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Original Article
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Pharmacoacupuncture for the Treatment of Frozen Shoulder: protocol for a systematic review and meta-analysis

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Objectives: Frozen shoulder (FS) is one of the most challenging shoulder disorders for patients and clinicians. Its symptoms mainly include any combination of stiffness, nocturnal pain, and limitation of active and passive glenohumeral joint movement. Conventional treatment options for FS are physical therapy, nonsteroidal anti-inflammatory drugs, injection therapy, and arthroscopic capsular release, but adverse and limited effects continue to present problems. As a result, pharmacoacupuncture (PA) is getting attention as an alternative therapy for patients with FS. PA is a new form of acupuncture treatment in traditional Korean medicine (TKM) that is mainly used for musculoskeletal diseases. It has similarity and specificity compared to corticosteroid injection and hydrodilatation, making it a potential alternative injection therapy for FS. However, no systematic reviews investigating the utilization of PA for FS have been published. Therefore, this review aims to standardize the clinical use of PA for FS and validate its therapeutic effect.
Methods: The protocol was registered in Prospero (CRD42023445708) on 18 July 2023. Until Aug. 31, 2023, seven electronic databases will be searched for randomized controlled trials of PA for FS. Authors will be contacted, and manual searches will also be performed. Two reviewers will independently screen and collect data from retrieved articles according to predefined criteria. The primary outcome will be pain intensity, and secondary outcomes will be effective rate, Constant-Murley Score, Shoulder Pain and Disability Index, range of motion, quality of life, and adverse events. Bias and quality of the included trials will be assessed using the Cochrane handbook's risk-of-bias tool for randomized trials. Meta analyses will be conducted using Review Manager V.5.3 software. GRADE will be used to evaluate the level of evidence for each outcome.
Results: This systematic review and meta-analysis will be conducted following PRISMA statement. The results will be published in a peer-reviewed journal.
Conclusion: This review will provide scientific evidence to support health insurance policy as well as the standardization of PA in clinical practice.

Keywords: pharmacoacupuncture, frozen shoulder, adhesive capsulitis, periarthritis of shoulder, systematic review, meta-analysis

INTRODUCTION

Frozen shoulder (FS), or adhesive capsulitis or periarthritis of the shoulder, is challenging for both patients and clinicians. FS symptoms include any combination of stiffness, nocturnal pain, and limitation of active and passive glenohumeral joint movement. Symptom severity typically varies with disease progression [1]. FS commonly has a spontaneous prognosis and involves three phases: phase 1, the painful phase, involves 10- to 36 weeks of progressive pain and limited range of motion (LROM); phase 2 involves progressive stiffness, with 4 to 10 months of stiffness, gradual pain relief, and persistent LROM;

and phase 3, or thawing, with 12 to 40 months of gradual LROM improvements [1].

While the pathology of FS is poorly understood, major concerns include the proliferation of type I and type III fibroblasts, similar to Dupuytren's disease, and capsular and bursal tissue inflammation [2]. FS can be classified as primary, with no significant cause, or secondary, with underlying triggers, such as articular trauma [3]. FS prevalence in the general population varies between 2-5%, and it is most common in females and patients older than 40. In Korea, 10,447 patients had FS in 2014, a 1.58 million USD economic burden to the national health insurance [4, 5].

Nonsurgical treatment is often recommended for FS. Physical therapy is the first-line treatment for early-stage patients [3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide short-term pain relief, and injection therapy (e.g., corticosteroid injection [CSI] or hydrodilatation [HD]) may improve pain and shoulder function more quickly than oral medications [3]. Arthroscopic capsular release has recently emerged as a minimally invasive treatment option [6]. Although these interventions may have therapeutic effects on FS symptoms, the adverse effects often persist [7, 8].

There is growing interest in complementary and alternative therapies due to the limitations of conventional FS treatments. Studies indicate that traditional Korean medicine (TKM), which uses acupuncture, moxibustion, cupping therapy, and herbal medicines, has potential therapeutic effects on FS [9-11]. Pharmacoacupuncture (PA), or herbal acupuncture, is a novel form of TKM acupuncture that combines conventional acupuncture with herbal or animal-based extract injections into acupoints. In China, PA is known as acupoint injection, although it has a different origin and is sometimes used in combination with Western injections. Compared with traditional acupuncture, PA has a rapid therapeutic effect, combines the synergistic effects of biochemical herbal components and the physical stimulation of acupoints, and easy dosage control [12-14]. Although PA is primarily utilized for musculoskeletal diseases, research suggests it may be used to treat idiopathic Parkinson's disease, asthma, cancer, and post-stroke management [15-19].

PA could be an alternative injection therapy for FS owing to its similarity with CSI and HD and its comparable specificity. Both PA and CSI are injected into the affected lesion to exert anti-inflammatory effects [15, 20]. PA and HD also have volume effects, with the injected material distending the surrounding tissue [3, 21]. However, CSI and HD are injected into intra-articular lesions, presenting an infection risk, and possibly negatively impacting the surrounding rotator cuff tissue [3, 22, 23]. Furthermore, CSI has a short-lived clinical effect, and HD's therapeutic effect is unclear [24, 25]. Meanwhile, PA mainly targets soft tissue reaction points or acupoints on the body's surface. The nontoxic aromatic substances in some of the herbal extracts are expected to have therapeutic effects [15].

There have been some clinical trials examining PA for FS. However, no review has covered the selected acupoints and their anatomical considerations; the dose, injection depth and frequency, and PA type; or PA's efficacy and safety. Therefore, our systematic review aims to standardize the use of PA in clinical practice and validate its therapeutic effect on FS compared with conventional and other TKM therapies.

MATERIALS AND METHODS

1. Study registration and reporting guidelines

This protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) 2015 statement guidelines, as displayed in the PRSIMA-P checklist (Supplementary Table S1) [26]. The protocol was registered in PROSPERO on 18 July 2023 (number CRD42023445708).

2. Eligibility criteria

1) Study types

This review will include randomized controlled trials (RCTs) that assess the effectiveness of PA as an intervention for FS. Crossover trials will be included only if the pre-washout outcome measurements were presented to prevent carryover effects. We will exclude nonrandomized trials, laboratory studies, literature reviews, and trials that include healthy or improperly randomized participants. There will be no limitations regarding the publication language.

2) Participants

Patients diagnosed with FS will be included, regardless of the diagnostic criteria. Patients in all phases of FS are eligible for this review. There will be no restrictions on participants' age, gender, or race imposed.

3) Intervention types

RCTs that used PA as an intervention will be included. Trials evaluating Western injections alone (ex., lidocaine, dexamethasone, etc.) or in combination with herbal extracts will be excluded. However, trials investigating a mixture of herbal extracts with normal saline for dilution will be included. There will be no limitations on dose, frequency, duration, or herbal extract components.

4) Comparator types

There are no limits on comparators. Trials including placebo or sham, conventional, and other alternative therapies will be considered for this review. If combination therapy was applied for both the intervention and control groups, the comparators should be consistent, except for the inclusion of one therapy against PA.

5) Outcome measures

The primary outcome measure will be pain intensity, as evaluated by confirmed pain scales such as the visual analog scale (VAS) and the numerical rating scale (NRS). Secondary outcomes will include effective rate, Constant-Murley Score (CMS), Shoulder Pain and Disability Index (SPADI), range of motion (ROM), quality of life (QoL), and adverse events.

3. Search strategies for study identification

1) Electronic databases

We will search the following electronic databases for RCTs up to Aug. 31, 2023: Oriental Medicine Advanced Searching Integrated System (OASIS), Science-On, PubMed, Cochrane Library, Excerpta Medica database (Embase), CiNii, and the China National Knowledge Infrastructure (CNKI). We will use search terms such as "frozen shoulder," "adhesive capsulitis," "periarthritis of shoulder," "shoulder pain," "pharmacoacupuncture," "pharmacopuncture," "acupoint injection," and "randomized controlled trial" in each database. Table 1 shows an example of a PubMed search strategy.

2) Other resources

We will manually search for additional studies from the reference lists of retrieved articles. We will email the corresponding author if needed.

Table 1. PubMed search strategy

	PubMed
Searches	
#1	"Shoulder pain"
#2	"Periarthritis"
#3	"Frozen shoulder" OR "adhesive capsulitis"
#4	#1 OR #2 OR #3
#5	"Pharmacopuncture" OR "pharmacoacupupncture" OR "herbal acupuncture"
#6	"Bee venom acupuncture" OR "sweet bee venom" OR "bee venom" OR "sweet BV"
#7	"Point injection" OR "hydro-acupuncture" OR "acupoint injection"
#8	#5 OR #6 OR #7
#9	#4 AND #8
#10	Randomiz* OR RCT OR "controlled trial"
#11	Search: #9 AND #10

*Means a broaden search by finding words that start with the same letters.

4. Data collection and analysis

1) Study selection

Two reviewers (JHL and SangHP) will screen and review all articles for eligibility. First, the studies' titles and abstracts will be screened. Irrelevant articles will be removed, and then the full text of screened trials will be reviewed according to the inclusion and exclusion criteria. Any disagreements during the study selection process will be resolved by a third party (SeoHP) (Fig. 1).

2) Data extraction and management

Search results will be organized by the citation management program EndNote 20. Two reviewers (JHL and HSP) will independently extract the following data from eligible trials: author(s), publication year, country, study design, patient information, intervention and comparator details, outcome measures, results, and adverse events. A third party (SangHP) will verify the data. All five reviewers will settle disagreements via a discussion. For incomplete and uncertain data, further information will be requested from the corresponding authors. In the case of no reply, we will extract the available data and describe the reason for and expected impact of this exclusion in the manuscript.

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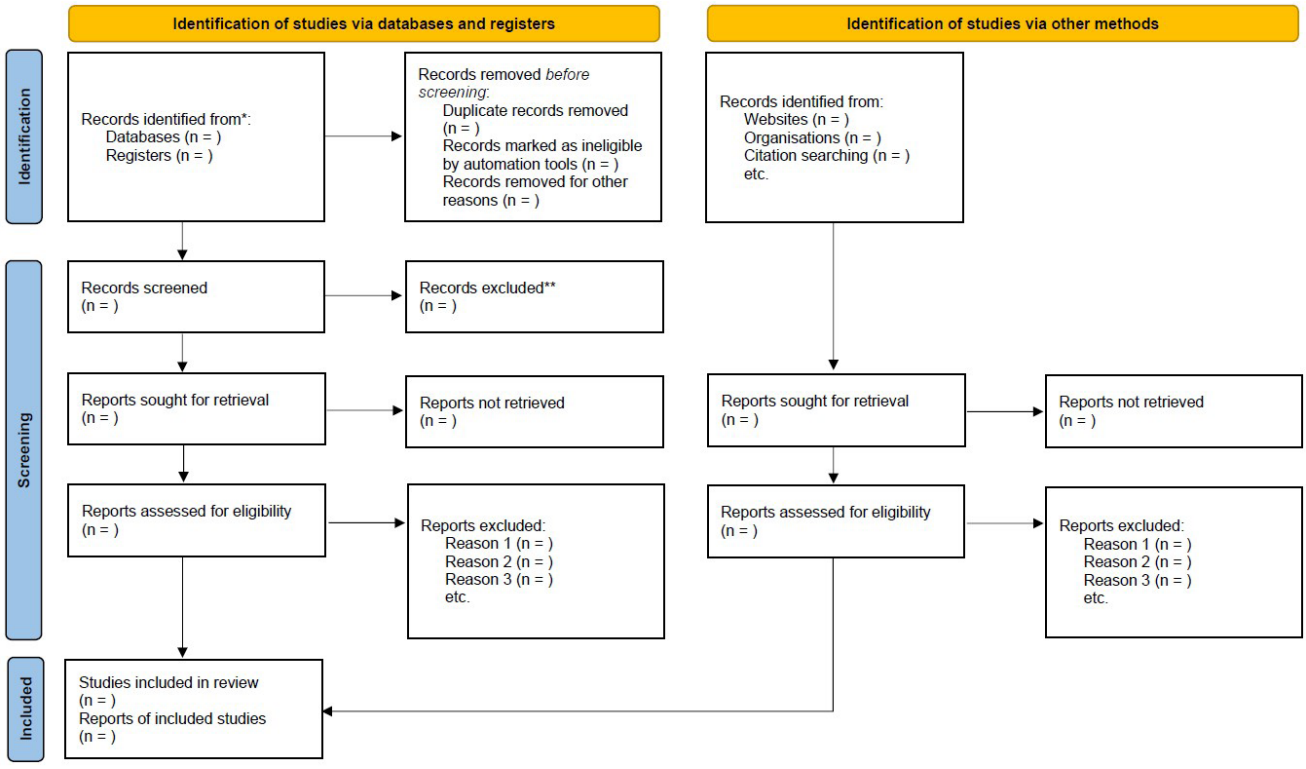

Figure 1. PRISMA 2020 flow diagram.

3) Data synthesis and analysis

We will evaluate changes in outcome measures between the intervention and control groups. We will apply random- or fixed-effect models for data synthesis and use Review Manager version 5.3 (Copenhagen, the Nordic Cochrane Centre, the Cochrane Collaboration, 2014) to conduct meta-analyses. Dichotomous data will be calculated as risk ratios (RR) with 95% confidence intervals (CIs). For continuous data, we will calculate the mean difference with 95% CI in the same scales and the standardized mean difference with 95% CI in different scales.

We will assess heterogeneity using the I^2 and Q^2 statistics based on the Cochrane Handbook for Systematic Reviews of Interventions [27]. The results of the I^2 statistic will be interpreted as 0%-40%, unimportant heterogeneity; 30%-60%, moderate heterogeneity; 50%-90%, substantial heterogeneity; and 75%-100%, considerable heterogeneity. For the Q^2 statistic, $p < 0.10$ will be considered statistically significant. We will perform sensitivity analyses and meta-regressions to resolve high levels of heterogeneity, with subgroup analyses if possible. Narrative synthesis will only be considered if the data from the included trials are insufficient for quantitative synthesis.

4) Reporting biases

We will assess reporting bias through visual asymmetry of a funnel plot if more than 10 RCTs are included in the study [28]. If needed, we will apply Egger's or Begg's test for further analysis.

5) Subgroup analysis

To identify the therapeutic effect of PA on FS against conventional and other TKM therapies, we will first conduct a subgroup analysis based on the homogeneous comparators. To further identify the source of heterogeneity, we will perform a subgroup analysis for each outcome measure using various effect modifiers, if possible: (1) participants: FS type (primary or secondary) and baseline scores of the outcome measure; and (2) treatment intervention: PA type, dose, duration, and session. These results will be interpreted with caution.

6) Sensitivity analysis

If possible, we will conduct sensitivity analyses to identify the impact of various factors on effect sizes and to assess the robustness of the results. The criteria will be: (1) excluding each trial individually; (2) excluding trials according to the risk of bias determined by the risk-of-bias assessment tool; (3) using

different meta-analysis models; and (4) other factors, such as publication language and country.

7) Grading the level of evidence

Two reviewers (JHL and HSP) will evaluate the level of evidence for each outcome and categorize them as high, moderate, low, and very low based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [29]. Any disagreements during the GRADE assessment will be resolved by discussion with a third party (DHK). We will use the GRADEpro Guideline Development Tool to present the results and summarize the findings in a concise tabular format.

8) Risk of bias assessment

Two reviewers (JHL and SangHP) will independently assess the risk of bias using the Cochrane Handbook's risk-of-bias assessment tool version 5.1.0, which accounts for these seven domains: sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The reviewers will resolve any disagreements through discussion.

5. Ethics and dissemination

Ethical approval is not required for this review, as it does not involve patients' private data.

RESULTS

This systematic review and meta-analysis will be conducted according to the PRISMA statement. The results will be published in a peer-reviewed journal.

DISCUSSION

FS is a challenging musculoskeletal disease that affects patients' quality of life by limiting their range of motion and inflicting nocturnal pain. While conventional treatments are widely used to alleviate the physical and economic burdens associated with this condition, their therapeutic effects are often lacking, necessitating alternative and complementary therapies. There are many ongoing and published studies evaluating the clinical effectiveness of TKM as an alternative FS treatment.

PA is a novel TKM acupuncture therapy that targets soft tissues on the body's surface via the injection of nontoxic substances— herbal or animal extracts—into acupoints. PA's anti-inflammatory and volume effects are similar to those of conventional CSI and HD, which are widely used for FS, despite their limited and adverse effects. Given PA's similarities to CSI and HD and comparable specificity, PA is a possible alternative injection therapy for FS.

We will use pain scales as the primary outcome when evaluating PA's effectiveness in clinical applications because pain is one of the most critical characteristics of FS. We will first consider VAS and NRS, which are frequently used to assess pain because of their simplicity and objectivity. Functional shoulder improvement will be evaluated by the CMS, SPADI, ROM, and QoL, and adverse events will be collected to confirm the safety.

If possible, we will discuss dosage, injection depth and frequency, PA type, and selected acupoints with their anatomical analysis to standardize clinical practice. This may suggest the mechanism of action for PA's therapeutic effect on FS and propose directions for future research.

Our review will have some expected limitations. First, we anticipate that the majority of included trials will be conducted in China, as this is the leading nation in clinical trials regarding traditional oriental medicine [30]. This may lead to publication bias in the pooled results. Second, an insufficient number of well-designed trials and a small sample size may result in clinical heterogeneity across studies and a small study effect. Third, variance in the application of pharmacoacupuncture and broad inclusion of comparators may lead to the risk of significant heterogeneity between the included studies.

CONCLUSION

To our knowledge, no previous reviews have provided scientific evidence regarding the use of PA for FS, impeding standardization of its clinical application and coverage by health insurance policies. Clinical practice and health policy should be guided by robust scientific evidence. This review provides evidence to establish health insurance policies and PA standardization in clinical practice.

ABBREVIATIONS

FS, Frozen shoulder; LROM, Limited range of motion; PA, Pharmacoacupuncture; TKM, Traditional Korean Medicine; CSI, Corticosteroid injection; HD, Hydrodilatation; RCT, Ran-

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domized controlled trial; VAS, Visual Analogue Scale; NRS, Numeral Rating Scale; CMS, Constant Murley Score; SPADI, Shoulder Pain And Disability Index; ROM, Range Of Motion; QoL, Quality of Life; CI, Confidence interval.

AUTHORS' CONTRIBUTIONS

Conceptualization: Ji-Ho Lee, Seo-Hyun Park. Methodology: Hyeon-Sun Park, Sang-Hyeon Park. Investigation: Ji-Ho Lee, Hyeon-Sun Park, Sang-Hyeon Park. Project administration: Seo-Hyun Park, Dong-Ho Keum. Funding acquisition: Seo-Hyun Park. Supervision: Seo-Hyun Park. Writing – Original draft: Ji-Ho Lee, Seo-Hyun Park. Writing – Review & Editing: Hyeon-Sun Park, Sang-Hyeon Park, Dong-Ho Keum.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this work.

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SUPPLEMENTARY MATERIALS

Supplementary data is available at https://doi.org/10.3831/KPI.2024.27.1.14.

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