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CLINICAL TRIAL REPORT

A Pilot Study for Effectiveness and Safety of Adjunctive Pharmacopuncture to Acupuncture Treatment for Rotator Cuff Diseases: A Pragmatic Randomized Controlled Trial

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Purpose: Pharmacopuncture therapy has been used in the conservative treatment of rotator cuff disease adjuvant to acupuncture treatment. Despite the increasing utilization of pharmacopuncture therapy, there is still a lack of high-quality research to support its effectiveness. This pilot study aimed to assess the feasibility of pharmacopuncture therapy adjuvant to acupuncture treatment for rotator cuff disease.

Patients and Methods: This was a parallel-grouped, pragmatic randomized controlled, pilot study. Forty patients were randomly allocated to either the experimental or the control group. All patients received acupuncture treatment for four weeks, and pharmacopuncture was additionally administered to the experimental group. After eight treatments were delivered over four weeks, follow-up assessments were performed. The primary outcome was the mean change in the visual analog scale (VAS) score for shoulder pain from baseline to visit 8. Secondary outcomes included shoulder pain and disability index (SPADI) at visits 4, 8, and 9, shoulder range of motion (ROM) at visits 4, 8, and 9, EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) at visits 8 and 9, patient global impression of change (PGIC) at visits 8 and 9, and mean rescue medication consumption at visits 8 and 9.

Results: Both groups showed that each treatment effectively improved rotator cuff disease in most assessments. Particularly, the group that received acupuncture plus pharmacopuncture required fewer rescue medications than the group that received acupuncture alone. However, there was little statistically significant difference between the two groups. There were no serious adverse events experienced by patients in this study.

Conclusion: Although there was little statistical difference between the two groups, the combination of acupuncture and pharmacopuncture for rotator cuff disease was associated with a reduction in the rescue medicine dosage compared with acupuncture alone. Also, it confirmed the safety of pharmacopuncture therapy. This pilot study would help design future research on the effectiveness of pharmacopuncture in rotator cuff disease.

Keywords: rotator cuff disease, pharmacopuncture, acupuncture, pragmatic trial, randomized controlled trial

Introduction

Shoulder pain is a common symptom that ranks third among musculoskeletal pain[1] and it affects approximately 18–26% of adults.[2–4] Rotator cuff disease (RCD) is the most common cause of continuous shoulder pain and disability.[5] RCD is a generic term for anatomical deformities, symptoms, and signs of the shoulder region, and it contains shoulder diseases, including

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subacromial impingement syndrome, adhesive capsulitis, rotator cuff syndrome, calcific tendinitis, and rotator cuff rupture.[6–8] The symptoms of RCD interfere with an individual's daily activities and place a significant health-economic burden on society.[9–11] RCD has a multifactorial etiology, including intrinsic, extrinsic, and biopsychosocial factors.[12,13] In RCD, tendon damage occurs in a series of acute to chronic changes, ranging from tendinopathy without tendon fraying to full-thickness tendon rupture.[14–16] Conservative treatment is recommended for RCD initially, and in cases when muscle weakness is significant due to rotator cuff rupture, surgical treatment is considered.[15,17–19] Subacromial decompression (SAD) surgery is a common surgical procedure for shoulder pain,[15] but recent studies have shown that SAD and non-surgical treatments provide similar results in RCD except for full-thickness tendon lesions.[20–23]

In the Republic of Korea, Korean Medicine (KM) has been used as another method of conservative treatment. Many patients begin KM treatment after surgery due to pain and other discomforts.[24] Regarding various research on KM treatment of shoulder pain have been conducted, Korean Medicine clinical practice guidelines for shoulder pain and postoperative treatment of rotator cuff injuries have been published in Korea.[25,26] KM treatments, including acupuncture, electro-acupuncture, and Chuna therapy, have been applied to RCD.[25,26] Among them, pharmacopuncture, a new form of acupuncture combining acupuncture with herbal medicine to administer herbal extracts to acupoints, is combined with conventional KM.[27] Pharmacopuncture has been used in diverse diseases, among which musculoskeletal disorders are the most common.[27,28] Various types of injectable solutions are used in pharmacopuncture involving Bee venom,*Hominis placenta*, and *Aconitum ciliare Decaisne* solutions.[28–30] However, most of the studies on pharmacopuncture are retrospective studies such as case reports, and there is a lack of large-scale randomized studies or prospective studies with a high level of evidence.

Recently, research on pharmacopuncture has been conducted using a pragmatic clinical trial (Practical Clinical Trial, PCT) design,[31–35] which allows customized rather than standardized treatment for each patient. This reflects the complexity of individualized treatment, which is a characteristic of KM.[36] Also, evaluating the effectiveness of "pharmacopuncture therapy" when applied to actual treatment rather than the efficacy of each pharmacopuncture solution is possible.

In this preliminary study, we aimed to evaluate the effectiveness and safety of pharmacopuncture combined with acupuncture for treating RCD.

Methods

Study Design and Setting

This was a parallel-grouped, pragmatic randomized controlled, pilot study. Subjects were recruited from patients who visited the Daejeon Korean Medical Hospital of Daejeon University in the Republic of Korea between July and December 2022. On their first visit, all participants were given a written information sheet about the study by the Korean Medicine Doctor (KMD) and a clinical research coordinator and signed written informed consent.

Eligible participants were randomized to the experimental or control group at a 1:1 ratio. All patients underwent eight sessions of acupuncture treatment for four weeks, and pharmacopuncture was additionally applied to the experimental group. Outcome assessments were performed after the 4th and 8th treatments and the follow-up visit that scheduled after 4 weeks from the 8th treatment. (Figure 1).

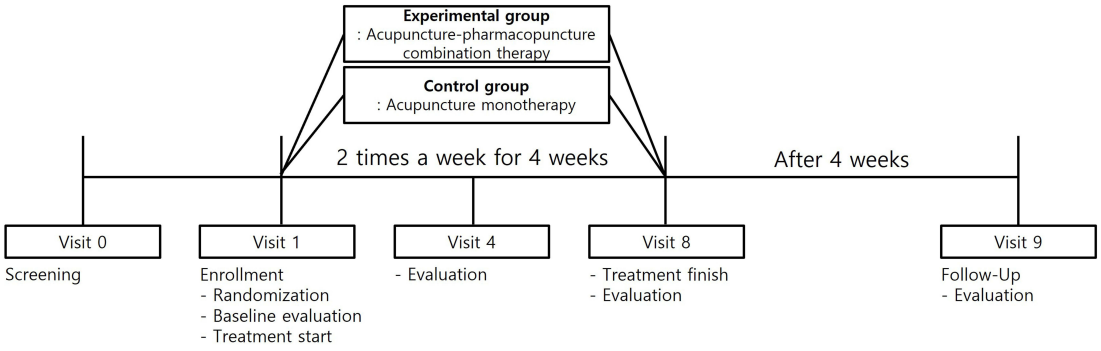

Figure 1 The flow of visits and follow-up.

This study was approved by the Institutional Review Board of Daejeon University Daejeon Korean Medicine Hospital (DJDSKH-22-BM-05). The protocol was registered at cris.nih.go.kr (identifier: KCT0007416) and published in 2023.[37] This study was conducted following the Korean Clinical Practice Guidelines and Declaration of Helsinki.

Recruitment

Inclusion Criteria

1. The age range is 19–75 years, both sexes.
2. Diagnosed as rotator cuff disease by the study principal investigator or another specialist with X-ray, physical examination (including Apley scratch test, Lift-off test, Empty can test, Yergason test), and ROM of the shoulder before enrollment.
3. Visual Analogue Scale (VAS) shoulder pain score of ≥ 40 points.
4. Capacity and willingness to provide informed consent.

For the disease codes of rotator cuff disease, M75 of the seventh revision of the Korean Standard Classification of Diseases (KCD-7) was used. KCD-7 is the Korean version of the International Classification of Diseases and Causes of Death-10 (ICD-10).

Exclusion Criteria

1. Shoulder surgery within the previous 3 months.[38]
2. Diagnosis of malignancy or fracture, among others, which may account for shoulder pain.
3. Anticipating shoulder surgery within the study period.
4. Underlying diseases (stroke, myocardial infarction, kidney disease, severe diabetes, dementia, epilepsy, severe hemorrhagic disease, etc.) that may interfere with the treatment effect or result interpretation.
5. Treatment with steroids, immunosuppressants, psychotropic medication, or any other drug that may affect outcomes within the previous 3 months.
6. Severe abnormalities in blood test results, such as aspartate aminotransferase (AST) or alanine transferase (ALT) levels three times the upper normal range limit or blood creatinine levels twice the upper normal range limit.
7. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)[39] or pharmacopuncture, acupuncture, and physical therapy within 1 week.
8. Present or planned pregnancy and lactation.
9. Active or planned participation in another clinical trial within 1 month or during the follow-up period, respectively.
10. Unsuitability for the trial, as judged by the principal investigator.

Intervention

The treatment protocol for each group was determined in advance, but the specific details of the treatment were determined at the clinician's discretion, depending on the patient's condition. Intervention details were reported in the CRFs and reviewed retrospectively.

Experimental Group

Acupuncture-pharmacopuncture combination therapy was performed eight times in total, twice weekly for 4 weeks as a standard; it was performed 1–3 times per week, as required. A licensed KM doctor with at least two years of clinical experience in acupuncture and pharmacopuncture conducted the therapy and interacted with the participants as in the actual field.

The acupoints performed in pharmacopuncture therapy were selected in local acupoints around the rotator cuff regarding subjects' pain points. The sorts of pharmacopuncture solutions were *Hominis Placenta* and *Aconiti ciliare Decaisne*, and the usage of the solution was between 1 to 4 mL. Needles for the syringe were selected between 30-gauge 1/2 inch and 30-gauge 1 1/2 inch regarding the subject's pain area. Pharmacopuncture therapy was applied individually according to the patient's symptoms and conditions through KM doctor's decision.

Control Group

Acupuncture monotherapy was administered via dry needling without additional intervention. The course involved eight treatments delivered twice a week for 4 weeks in general; this treatment was delivered 1–3 times a week, as required. A licensed KM doctor with at least two years of clinical experience in acupuncture performed all treatments and interacted with the patient in an actual field.

The acupoints were selected in an affected shoulder, trunk, and extremities which was relevant shoulder pain according to the clinical judgment of the KM doctors. Manual acupuncture was applied and techniques for De-Qi were not implemented. The needle retention time was set to 20 minutes without other treatment techniques such as hot packs, infrared therapy, or electroacupuncture. To measure the effect of acupuncture and pharmacopuncture combined treatment, the control group was set as the experimental group.

Co-Interventions

During this study, all participants were permitted other treatments, including physical and exercise therapy, at other medical centers for the onset of severe shoulder pain. However, invasive treatments, including medication, surgery, and other Korean medical treatments, are not allowed. In cases where external treatments interfered with the study, the participants were excluded. At every visit, the type and frequency of treatment received elsewhere were recorded on the CRFs.

Acetaminophen with a maximum dose of ≤ 4000 mg (8T/day)[40,41] per day was provided as a rescue drug at visits 1, 4, and 8 for relief of intolerable pain. Each time the participants consumed rescue medication, the date and dose were recorded separately. Intervention assessments were performed without drug intake during assessment visits 4, 8, and 9. Treatment safety and effectiveness were assessed at baseline and weeks 2, 4, and 8.

Primary and Secondary Outcomes

The primary outcome of this study was the average change in the VAS score for shoulder pain at visit 8 compared to baseline. The VAS helps to evaluate subjective pain levels objectively.[42] Subjects marked the point representing their pain level in the recent 2 days on a straight 100-mm line, which had a range from "no pain at all" to "maximum imaginable pain." For secondary outcomes, the average change of the VAS at visits 4 and 9, SPADI (Shoulder pain and disability index)[43] at visits 4, 8, and 9; Range of motion in the shoulder (ROM)[44,45] at visits 4, 8, and 9; EQ-5D-5L (EuroQol 5-dimension 5-level questionnaire) at visits 4, 8, and 9; EQ-VAS[46,47] at visits 4, 8, and 9; PGIC (Patient Global Impression of Change)[48] at visits 4, 8, and 9; and consumption of rescue medication were measured[49–51] at visit 4, 8, and 9. Safety was assessed based on adverse events by reporting the patient's condition at every visit.

Sample Size Estimation

To the best of our knowledge, no previous study has evaluated the adjuvant effectiveness of pharmacopuncture, which could have provided a basis for calculating the sample size in this study. As a preliminary pilot study designed to confirm the feasibility of a follow-up study, the sample size included the minimum number of participants required to evaluate treatment effectiveness. The sample size was based on similar pilot studies[39,52] rather than on statistical calculations. Therefore, 40 patients (20 per group) were recruited for this study.

Randomization

Using a randomization table, eligible participants (n = 40) were assigned to the two groups at a ratio of 1:1. A randomization table was created in advance by a statistician who was not involved in the study, using SAS® Version 9.4 (SAS Institute. Inc., Cary, NC). The generated randomization results were sealed in an opaque envelope and stored in a double-locked cabinet, which was opened the randomization envelope for each patient to proceed with the group assignment. The researcher recorded the day and time of opening the envelope and signed it before entering the group allocation into the participants' electronic records.

Blinding

Due to the nature of the interventions in this study, blinding was not possible. However, the study assessors were blinded to group allocation and were not involved in the intervention. All evaluations and analyses were performed separately.

All participants were strictly assigned an identification number. This was done to make certain that the assessors were unaware of the intervention participants were receiving.

Statistical methods

Statistical analysis of this clinical trial was performed by an independent statistician using SAS® version 9.4. A two-sided test was used, and statistical significance was set at 5%.

The data acquired from this study were used as a Full Analysis Set (FAS). The FAS group minimized the number of people excluded from the analysis by excluding only those who stopped or dropped out for valid reasons among the subjects who were randomly assigned to the overall analysis group. The exclusion criteria were cases where data could not be collected because the main inclusion/exclusion criteria were violated, the intervention was never received, or the evaluation was never conducted after random assignment. In the case of missing data in the main outcome analysis, intent-to-treat was applied with multiple imputations.

Before starting the treatment, descriptive statistics were prepared for variables related to the participant's demographic characteristics and basic clinical data. To compare each group, an independent *t*-test or Wilcoxon rank-sum test was used after presenting the mean and standard deviation for continuous variables, and frequency and percentage were used for categorical variables, followed by the chi-square test or Fisher's exact test.

The primary outcome was set as the average change in the VAS score at visit 8 compared with that before treatment. Analysis of Covariance (ANCOVA) was performed with the VAS before treatment as a covariate and each treatment group as a fixed factor. Analysis of secondary outcomes was performed using the same method as that used to analyze primary outcomes.

Among the secondary outcomes, VAS, SPADI, ROM, EQ-5D-5L, and EQ-VAS were analyzed by comparing the average change at visits 4, 8, and 9 with the baseline, and PGIC and rescue medication consumption were analyzed by comparing the change at visits 8 and 9 with visit 4.

Repeated-measures analysis of variance (RM-ANOVA) was performed to evaluate the differences in trend changes by visit between the two groups, and the Greenhouse-Geisser epsilon was used to correct for the sphericity assumption.

Results

Recruitment

From July 2022 to December 2022, 42 patients underwent screening. Among those recruited, 40 patients were judged eligible for this study and were randomly allocated to the two groups at a 1:1 ratio. Of 40 participants, 35 completed the study. Of the five who dropped out, one withdrew consent because they no longer wanted to participate in the study, one violated the exclusion criteria during the study, and three dropped out because they took prohibited drugs during the study period. Among the dropouts, three were from the experimental group, and two were from the control group. Consequently, FAS analysis was conducted on 39 patients (n=20 in the experimental group and n=19 in the control group). (Figure 2).

Baseline Characteristics

Of the 39 participants, 53.84% and 46.15% were male and female, respectively. The mean age was 56.63 ± 6.83 in the experimental group and 53.40 ± 6.51 in the control group. The average duration of shoulder pain was 37.40 ± 26.42 months in the experimental group and 57.58 ± 42.48 months in the acupuncture treatment group alone. The two groups had no statistically significant differences regarding demographic or clinical characteristics. (Table 1)

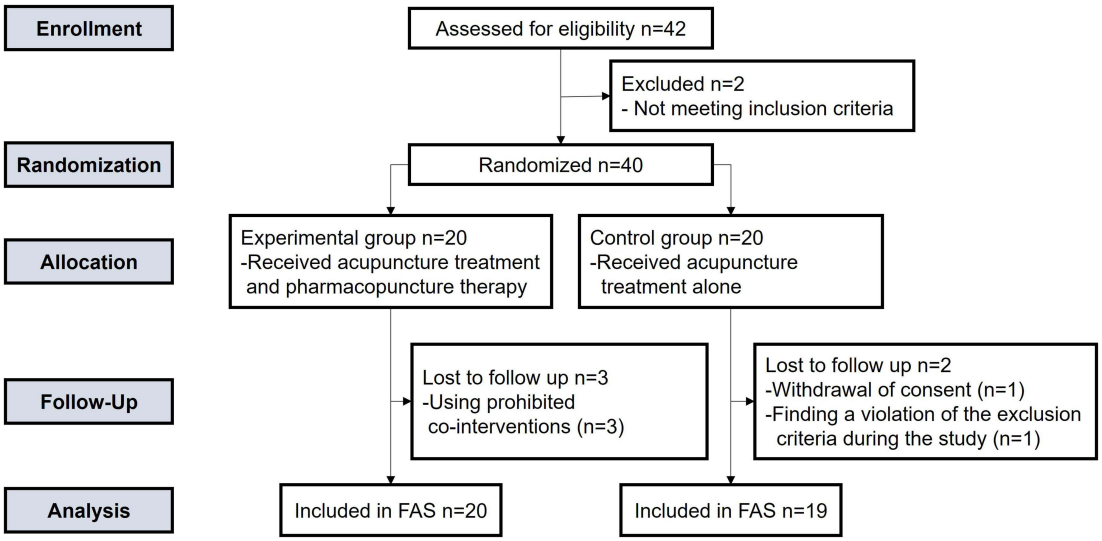

Figure 2 Flow diagram of the study.

Intervention

In the experimental group, 148 pharmacopuncture therapies were administered, among which *Hominis Placenta* pharmacopuncture was performed 118 times (79.7%), and *Aconiti ciliare Decaisne* pharmacopuncture was performed 30 times (20.3%). The pharmacopuncture dose was started at 1.0 mL and increased to 4.0 mL, depending on the subject's pain level. By dose, *Hominis Placenta* was administered 1 mL once, 2 mL 113 times, and 4 mL 4 times, while *Aconitum ciliare Decaisne* was administered 1 mL 21 times, 2 mL 9 times, and 4 mL 0 times. (Table 2)

Pharmacopuncture was performed at the following acupoints: SI9, LU1, SI11, GB21, and SI14. Acupuncture was performed 148 and 145 times in the experimental and control groups, respectively. The acupoints selected with high frequency were similar between the two groups and included local acupoints around the rotator cuff, such as SI9, TE15, SI14, GB21, and BL43, and distal acupoints, such as GB30, KI10, KI3, KI9, and BL24.

Table 1 Analysis of Homogeneity

Characteristics	Experimental Group (n=20)	Control Group (n=19)	p-value
Gender (M/F)†	13 (65.00) / 7 (35.00)	8 (42.11) / 11 (57.89)	0.1517
Age (year)‡‡	53.40 (46.57, 60.23)	56.63 (50.12, 63.14)	0.5125
BMI (kg/m^2)‡	25.09 (23.52, 26.65)	23.46 (21.84, 25.08)	0.1395
SBP (mmHg)‡	132.70 (125.96, 139.44)	127.00 (120.62, 133.38)	0.2067
DBP (mmHg)‡	78.30 (73.35, 83.25)	74.74 (70.69, 78.79)	0.2530
Exercise (Y/N)††	15 (75) / 5 (25)	18 (94.74) / 1 (5.26)	0.1818
Exercise frequency (n/week))††			0.4114
1	1 (6.67)	2 (11.11)	
2	1 (6.67)	1 (5.56)	
3	5 (33.33)	9 (50.00)	
4	4 (26.67)	1 (5.56)	
5	0	3 (16.67)	
6	2 (13.33)	1 (5.56)	
7	2 (13.33)	1 (5.56)	
Duration of shoulder pain (month)‡‡	37.40 (10.98, 63.82)	57.58 (14.74, 100.42)	0.3501
Drink (Y/N)†	10 (50.00) / 10 (50.00)	7 (36.84) / 12 (63.16)	0.4075
Smoking (Y/N)††	3 (15.79) / 16 (84.21)	2 (10.53) / 17 (89.47)	1.0000

Notes: †Chi-square test, ††Fisher`s Exact test. ‡Independent *t*-test, ‡‡Wilcoxon rank sum test.

Table 2 Pharmacopuncture Status in the Experimental Group

Patient	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
1	▲	▲	▲	▲	▲	▲		
2	●	●	●	●				
3	▲	▲	▲	▲	▲	●	▲	▲
4	▲	▲	●	●	●	●	●	▲
5	●	▲	●	▲	●	▲	▲	▲
6	▲	▲	▲	▲	▲	▲	▲	●
7	●	●	●	▲	▲	●	●	●
8	▲	▲						
9	▲	▲	▲	▲	▲	▲	▲	▲
10	▲	▲	▲	▲	▲	▲	▲	▲
11	●	●	▲	▲	▲	▲	▲	▲
12	▲	●	▲	▲	▲	▲	▲	▲
13	●	▲	▲	▲	▲	▲	▲	▲
14	▲	◆	▲	◆	▲	◆	◆	▲
15	▲	▲	▲	▲	▲	▲	▲	▲
16	▲	▲	▲	▲	▲	▲	▲	▲
17	▲	▲	▲	▲	▲	▲	▲	▲
18	▲	▲	▲	▲	▲	▲	▲	▲
19	▲	▲	▲	▲	▲	▲	▲	▲
20	▲	▲	▲	▲	▲	▲	▲	▲

Notes: Types ▩ Hominis Placenta ▢ Aconitum ciliare Decaisne ▢ Unvisited. Dose ●1cc ▲2cc ◆4cc.

Clinical Outcome

Primary Outcome: VAS at Visit 8

The VAS score, which was the primary outcome, showed no significant difference between the two groups at visit 8 compared with baseline. However, the VAS score at visit 8 decreased by 24.96 mm (95% CI:22.39 to 27.53, p<0.0001) in the experimental group and by 30.00 (95% CI:26.82 to 33.17, p<0.0001) in the control group with statistical significance. (Table 3)

Secondary Outcome

VAS at Visit 4 and 9

The VAS score improved significantly in both groups with statistical significance (VAS in the experimental group: Visit 4, 7.80, p<0.0001; Visit 9, 25.83, p<0.0001; VAS in the control group: Visit 4, 11.31, p<0.0001; Visit 9, 28.59, p<0.0001). The difference in the average change in VAS score between the two groups by visit was 3.74 at visit 4 and 3.52 at visit 9 but not statistically significant at visits 4 and 9. (Table 3)

SPADI

The SPADI significantly decreased in both groups statistically significantly (SPADI in the experimental group: Visit 4, 8.40, p<0.0001; Visit 8, 17.96, p<0.0001; Visit 9, 18.62, p<0.0001; SPADI in the control group: Visit 4, 9.99, p<0.0001; Visit 8, 21.73, p<0.0001; Visit 9, 24.14, p<0.0001). However, the differences between the two groups were not statistically significant (Visit 4, p=0.8035; Visit 8, p=0.6885; Visit 9: p=0.5172). (Table 4)

Table 3 Analysis of VAS

VAS	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	p-value†
Baseline	64.00 (62.52, 65.48)	62.63 (60.74, 64.53)		
Visit 4	56.20 (53.93, 58.47)	51.32 (48.67, 53.98)		
Difference‡	7.80 (5.76, 9.84)	11.31 (9.28, 13.34)	3.74 (−5.79, 13.27)	0.4414
P-value‡	<0.0001*	<0.0001*		
Visit 8	39.04 (36.56, 41.53)	32.64 (29.89, 35.38)		
Difference‡	24.96 (22.39, 27.53)	30.00 (26.82, 33.17)	6.06 (−6.18, 18.31)	0.3315
P-value‡	<0.0001*	<0.0001*		
Visit 9	38.17 (35.27, 41.06)	34.04 (31.27, 36.81)		
Difference‡	25.83 (23.12, 28.55)	28.59 (25.52, 31.66)	3.52 (−9.55, 16.59)	0.5973
P-value‡	<0.0001*	<0.0001*		

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. ‡Mean difference and p-value were analyzed using a paired *t*-test for the baseline value and each point value (Visit 4, Visit 8, Visit 9). *p-value < 0.05.

Table 4 Analysis of SPADI

SPADI	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	p-value†
Baseline	50.90 (49.10, 52.70)	54.05 (51.03, 57.08)		
Visit 4	42.50 (40.50, 44.51)	44.06 (41.02, 47.10)		
Difference‡	8.40 (6.95, 9.84)	9.99 (8.06, 11.92)	0.97 (−6.66, 8.60)	0.8035
P-value‡	<0.0001*	<0.0001*		
Visit 8	32.94 (30.75, 35.12)	32.32 (29.39, 35.24)		
Difference‡	17.96 (15.85, 20.08)	21.73 (18.86, 24.61)	2.27 (−8.13, 12.68)	0.6685
P-value‡	<0.0001*	<0.0001*		
Visit 9	32.28 (29.84, 34.72)	29.91 (27.03, 32.79)		
Difference‡	18.62 (16.29, 20.95)	24.14 (20.95, 27.33)	3.78 (−7.66, 15.23)	0.5172
P-value‡	<0.0001*	<0.0001*		

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. ‡Mean difference and p-value were analyzed using a paired *t*-test for the baseline value and each point value (Visit 4, Visit 8, Visit 9). *p-value < 0.05.

ROM

Shoulder ROM measured five items of flexion, extension, abduction, internal rotation, and external rotation and analyzed the average change at visits 4, 8, and 9 compared with baseline.

The ROM of flexion, abduction, internal rotation, and external rotation significantly improved in both groups. However, the differences between the two groups were not statistically significant. (Tables 5 and 6)

In the case of extension, there was a statistically significant increase in visits 4, 8, and 9 in the experimental group; in the control group, there was an increase in visits 4, 8, and 9, but it was statistically significant in visits 8 and 9. (in the experimental group, Visit 4, 4.94, p<0.0001; Visit 8, 6.00, p<0.0001; Visit 9, 8.53, p<0.0001, in the control group; Visit 4, 0.38, p=0.0921; Visit 8, 3.18, p<0.0001; Visit 9, 5.00, p<0.0001) The difference between the two groups was statistically significant in visit 4. (p=0.0340)

EQ-5D-5L and EQ-VAS

The EQ-5D-5L showed a statistically significant improvement in the two groups (EQ-5D-5L in the experimental group: Visit 4, 0.04, p<0.0001; Visit 8, 0.08, p<0.0001; Visit 9, 0.09, p<0.0001; EQ-5D-5L in the control group: Visit 4, 0.04, p<0.0001; Visit 8, 0.09, p<0.0001; Visit 9, 0.11, p<0.0001). The difference in the average change between the two groups at each visit was not statistically significant. (Table 7)

The EQ-VAS score showed improvement (EQ-VAS score in the experimental group: Visit 4, 0.31, p=0.5733; Visit 8, 9.62, p<0.0001; Visit 9, 6.10, p<0.0001; EQ-VAS score in the control group: Visit 4, 2.44, p=0.7041; Visit8, 3.06,

Table 5 Analysis of ROM (Flexion, Extension, Abduction)

ROM	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	p-value†
Flexion				
Baseline	140.50 (136.94, 144.06)	147.89 (143.09, 152.70)		
Visit 4	146.06 (142.56, 149.55)	149.72 (145.18, 154.26)		
Difference‡	−5.56 (−7.83, −3.28)	−1.82 (−3.18, −0.47)	2.69 (−5.79, 11.16)	0.5343
P-value‡	<0.0001*	0.0004*		
Visit 8	154.52 (150.99, 158.04)	155.32 (150.86, 159.77)		
Difference‡	−14.02 (−16.58, −11.46)	−7.42 (−9.82, −5.02)	4.95 (−6.11, 16.00)	0.3803
P-value‡	<0.0001*	<0.0001*		
Visit 9	155.88 (152.45, 159.31)	159.17 (155.19, 163.14)		
Difference‡	−16.18 (−18.74, −13.62)	−13.06 (−15.77, −10.34)	1.85 (−8.15, 11.85)	0.7168
P-value‡	<0.0001*	<0.0001*		
Extension				
Baseline	46.5 (44.84, 48.16)	51.05 (49.7, 52.40)		
Visit 4	51.44 (49.8, 53.09)	51.43 (50.1, 52.76)		
Difference‡	−4.94 (−5.75, −4.14)	−0.38 (−1.13, 0.38)	3.92 (0.30, 7.54)	0.0340*
P-value‡	<0.0001*	0.0921		
Visit 8	52.5 (51.12, 53.88)	54.23 (53.09, 55.37)		
Difference‡	−6.00 (−6.77, −5.23)	−3.18 (−4.47, −1.89)	1.05 (−3.08, 5.19)	0.6175
P-value‡	<0.0001*	<0.0001*		
Visit 9	54.41 (53.31, 55.51)	55.56 (54.64, 56.47)		
Difference‡	−8.53 (−9.77, −7.29)	−5.00 (−5.98, −4.02)	0.90 (−2.20, 4.00)	0.5693
P-value‡	<0.0001*	<0.0001*		
Abduction				
Baseline	125.75 (121.62, 129.88)	126.58 (120.83, 132.33)		
Visit 4	133.31 (129.97, 136.64)	133.63 (128.18, 139.08)		
Difference‡	−7.56 (−9.93, −5.18)	−7.05 (−8.66, −5.44)	1.05 (−7.57, 9.68)	0.8108
P-value‡	<0.0001*	<0.0001*		
Visit 8	140.85 (136.95, 144.75)	145.75 (140.98, 150.53)		
Difference‡	−15.10 (−17.9, −12.30)	−19.17 (−22.02, −16.32)	−5.19 (−17.28, 6.91)	0.4006
P-value‡	<0.0001*	<0.0001*		
Visit 9	147.65 (143.22, 152.08)	149.44 (144.67, 154.22)		
Difference‡	−23.24 (−26.66, −19.81)	−20.83 (−23.86, −17.81)	−0.25 (−12.83, 12.34)	0.9692
P-value‡	<0.0001*	<0.0001*		

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. ‡Mean difference and p-value were analyzed using a paired *t*-test for the baseline value and each point value (Visit 4, Visit 8, Visit 9). *p-value < 0.05.

p=0.0086; and Visit 9, 7.08, p<0.0001). The difference in the average change between the two groups at each visit was not statistically significant. (Table 8)

PGIC

The average changes in PGIC at visits 4, 8, and 9 were analyzed. In the experimental group, the scores were 2.74, 2.27, and 2.39 for visits 4, 8, and 9, respectively, and in the control group, they were 2.78, 2.33, and 2.06, respectively. The differences between the two groups at visits are 0.04, 0.06, and −0.33 at visit 4, 8, and 9. There was a statistically significant difference at visit 9. (p=0.5822, p=0.5509, p<0.0001) (Table 9)

Consumption of Rescue Medication

The average dose of rescue medication was analyzed at visits 4, 8, and 9.

Table 6 Analysis of ROM (Internal Rotation, External Rotation)

ROM	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	p-value†
Internal rotation				
Baseline	59.5 (57.67, 61.33)	56.32 (53.79, 58.84)		
Visit 4	64.00 (62.57, 65.43)	61.45 (59.2, 63.70)		
Difference‡	−4.50 (−5.47, −3.53)	−5.14 (−6.13, −4.14)	0.71 (−3.23, 4.66)	0.7228
P-value‡	<0.0001*	<0.0001*		
Visit 8	67.33 (65.92, 68.75)	63.16 (61.25, 65.07)		
Difference‡	−7.83 (−10.07, −5.59)	−6.84 (−8.25, −5.44)	2.74 (−4.46, 9.93)	0.4550
P-value‡	<0.0001*	<0.0001*		
Visit 9	67.06 (66.05, 68.07)	65.00 (63.59, 66.41)		
Difference‡	−8.24 (−9.96, −6.51)	−9.44 (−10.98, −7.91)	1.48 (−2.42, 5.39)	0.4562
P-value‡	<0.0001*	<0.0001*		
External rotation				
Baseline	59.00 (55.52, 62.48)	50.79 (46.80, 54.78)		
Visit 4	65.42 (61.70, 69.13)	58.69 (55.17, 62.22)		
Difference‡	−6.42 (−8.38, −4.45)	−7.90 (−10.28, −5.53)	−0.25 (−10.37, 9.87)	0.9609
P-value‡	<0.0001*	<0.0001*		
Visit 8	70.29 (67.11, 73.46)	61.92 (57.99, 65.85)		
Difference‡	−11.29 (−13.29, −9.29)	−11.13 (−13.90, −8.36)	0.84 (−10.35, 12.03)	0.8832
P-value‡	<0.0001*	<0.0001*		
Visit 9	70.00 (66.62, 73.38)	63.61 (59.62, 67.60)		
Difference‡	−14.71 (−17.00, −12.41)	−15.00 (−17.53, −12.47)	0.50 (−10.45, 11.45)	0.9283
P-value‡	<0.0001*	<0.0001*		

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. ‡Mean difference and p-value were analyzed using a paired *t*-test for the baseline value and each point value (Visit 4, Visit 8, Visit 9). *p-value < 0.05.

Table 7 Analysis of EQ-5D-5L

EQ-5D-5L	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	P-value†
Baseline	0.73 (0.71, 0.75)	0.72 (0.70, 0.74)		
Visit 4	0.77 (0.76, 0.79)	0.76 (0.74, 0.78)		
Difference‡	−0.04 (−0.06, −0.03)	−0.04 (−0.06, −0.02)	0.01 (−0.05, 0.07)	0.7830
P-value‡	<0.0001*	<0.0001*		
Visit 8	0.82 (0.80, 0.83)	0.80 (0.78, 0.82)		
Difference‡	−0.08 (−0.10, −0.06)	−0.09 (−0.11, −0.06)	0.01 (−0.06, 0.08)	0.7429
P-value‡	<0.0001*	<0.0001*		
Visit 9	0.82 (0.81, 0.83)	0.83 (0.81, 0.84)		
Difference‡	−0.09 (−0.10, −0.07)	−0.11 (−0.13, −0.09)	−0.01 (−0.07, 0.04)	0.6301
P-value‡	<0.0001*	<0.0001*		

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. ‡Mean difference and p-value were analyzed using a paired *t*-test for the baseline value and each point value (Visit 4, Visit 8, Visit 9). *p-value < 0.05.

In the experimental group, there were 21 tablets, 21 tablets, and 11.5 tablets based on 500 mg, and the number of subjects who took it was two, one, and four, respectively, at visits 4, 8, and 9. In the control group, there were 30.5 tablets, 37.7 tablets, and 34.8 tablets based on 500 mg, and the number of subjects who took it was two, three, and five, respectively, at visits 4, 8, and 9.

The number of participants who received rescue medication was lower in the experimental group than in the control group, and the average dose was also lower. (Table 10)

Table 8 Analysis of EQ-VAS

EQ-VAS	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	P-value†
Baseline	65.80 (63.62, 67.98)	65.63 (63.11, 68.15)		
Visit 4	66.11 (64.28, 67.94)	68.08 (66.35, 69.80)		
Difference‡	−0.31 (−2.31, 1.70)	−2.44 (−5.20, 0.31)	−2.01 (−10.00, 5.97)	0.6211
p-value‡	0.5733	0.7041		
Visit 8	75.42 (73.81, 77.04)	68.70 (65.64, 71.75)		
Difference‡	−9.62 (−11.87, −7.37)	−3.06 (−6.03, −0.10)	6.66 (−3.82, 17.14)	0.2130
P-value‡	<0.0001*	0.0086		
Visit 9	71.90 (69.75, 74.06)	73.43 (70.88, 75.99)		
Difference‡	−6.10 (−8.39, −3.82)	−7.80 (−10.60, −5.00)	−1.60 (−11.75, 8.55)	0.7571
P-value‡	<0.0001*	<0.0001*		

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. ‡Mean difference and p-value were analyzed using a paired *t*-test for the baseline value and each point value (Visit 4, Visit 8, Visit 9). *p-value < 0.05.

Table 9 Analysis of PGIC

PGIC	Experimental Group (n=20)	Control Group (n=19)	Mean difference†	p-value†
Visit 4	2.74 (2.63, 2.84)	2.78 (2.67, 2.88)	0.04 (−0.11, 0.19)	0.5822
Visit 8	2.27 (2.19, 2.36)	2.33 (2.15, 2.52)	0.06 (−0.14, 0.26)	0.5509
Visit 9	2.39 (2.29, 2.49)	2.06 (1.94, 2.17)	−0.33 (−0.48, −0.18)	<0.0001*

Notes: †Least squares mean difference and p-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group as the fixed factor. *p-value < 0.05.

Table 10 Analysis of Rescue Medication Taking

Rescue medication taking	Experimental Group (n=20)	Control Group (n=19)
Visit 4	2, 21.0 (0)†	2, 30.5 (20.5)
Visit 8	1, 21.0	3, 37.7 (21.2)
Visit 9	4, 11.5 (17.2)	5, 34.8 (21.6)

Notes: Analysis of validity was not conducted because patients' number of per visit is minimum of 1 to maximum of 5. †Number of patients, tablets of rescue medicine.

Analysis of Trends Over Time

Repeated-measures analysis of variance was performed to analyze changes in trends over time. There was no significant interaction between the time and group in any assessment. The trends in the VAS, SPADI, ROM, EQ-5D-5L, and PGIC scores showed statistically significant changes depending on the visit. (VAS; p<0.0001, SPADI; p<0.0001, ROM; p<0.0001, EQ-5D-5L; p<0.0001, PGIC; p=0.0003) (Figures 3–12)

Adverse Events

A total of 6 cases of AEs were observed in 4 subjects (3 cases in each group). 4 AEs were "definitely not related" to the intervention in terms of causality (2 AEs were COVID-19 infection in the experimental group, 2 AEs were the common cold and contusion in the control group), and 2 AEs were "possibly related" to the intervention that subcutaneous bleeding at acupoints in both groups. Consequently, all AEs were mild in this study. Additionally, no abnormal findings were observed in the blood tests performed before and after the study.

Co-Interventions

Only one subject received physical therapy just one time. It was excluded from statistical analysis because it could not be compared.

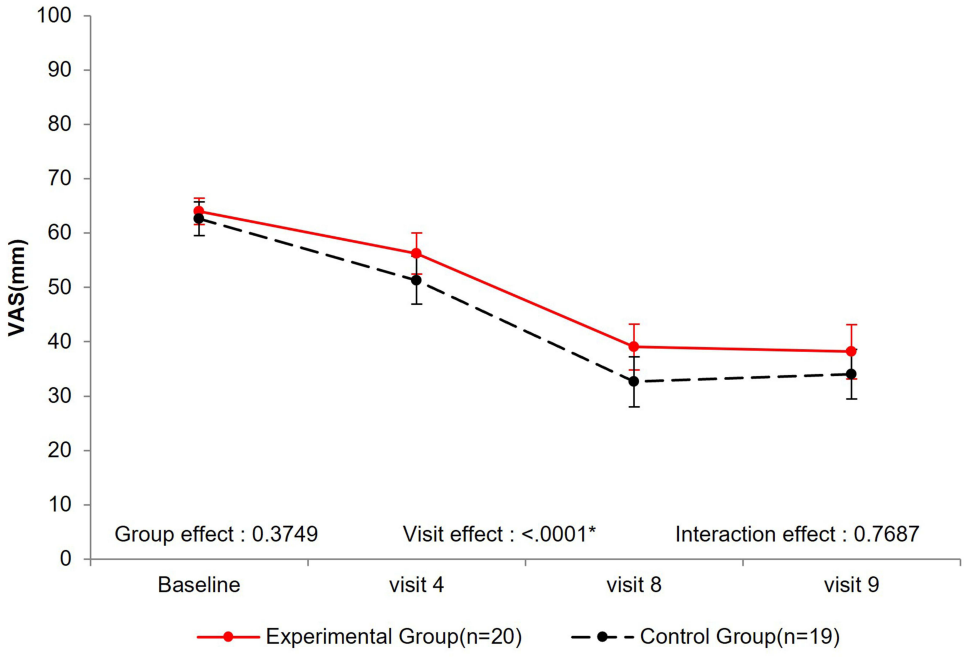

Figure 3 Change over time in VAS.

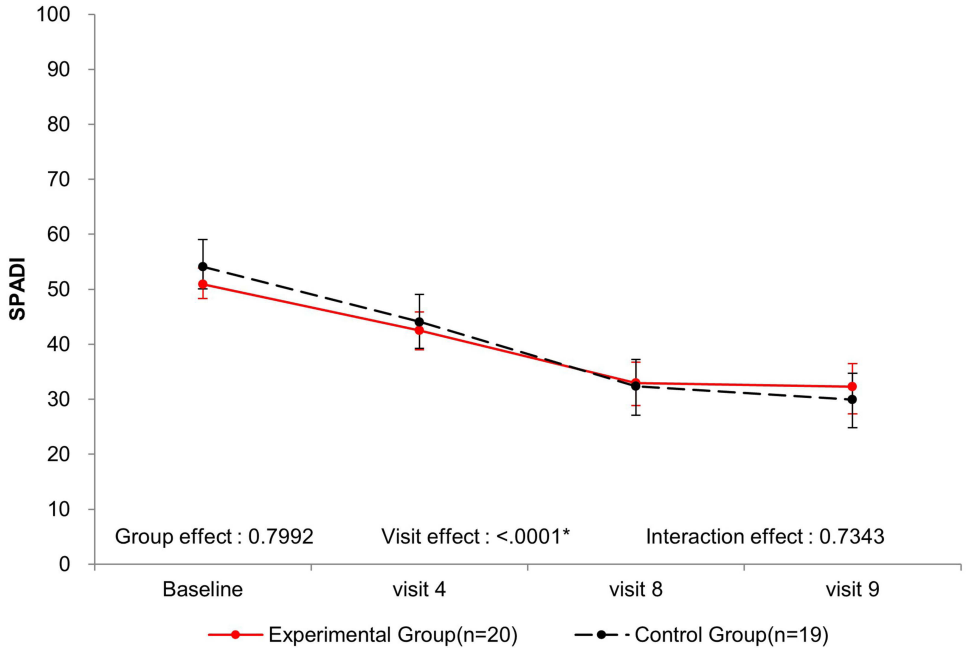

Figure 4 Change over time in SPADI.

Discussion

This clinical study was a preliminary study to verify the effectiveness of pharmacopuncture when administered as an adjunct to acupuncture treatment by comparing it with acupuncture treatment alone and to confirm the feasibility and safety of a large-scale study.

Depending on the intervention method, subjects were randomly assigned to a combination treatment of acupuncture and pharmacopuncture or an acupuncture treatment alone group. Demographic characteristics did not show statistically

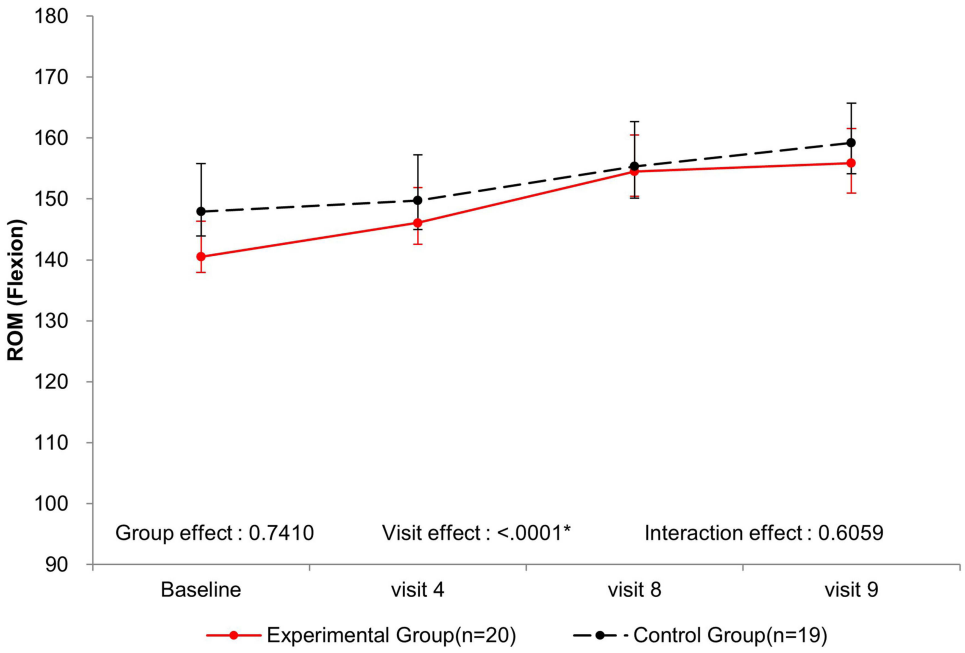

Figure 5 Change over time in ROM (Flexion).

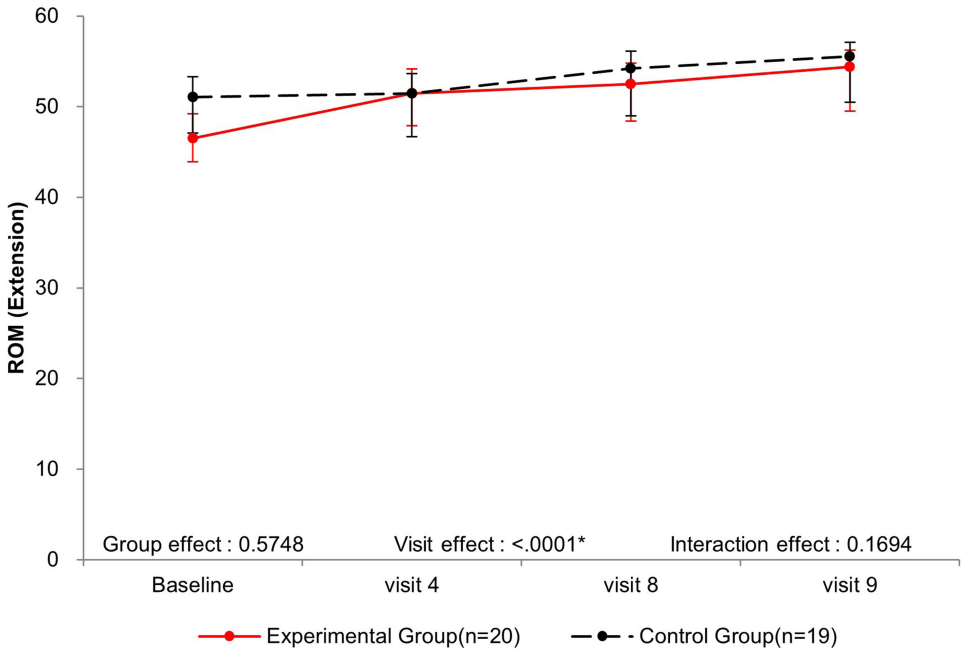

Figure 6 Change over time in ROM (Extension).

significant differences between the two groups. The average change in the VAS score at visit 8 compared with baseline was analyzed as a primary outcome. The VAS score decreased significantly compared with the baseline in both the acupuncture and pharmacopuncture combined treatment group and the acupuncture treatment alone group. In the secondary outcomes, SPADI, shoulder range of motion, EQ-5D-5L, EQ-VAS, and PGIC, excluding the average dose of rescue medication, both groups tended to show improvement as the treatment accumulated, and the effect appeared to be maintained during the follow-up period after 4 weeks. However, except for the ROM (extension) at visit 4 and PGIC of visit 9, there were no statistically significant differences between the groups. This can be attributed to a combination of

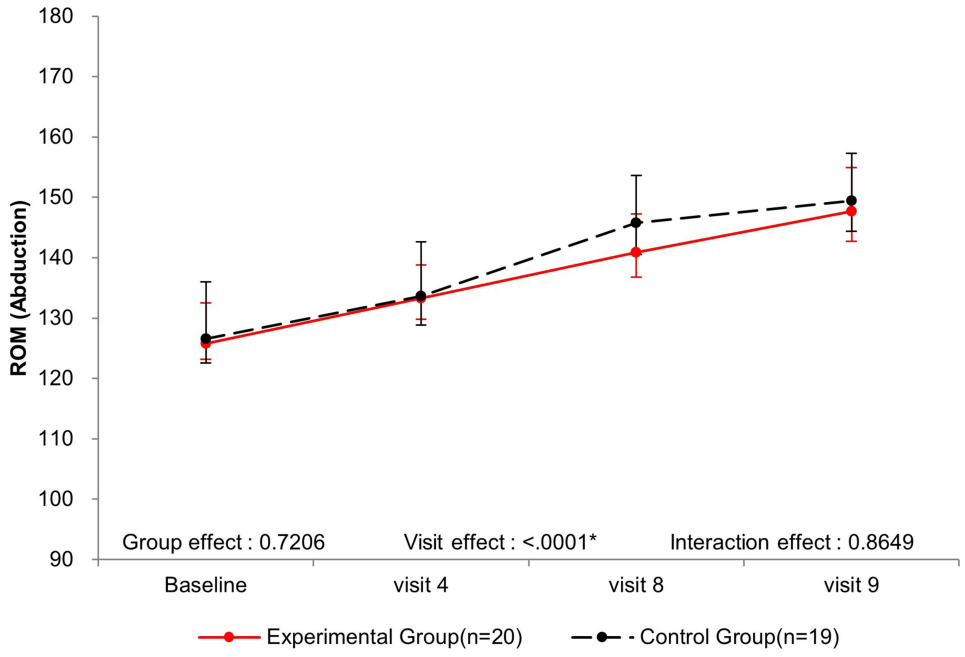

Figure 7 Change over time in ROM (Abduction).

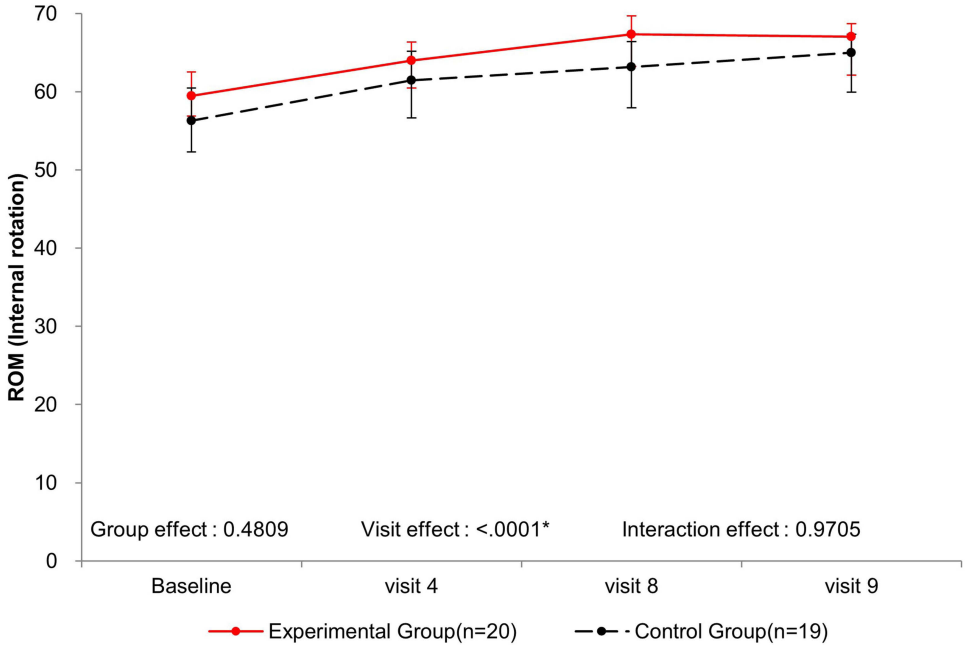

Figure 8 Change over time in ROM (Internal rotation).

factors. The first is the number and duration of treatments. It may not be enough to show additional effects of pharmacopuncture just eight times over four weeks. Additionally, the 4-week follow-up period, which is meant to confirm long-term effects, may be insufficient. The second factor is the type and dosage of the injectable pharmacopuncture solution. Various pharmacopuncture solutions, such as *Hominis Placenta, Aconitum ciliare Decaisne*, and Bee venom, have been used for RCD.[53–56] In this study, the KMDs mainly used the *Hominis Placenta* and *Aconitum ciliare Decaisne* pharmacopuncture based on the patient's condition. Despite research showing that *Hominis Placenta* and *Aconitum ciliare Decaisne* pharmacopuncture are effective for musculoskeletal diseases,[57–61] the difference between

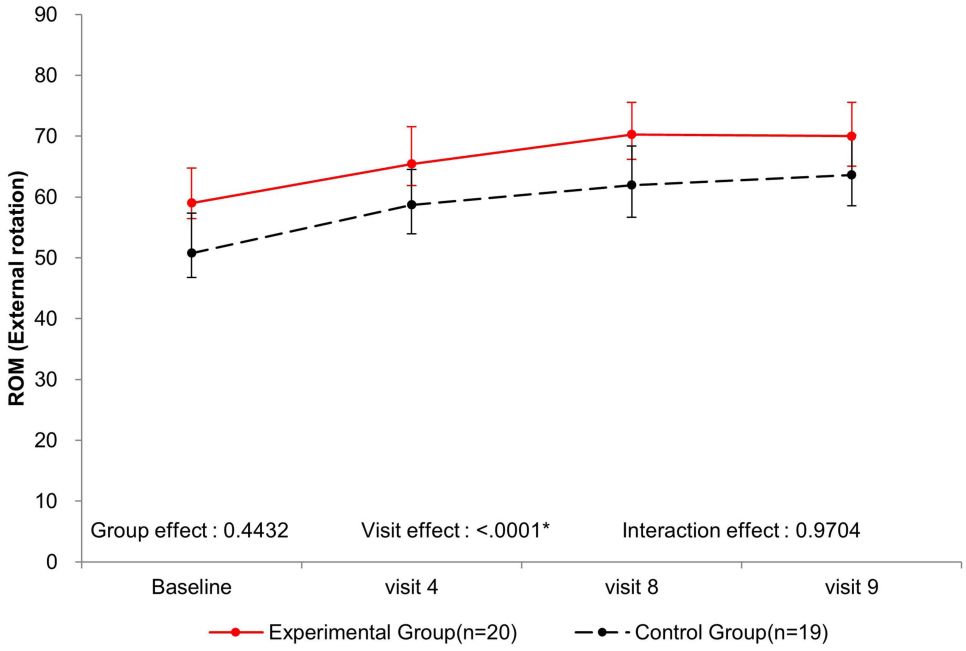

Figure 9 Change over time in ROM (External rotation).

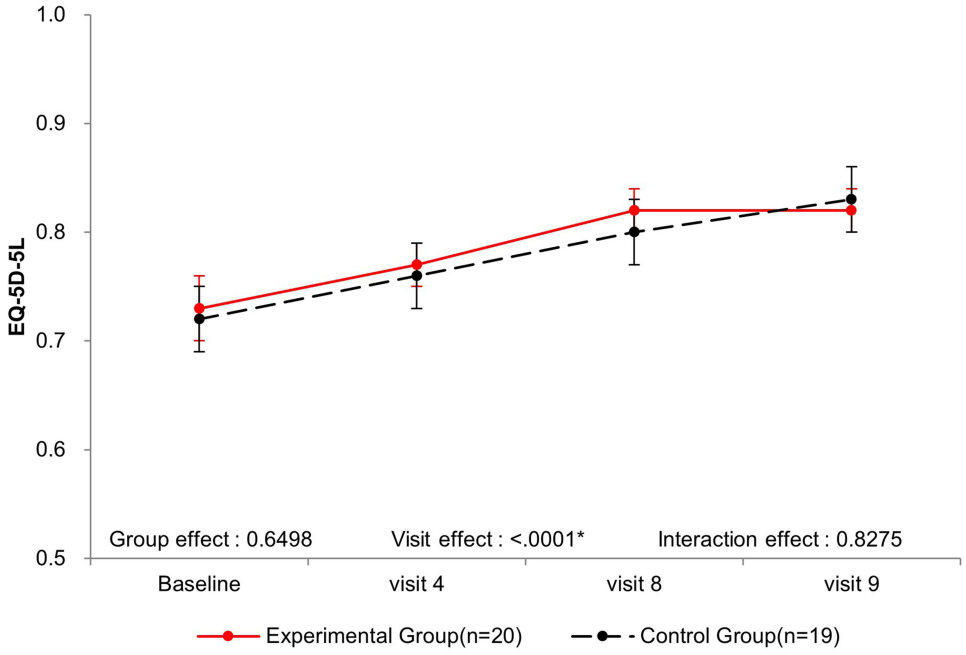

Figure 10 Change over time in EQ-5D-5L.

acupuncture, pharmacopuncture combination, and acupuncture alone was unclear in this study. In addition, it may not have been sufficient to produce a significant therapeutic effect in RCD because the injectable pharmacopuncture solution was mainly used at 2 cc per treatment. Based on the results of this study, additional research is needed to determine the appropriate type, dose, and frequency at which pharmacopuncture shows significant therapeutic effects in RCD. The third option is rescue medication. There was a difference in the amount of medication taken between the acupuncture plus pharmacopuncture and acupuncture alone groups, as well as a difference in the average amount of medication taken

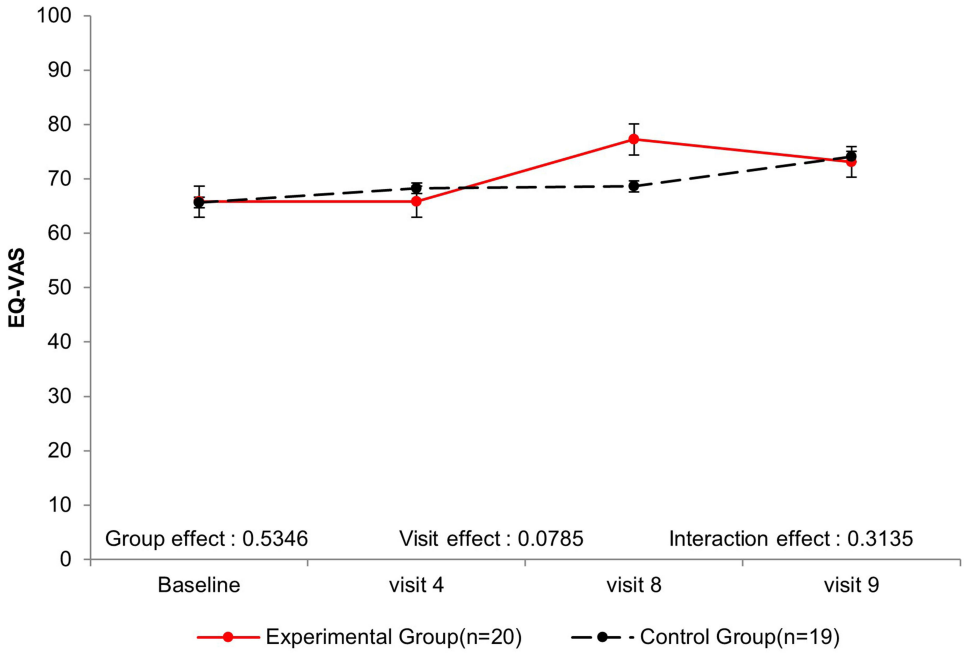

Figure 11 Change over time in EQ-VAS.

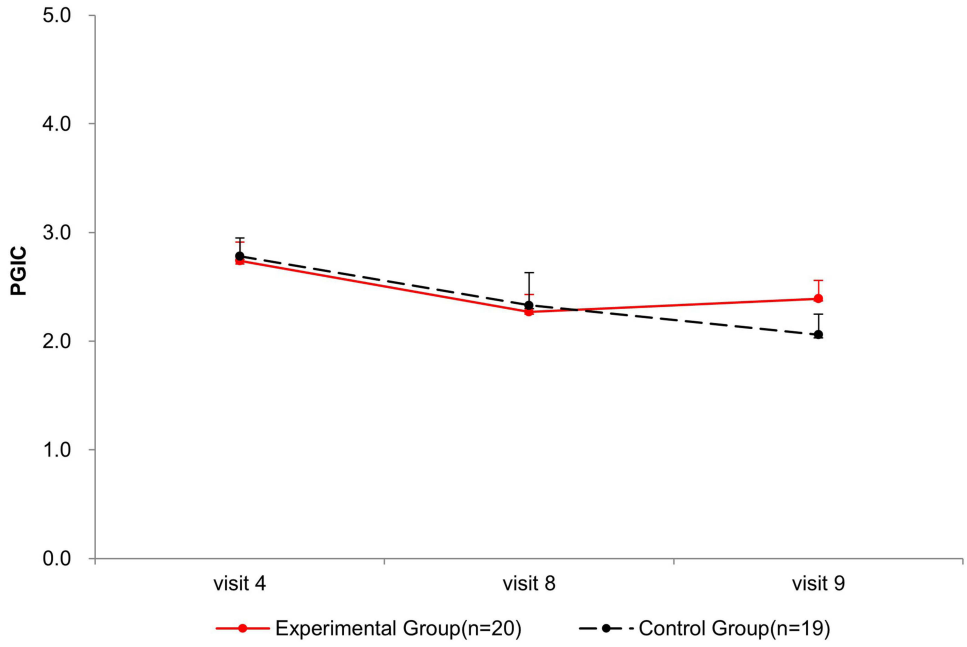

Figure 12 Change over time in PGIC.

between the two groups. In the experimental group, the dose decreased by approximately 54.8% compared with visit 4 at the end of the study to 21.0, 21.0, and 11.5 at visits 4, 8, and 9, respectively. However, in the control group, the dosage of rescue medication increased to 30.5, 37.7, and 34.8 tablets at visits 4, 8, and 9, respectively. In addition to the average dose of rescue medication, the number of subjects who took rescue medication was lower in the experimental group than in the control group. Owing to the small number of subjects in this study, it was not possible to determine the effect of rescue medication on the treatment effect; however, future studies should consider a study design that minimizes the bias caused by taking rescue medicine.

This study began recruiting the first subject on July 25, 2022, and completed recruiting the last subject on November 3, 2022; the recruitment rate, which is one of the feasibility indicators, was 100%. At the time of screening, all subjects voluntarily signed a consent form to participate, and one patient (2.5%) withdrew consent during the study. Among the 40 randomly assigned participants after screening, 17 in the experimental group and 18 in the control group completed the study until follow-up, with study completion rates of 85% and 90%, respectively. The completion rate of follow-up observation was 87.5%, and the completion rate of clinical outcome indicator measurements was 97.5%, confirming the feasibility of conducting this study. Additionally, it was confirmed to be a relatively safe intervention regarding adverse reactions.

This study has several limitations. First, because blinding of clinicians and subjects was impossible owing to the nature of the intervention, there is a possibility that nonspecific effects, such as treatment expectations for additional intervention compared with the control group, might have occurred. Second, it was difficult to secure test power because the sample size was small. Although the purpose of the preliminary study was to focus on the feasibility of the main study rather than hypothesis testing,[62] it had the disadvantage of being difficult to calculate the sample size and validate the main study. Third, because this study was a practical clinical study and did not set up a placebo control group, and the detailed method of intervention was determined by the clinician's judgment, the intervention might have been biased depending on the research environment. Fourth, the follow-up period was only 4 weeks, making long-term evaluation difficult. Therefore, more long-term studies are needed to evaluate the additional and lasting effects of pharmacopuncture on acupuncture treatment of RCD. In addition, we propose to design and analyze the study by considering the specifications of the research subjects, the establishment of an appropriate control group, the setting of variables for confounding factors, and the risk of bias due to rescue medicine.

Despite these limitations, this study is significant because it confirmed the feasibility of a preliminary study to verify the effectiveness of pharmacopuncture for RCD. High recruitment and completion rates were observed within the given period, and research ethics and clinical trial management standards were observed throughout the entire research process. Also, this study tried to reflect real clinical practice as much as possible by using pragmatic trial methodology. The data from this study are expected to provide important information for future research.

Conclusion

This study showed significant improvement in both groups but did not verify the distinct adjuvant effects of pharmacopuncture for rotator cuff disease. However, it was suggested that pharmacopuncture therapy may have positive additional effects in the aspect of the safety therapy and smaller dosage of rescue drugs. In addition, this pilot study demonstrated the feasibility of conducting a large-scale RCT that confirms the additional effect of pharmacopuncture therapy on conventional acupuncture for RCD. Further studies on the effects of pharmacopuncture on RCD are required in diverse aspects including a more adequate study period, the sample size, and the usage of pharmacopuncture solutions.

Abbreviations

RCD, Rotator cuff disease; KM, Korean Medicine; KMD, Korean Medicine Doctor; PCT, Pragmatic clinical trial (or Practical clinical trial); VAS, Visual analog scale; SPADI, Shoulder pain and disability index; ROM, Range of motion; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; EQ-VAS, EuroQol-visual analog scales; PGIC, Patient Global Impression of Change; FAS, Full Analysis Set.

Data Sharing Statement

Raw data will not be made publicly available following the ethical approval of this study, but anonymized data can be made available upon request from the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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