. Participants

A total of 50 participants were recruited between April and September 2022. After randomization, 24 and 26 patients were allocated to the PPT and PT groups, respectively, and the same number of participants in each group was included in the ITT analysis (Supplement 8). The baseline characteristics of the study participants are presented in Table 1. No intergroup difference was observed in any of the baseline characteristics.

3.2. Treatment

Details of the treatments received by the two groups during the intervention period are summarized in Supplement 2. In the PPT group, pharmacopuncture therapy was administered to all participants, and the average number of treatment sessions was 11.2 ± 2.3 per participant. Regarding the types of pharmacopuncture administered, Shinbaro2 pharmacopuncture was used for all patients in the PPT group, and Shinbaro3 pharmacopuncture for 13 patients (54.2 %). In addition, Hominis placenta and Hwangryunhaedok-tang were used in some cases. SI9 and SI15 acupuncture points, located on the shoulders, were used most frequently (n = 21, 87.5 %) in the PPT group.

The PT group received an average of 11.7 ± 0.9 PT sessions per participant, of which interferential current therapy and deep heat therapy were administered in 22 participants (84.6 %), and other types of PT used included laser therapy, hot pack, transcutaneous electrical nerve stimulation, and extracorporeal shock-wave therapy.

3.3. Outcome changes

At week 7, which corresponded to 1 week after the end of the intervention period, the PPT group showed significantly superior outcomes to the PT group for NRS, VAS, SPADI, ROM (flexion, extension, abduction, and adduction), EQ-5D-5L, physical component summary (PCS), and PGIC scores. Furthermore, these improvements were sustained until week 13 of follow-up for most outcomes (Table 2, Supplement 3 and Fig. 1). The results showed similar trends in the PP and sensitivity analyses (Supplement 4–6). At week 7, the difference in outcome changes between the two groups was 2.21 (95 % confidence interval [CI] 1.24–3.19, $p < 0.001$) for the shoulder pain NRS, 22.27 (95 % CI 11.31–34.03, $p < 0.001$) for the total SPADI score, and -18.56 (95 % CI -30.70 to -6.42, $p < 0.001$) for ROM for flexion.

In the AUC analysis comparing the 12-week cumulative measurements for each outcome, the PPT group showed a significant difference in improved outcomes compared with the PT group based on the NRS, VAS, SPADI, ROM (flexion, extension, abduction, and adduction), EQ-5D-5L, PCS, and PGIC scores (Table 3).

3.4. Survival analysis

A decrease in NRS scores by 50 % or more was considered "recovery," and survival analysis was conducted based on the assumption. The recovery rate from shoulder pain was significantly faster in the PPT group than that in the PT group (log-rank test, $p < 0.001$). Median survival time was 16 [14–3] days in the PPT group and 60 [34–NA] days in the PT group, and the hazard ratio was 3.71 (95 % CI 1.84–7.47) (Fig. 2).

3.5. Safety

No AE indicating causality with the intervention was observed in either group. In the PPT group, three AEs, including headache, cystitis, and coronavirus disease, were observed. However, the causal relationship with the intervention was classified as "unlikely" for all the events. In addition, all three participants recovered completely after medication.

Furthermore, all the participants underwent blood tests before and after treatment, and no significant intergroup differences were found in the blood test results (Supplement 7). Although the eosinophil counts significantly differed between the two groups after treatment, the difference was attributable to the fact that two patients in the PPT group who were in the not clinically significant range before treatment did not undergo the post-treatment blood test.

Table 1
Baseline characteristics of the participants.

	PPT (n = 24)	PT (n = 26)	P-value*
Sex			
Female	14 (58.3)	14 (53.8)	0.973
Male	10 (41.7)	12 (46.2)	
Age (years)	53.9 (8.6)	53.7 (7.5)	0.923
Height (cm)	164.7 (6.9)	166.0 (6.8)	0.503
Weight (kg)	65.3 (13.3)	66.4 (14.4)	0.785
BMI (kg/ m^2)	24.0 (4.1)	23.9 (3.8)	0.953
Hypertension (%)	7 (29.2)	5 (19.2)	0.624
Hyperlipidemia (%)	3 (12.5)	2 (7.7)	0.6613
Diabetes mellitus (%)	1 (4.2)	1 (3.8)	1
Pain site			
Left	7 (29.2)	6 (23.1)	0.867
Right	17 (70.8)	20 (76.9)	
Months from onset	22.1 (52.9)	21.8 (25.3)	0.981
Degeneration	3 (12.5)	7 (26.9)	0.2938
Calcification	4 (16.7)	1 (3.8)	0.1815
Osteopenia	2 (8.3)	1 (3.8)	0.602
Prior medications	3 (12.5)	5 (19.2)	0.7041
Treatment expectancy_pharmacopuncture therapy	7.4 (1.1)	7.5 (1.1)	0.688
Treatment expectancy_usual care	5.6 (1.4)	5.8 (1.4)	0.581
NRS	6.8 (1.0)	6.7 (0.8)	0.941
VAS	69.0 (10.3)	68.1 (9.0)	0.737
SPADI			
Pain	68.7 (12.6)	72.7 (9.8)	0.213
Function	58.8 (16.1)	64.8 (12.7)	0.148
Total	62.6 (14.0)	67.8 (11.0)	0.145
ROM			
Flexion	138.8 (29.6)	124.8 (36.1)	0.144
Extension	36.0 (17.4)	32.9 (16.1)	0.508
Abduction	121.0 (31.9)	101.0 (30.6)	0.028
Adduction	44.0 (22.5)	38.1 (19.1)	0.323
Internal rotation	53.8 (20.5)	50.4 (23.4)	0.592
External rotation	45.0 (18.4)	40.4 (21.0)	0.415
EQ-5D-5L	0.6 (0.2)	0.6 (0.1)	0.715
PCS	41.2 (6.2)	43.1 (6.2)	0.269
MCS	42.0 (12.4)	42.1 (10.6)	0.98

* *P*-value was calculated using the chi-square test or Fisher's exact test.BMI, body mass index; EQ-5D-5L, EuroQoL 5-dimension 5-level instrument; MCS, mental component summary; NRS, numeric rating scale; PCS, physical component summary; PPT, pharmacopuncture therapy; PT, physiotherapy; ROM, range of motion; SPADI, Shoulder Pain And Disability Index; VAS, visual analogue scale.

4. Discussion

In this study, although both pharmacopuncture and physiotherapy strategies showed significant clinical effectiveness for the treatment of AC, pharmacopuncture therapy had superior effects for reducing pain, improving functional disability, and improving quality of life. In the PPT group, the NRS scores decreased significantly, from 6.8 ± 1.0 (pre-treatment) to 1.63 (95 % CI 0.91–2.36) (post-treatment), and the inter-group difference in scores was more than 2 points, which is larger than 1–2 points the score of minimal clinically important difference (MCID) used in the assessment of chronic pain and shoulder pain.[46-48] Furthermore, functional outcomes showed a significant improvement from approximately 60 points (pre-treatment) to 20 points (post-treatment) Further, the limitations in ROMs also showed significant improvements.

As discussed above, the results of this study confirmed significant improvements in pain and functional outcome scores in the PPT group. Although few studies have reported the effect of pharmacopuncture therapy in the treatment of AC, most of them have shown that pharmacopuncture therapy is effective for AC. In a literature review of clinical studies on pharmacopuncture therapy for AC that included nine clinical trials, pharmacopuncture therapy was concluded to be effective for pain relief and functional improvement.[34] In particular, in one RCT that compared the effects of BV acupuncture and normal saline,[33] after 8-week treatment, the SPADI and VAS scores in the BV group decreased from 62.55 ± 11.50 to 23.15 ± 12.82 and from 6.59 ± 1.76 to 2.66 ± 1.69, respectively, indicating a comparable improvement to the outcomes in this study. However, in another clinical study that compared the effectiveness of Scolopendrid pharmacopuncture and acupuncture,[49] after 10 pharmacopuncture treatment sessions, the VAS and SPADI scores decreased from 6.74 ± 2.28 to 3.39 ± 0.94 and 71.65 ± 22.03 to 49.87 ± 18.37, respectively, showing relatively smaller changes in the outcomes. Such differences in outcome changes or improvements may be caused by diverse factors, such as the type and volume of pharmacopuncture solution administered and the number of treatment sessions. Additional studies are needed for further investigation.

PT, the treatment method used in the control group in this study, also showed significant improvements in pain and functional outcomes, and the improvement score was greater than that of MCID. PT is one of the recommended treatment modalities for AC,[50] and several clinical studies have reported that PT improves pain scores, functional scores, and ROMs.[51] Therefore, PT is often used as a control or concurrent treatment to evaluate the effectiveness of a specific treatment modality for AC. One RCT compared the effectiveness of local corticosteroid injections and physical therapy.[52] For PT, the definition and details of methods included in the treatment vary between individual studies, making a direct comparison between different studies difficult; however, in this study, interventions in the PT group were determined by combining the methods of physiotherapy that are most commonly applied in Korea.[4] Therefore, the considerable difference in outcome values between the PPT and PT groups confirmed in this study has significant implications. Meanwhile, in the survival analysis, the occurrence of 3 patients who recovered only in the PT group in Week 13 is believed to be a coincidence

Table 2
Primary and secondary outcomes after treatment at each timepoint.

Assessment	Categories	Week 7	Week 13
NRS	PPT	1.63 (0.91 to 2.36)	2.03 (1.14 to 2.92)
	PT	3.85 (3.19 to 4.50)	3.77 (3.04 to 4.49)
	Difference in decrease	2.21 (1.24 to 3.19)	1.74 (0.59 to 2.89)
	P-value	<0.001***	0.004**
VAS	PPT	18.00 (10.16 to 25.83)	19.79 (9.95 to 29.63)
	PT	38.40 (31.46 to 45.34)	35.14 (25.26 to 45.01)
	Difference in decrease	20.40 (9.88 to 30.93)	15.35 (2.21 to 28.49)
	P-value	<0.001***	0.023*
SPADI_pain	PPT	23.29 (14.90 to 31.68)	23.54 (13.88 to 33.20)
	PT	45.96 (38.29 to 53.64)	41.57 (33.27 to 49.87)
	Difference in decrease	22.67 (11.31 to 34.03)	18.03 (5.37 to 30.69)
	P-value	<0.001***	0.006**
SPADI_function	PPT	19.72 (11.60 to 27.84)	15.26 (6.82 to 23.69)
	PT	40.12 (32.73 to 47.52)	36.91 (29.38 to 44.44)
	Difference in decrease	20.40 (9.34 to 31.47)	21.66 (10.27 to 33.05)
	P-value	<0.001***	<0.001***
SPADI_total	PPT	20.89 (13.20 to 28.58)	18.98 (10.24 to 27.71)
	PT	42.42 (35.24 to 49.60)	38.81 (31.10 to 46.52)
	Difference in decrease	21.52 (10.92 to 32.12)	19.83 (8.14 to 31.53)
	P-value	<0.001***	0.001**
ROM flexion	PPT	166.84 (157.87 to 175.82)	161.37 (149.25 to 173.50)
	PT	148.28 (140.14 to 156.42)	147.40 (136.78 to 158.03)
	Difference in decrease	-18.56 (-30.70 to -6.42)	-13.97 (-29.80 to 1.86)
	P-value	0.003**	0.082
ROM extension	PPT	49.96 (45.69 to 54.22)	49.31 (42.17 to 56.45)
	PT	43.99 (40.17 to 47.82)	42.43 (35.54 to 49.32)
	Difference in decrease	-5.96 (-11.68 to -0.25)	-6.88 (-16.51 to 2.75)
	P-value	0.041*	0.157
ROM abduction	PPT	157.81 (145.22 to 170.40)	157.63 (140.65 to 174.61)
	PT	130.85 (118.98 to 142.71)	132.16 (116.58 to 147.74)
	Difference in decrease	-26.96 (-44.52 to -9.40)	-25.47 (-48.30 to -2.64)
	P-value	0.003**	0.030*
ROM adduction	PPT	57.67 (53.11 to 62.23)	56.79 (49.92 to 63.66)
	PT	48.52 (44.46 to 52.58)	49.56 (43.11 to 56.00)
	Difference in decrease	-9.15 (-15.26 to -3.04)	-7.23 (-16.42 to 1.95)
	P-value	0.004**	0.12
ROM internal rotation	PPT	64.88 (58.61 to 71.15)	66.67 (58.25 to 75.10)
	PT	60.24 (54.43 to 66.05)	60.81 (52.76 to 68.87)
	Difference in decrease	-4.64 (-13.20 to 3.92)	-5.86 (-17.67 to 5.95)
	P-value	0.281	0.323
ROM external rotation	PPT	59.45 (53.15 to 65.76)	61.49 (52.69 to 70.30)
	PT	53.50 (47.89 to 59.12)	53.26 (44.59 to 61.94)
	Difference in decrease	-5.95 (-14.37 to 2.47)	-8.23 (-20.64 to 4.18)
	P-value	0.162	0.189

(*continued on next page*)

Table 2 (*continued*)

EQ-5D-5L	PPT	0.84 (0.79 to 0.90)	0.84 (0.80 to 0.88)
	PT	0.75 (0.70 to 0.80)	0.78 (0.75 to 0.82)
	Difference in decrease	-0.09 (-0.17 to -0.02)	-0.06 (-0.11 to 0.00)
	P-value	0.016*	0.048*
PCS	PPT	51.33 (48.61 to 54.06)	51.15 (48.16 to 54.14)
	PT	45.41 (42.99 to 47.83)	45.69 (43.27 to 48.11)
	Difference in decrease	-5.92 (-9.61 to -2.24)	-5.46 (-9.35 to -1.57)
	P-value	0.002**	0.007**
MCS	PPT	50.18 (46.54 to 53.82)	50.86 (47.82 to 53.90)
	PT	46.40 (43.06 to 49.74)	49.33 (46.59 to 52.07)
	Difference in decrease	-3.78 (-8.72 to 1.16)	-1.53 (-5.63 to 2.56)
	P-value	0.13	0.454
PGIC	PPT	1.86 (1.39 to 2.32)	1.92 (1.47 to 2.38)
	PT	2.77 (2.36 to 3.18)	2.81 (2.44 to 3.17)
	Difference in decrease	-0.91 (-1.53 to -0.29)	-0.88 (-1.47 to -0.30)
	P-value	0.005**	0.004**

Intergroup differences were analyzed using analysis of covariance with adjustments for baseline values, except for the patient's global impression of change. The primary endpoint was the outcome at week 7. Missing values were added using multiple imputations. Estimates for each group and intergroup differences in the decrease at each timepoint are displayed with 95 % confidence intervals (CI). EQ-5D-5L, EuroQoL 5-dimension 5-level instrument; MCS, mental component summary; NRS, numeric rating scale; PCS, physical component summary; PGIC, Patient Global Impression of Change; PPT, pharmacopuncture therapy; PT, physiotherapy; ROM, range of motion; SPADI, Shoulder Pain And Disability Index; VAS, visual analog scale.

Table 3
Areas under the curves for 12-week outcomes.

	PPT	PT	Difference (95 % CI)	*P* value
NRS	33.44 (27.31, 39.57)	54.31 (48.58, 60.04)	-20.87 (-29.26, -12.47)	<0.001
VAS	341.25 (274.09, 408.41)	542.60 (478.00, 607.20)	-201.35 (-293.41, -109.28)	<0.001
SPADI_pain	422.66 (350.12, 495.21)	612.77 (546.18, 679.36)	-190.11 (-288.65, -91.56)	<0.001
SPADI_function	349.71 (281.54, 417.87)	537.10 (474.18, 600.02)	-187.39 (-280.94, -93.85)	<0.001
SPADI_total	378.17 (311.49, 444.84)	566.82 (504.21, 629.42)	-188.65 (-280.91, -96.39)	<0.001
ROM flexion	1915.81 (1832.85, 1998.78)	1737.05 (1658.56, 1815.54)	178.77 (63.89, 293.65)	0.003
ROM extension	560.65 (519.95, 601.34)	497.69 (459.21, 536.16)	62.96 (7.77, 118.15)	0.026
ROM abduction	1780.68 (1664.47, 1896.90)	1525.09 (1413.85, 1636.33)	255.59 (91.27, 419.91)	0.003
ROM adduction	640.51 (598.99, 682.04)	567.33 (528.53, 606.13)	73.18 (16.54, 129.82)	0.012
ROM internal rt	747.27 (695.85, 798.69)	713.26 (663.76, 762.76)	34.01 (-37.62, 105.63)	0.344
ROM external rt	678.27 (619.68, 736.86)	620.26 (564.27, 676.25)	58.01 (-22.66, 138.68)	0.155
EQ-5D-5L	9.49 (9.06, 9.92)	8.76 (8.38, 9.13)	0.74 (0.16, 1.31)	0.013
PCS	588.07 (565.71, 610.43)	536.15 (516.02, 556.27)	51.92 (21.52, 82.33)	0.001
MCS	579.89 (551.78, 608.00)	552.60 (526.43, 578.77)	27.29 (-11.11, 65.70)	0.159

The area under the curve (AUC) was calculated using the trapezoidal rule. Intergroup differences were analyzed using independent *t*-tests. Missing values were added using multiple imputations. The AUC estimates for each group and intergroup differences are presented together with 95 % confidence intervals (CI). EQ-5D-5L, EuroQoL 5-dimension 5-Level instrument; MCS, mental component summary; NRS, numeric rating scale; PCS, physical component summary; PGIC, Patient Global Impression of Change; PPT, pharmacopuncture therapy; PT, physiotherapy; ROM, range of motion; Rt, rotation; SPADI, Shoulder Pain And Disability Index; VAS, visual analog scale.

due to the small sample size of this study. It will be necessary to carefully examine whether this tendency is found in a following large-scale study.

Interestingly, despite the relatively short follow-up period in this study, a significant difference in the quality of life measured by the EQ-5D was confirmed between the two groups. In addition, a significant difference was observed in PCS between the two groups, whereas no significant difference was found in the MCS. Quality of life is related to multiple dimensions, including physical, psychological, and social relationships.[53] The EQ-5D used in this study mainly focuses on physical functioning among different dimensions of quality of life.[54] In a previous study that investigated the correlation between quality of life and functional disability in patients with AC, only the physical domain showed a correlation with functional disability among factors of quality of life.[55] These findings suggest that compromised quality of life due to AC is particularly attributable to the physical aspects of functional disability from stiffness and limited ROMs. Therefore, PPT is considered an effective treatment for improving quality of life that may suffer due to the functional limitations of AC.

Pharmacopuncture is one of the treatments used in KM that combines traditional acupuncture with herbal medicine to confer the effects of both the physical stimulation of the needling and the chemical action of the pharmacopuncture solution.[28-30] According to a study that analyzed the data extracted from the electronic medical records of 12 hospitals

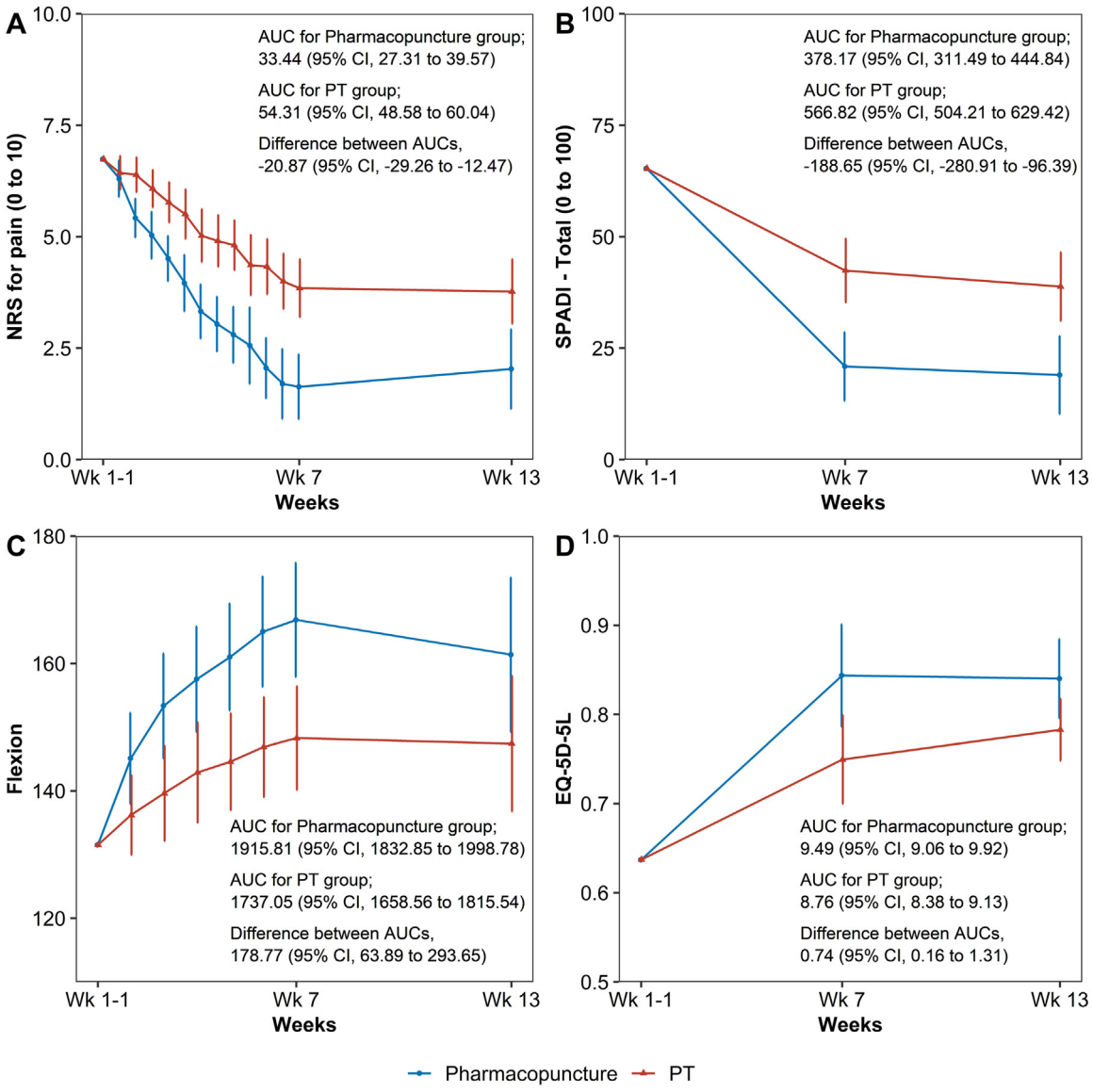

Fig. 1. Changes in outcomes over time and areas under the curves. (A) NRS for shoulder pain; (B) SPADI; (C) ROM for flexion; (D) EQ-5D-5L. The dots indicate the mean scores and error bars indicate the 95 % confidence intervals. Missing values were added using multiple imputation. EQ-5D-5L, EuroQoL 5-dimension 5-level instrument; NRS, numeric rating scale; SPADI, Shoulder Pain And Disability Index.

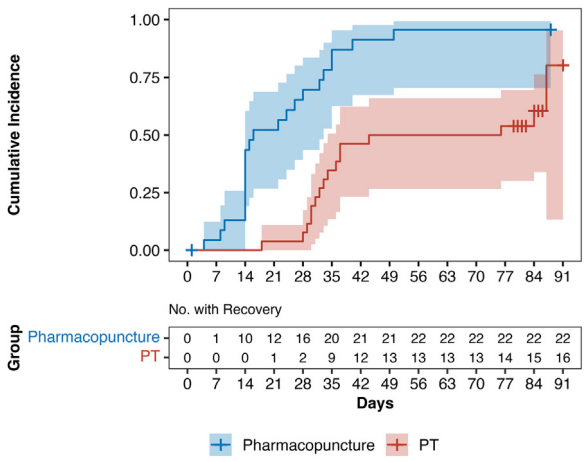

Fig. 2. Cumulative incidence curves of recovery by group.

and KM clinics in Korea[56] 98.6 % of inpatients and 77.6 % of outpatients received PPT over a 4-year period. In addition, in a study based on a survey conducted among KMDs, 88 % of the respondents reported that they used herbal acupuncture for treatment.[57] Kim et al. investigated the incidence of AEs related to pharmacopuncture in 80,523 patients with musculoskeletal disorders who visited KM hospitals and clinics, and their results demonstrated the safety of pharmacopuncture.[58]

The pharmacopuncture types used in this study were Shinbaro2 and Shinbaro3. Shinbaro2 pharmacopuncture is frequently used for the treatment of patients with cervical disk herniation[59] and lumbar spinal stenosis (LSS) .[60] In rat models of LSS[61] and lumbar disk herniation,[62] Shinbaro2 pharmacopuncture showed protective effects against inflammatory responses and improved locomotor function. In addition, GCSB-5 (Shinbaro®, Green Cross Corp., Yongin, Republic of Korea), a main constituent of Shinbaro2 marketed under the name Shinbaro, modulates inflammatory processes,[63] nerve regeneration,[64] and protection of articular cartilage from degeneration.[65] Shinbaro3 pharmacopuncture uses *Harpagophytum procumbens* as a single ingredient of medicinal herbs. Notably, *H. procumbens* has analgesic and anti-inflammatory proper-

ties.[66,67] *H. procumbens* showed superior effectiveness with a higher rate of improvement than the placebo in an RCT of patients with acute low back pain.[68] Further, in a rat model of LSS, *H. procumbens* showed neuroprotective effects and reduced inflammatory responses and oxidative stress.[69] Above active ingredients of pharmacopuncture solution may have contributed to superior outcomes of PPT group in this study.

This study has some limitations. First, owing to the nature of the intervention, the study design was open-label without the blinding of physicians and participants. However, the assessors were blinded to ensure the validity of this study as much as possible. Second, PPT is commonly used in KM clinics and hospitals; however, this study included only those who visited KM hospitals, which may have limited the generalizability of the results. Third, we could not evaluate the long-term treatment effect because of the short follow-up period in this study. However, in the following main study, we will investigate the long-term effects of PPT using a longer follow-up period. Finally, AC has a series of characteristic stages that lead to painful-frozen-thawing, but this study was unable to distinguish these stages due to limitations in manpower and budget. This will be supplemented in the following main study.

Nevertheless, this study is the first pragmatic RCT to investigate the effectiveness of PPT for patients with AC. Few high-quality clinical studies on pharmacopuncture have been published to date.[70] The results of this study showed that PPT has the potential to be an effective and safe treatment for patients with AC and showed the feasibility of the following main study. In addition, and the sample size of the following main study could be calculated using the result of this study. The effect size was 1.26, and a total of 48 participants were needed assuming 95 % power and 25 % dropout rate. Considering various subgroup analyzes such as AC stage, it was decided that the sample size in the main study should be 100 or more, but the exact sample size will be determined when the main study is conducted.

In this study, the PPT strategy showed significantly superior effectiveness to the PT strategy in terms of pain reduction, improvement in functional disability, and increase in ROM, thereby confirming the feasibility of the main study that is to be conducted in the future.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Doori Kim: Formal analysis, Writing – original draft, Writing – review & editing. **Kyoung Sun Park:** Investigation, Writing – review & editing. **Sun-A Kim:** Investigation. **Ji Yeon Seo:** Investigation. **Hyun-Woo Cho:** Investigation. **Yoon Jae Lee:** Formal analysis, Writing – review & editing. **Changsop Yang:** Methodology, Supervision, Project administration, Funding acquisition. **In-Hyuk Ha:** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition. **Chang-Hyun Han:** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition.

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Ethical statement

This research was reviewed and approved by the institutional review board of Jaseng Hospital of Korean Medicine (registration number JASENG 2022-02-013, JASENG 2022-02-014, JASENG 2022-02-015, and JASENG 2022-02-016). Informed consent was obtained from all participants.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101065.

Supplement 1. Time table of the trial.

Supplement 2. Detailed treatment of each group.

Supplement 3. Primary and secondary outcomes after treatment at each time points: main analysis.

Supplement 4. Primary and secondary outcomes after treatment at each time point: per protocol.

Supplement 5. Primary and secondary outcomes after treatment at each time point: linear mixed model.

Supplement 6. Primary and secondary outcomes after treatment at each time point: last observation carried forward.

Supplement 7. Comparison of pre- and post- treatment blood test results for safety assessment.

Supplement 8. Flowchart of participants.

Supplement 9. CONSORT checklist.

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