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STUDY PROTOCOL

Efficacy, Safety and Cost-Effectiveness of Thread-Embedding Acupuncture for Adhesive Capsulitis (Frozen Shoulder): A Study Protocol for a Multicenter, Randomized, Patient-Assessor Blinded, Controlled Trial

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Background: The aim of the present study is to confirm the efficacy, safety, and cost-effectiveness of thread-embedding acupuncture (TEA) in the treatment of adhesive capsulitis (AC).

Methods: This is a randomized, sham-controlled, patient-assessor blinded trial with two parallel arms in a 1:1 ratio. A total of 160 participants with AC, also known as frozen shoulder, will be recruited and screened according to the eligibility criteria. Those who meet the eligibility criteria will be randomly allocated to a TEA group or a sham TEA (STEA) group. Both groups will receive either real TEA or thread-removed STEA treatment on nine acupoints once a week for 8 weeks while being blinded to the intervention. The shoulder pain and disability index will be evaluated as a primary outcome measure. In addition, a 100-mm pain visual analogue scale, rotator cuff quality of life scale, European Quality of Life 5-dimension 5-level scale, treatment satisfaction, safety assessment, and economic evaluation will be assessed as secondary outcome measures. Outcome assessments will be conducted for a total of 24 weeks, including a treatment period of 8 weeks and follow-up of 16 weeks, according to the schedule.

Discussion: The results of this trial will provide a clinical basis for the efficacy, safety and cost-effectiveness of TEA in the treatment of patients with AC.

Trial Registration Number: KCT0005920 (Clinical Research Information Service of the Republic of Korea). Registered on 22 February 2021.

Keywords: thread-embedding acupuncture, adhesive capsulitis, frozen shoulder, randomized controlled trial, protocol

Introduction

Adhesive capsulitis (AC) of the shoulder joint, also known as frozen shoulder, is diagnosed with shoulder pain and limited range of motion (ROM) that occur for no identified reason. The incidence rate is about 2–4% of the general population, and it is characteristically more common in women and people 40–60 years of age.[1–3] Severe pain around the shoulder, especially at night where the pain usually commences, and long-lasting active and passive limited ROM significantly disrupt daily life and

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occupational activities.[4–6] AC is considered a self-limiting disorder that usually resolves completely within 1–3 years. However, symptoms may not be completely resolved in 20–50% of patients for up to 10 years.[7,8]

AC treatment focuses on managing shoulder pain and restoring movement function. During the period of severe pain, non-steroidal anti-inflammatory drugs and corticosteroids can be used for pain management. As the pain gradually decreases and the limitation of the ROM intensifies, treatment aimed at functional recovery, such as self-exercise, physical therapy, or surgical interventions, may be required.[9,10] Acupuncture has also been suggested as a therapeutic option to reduce pain and improve function in patients with AC.[11]

Thread-embedding acupuncture (TEA) is a unique type of acupuncture method, in which an absorbable thread, such as catgut or polydioxanone (PDO), is inserted and embedded into the body using acupuncture needles. Because the stimulation period is more prolonged by the inserted thread than that of conventional needle acupuncture, TEA has been increasingly used for various diseases, especially musculoskeletal diseases including low back pain, lumbar herniated intervertebral disc, knee osteoarthritis, and chronic neck pain.[12–15] According to a randomized clinical trial (RCT) using TEA for herniated intervertebral disc of the lumbar spine, TEA showed long-term maintenance effect after 8 weeks of the follow-up period.[16] Regarding AC, there was an observational study involving 57 patients with 10 sessions of TEA suggesting the effectiveness of TEA in pain and function.[17] Based on this, it is necessary to create high-quality evidence about TEA to confirm its effect on AC.

In this trial, the efficacy, safety, and cost-effectiveness of TEA will be compared with that of a sham TEA on a large scale and for a long term through a rigorously designed full-scale multicenter randomized controlled trial to provide a clinical basis for the use of TEA for AC.

Methods

Trial Design

This study is a multicenter, randomized, patient-assessor blinded, sham-controlled trial with two parallel arms (1:1 ratio). The trial will be conducted at the Kyung Hee University Hospital at Gangdong, Dongguk University Bundang Oriental Hospital, and Pusan National University Korean Hospital. The efficacy, safety, and cost-effectiveness of TEA in patients with AC will be evaluated by comparison with sham TEA (STEA). The flowchart of the trial is presented in Figure 1.

This protocol was approved by the Institutional Review Board (IRB) (approval number: KHNMCOH 2020-10-013) and registered at the Clinical Research Information Service of the Republic of Korea (registration number: KCT0005920). The methodology was established in accordance with the Standards for Reporting Interventions in Clinical Trials of Acupuncture and the Standard Protocol Items: Recommendation for Interventional Trials.[18,19]

Participants

Inclusion Criteria

Individuals who meet the following inclusion criteria will be included in this study:

1. adult men and women between the ages of 25 and 65
2. unilateral shoulder pain for more than 6 weeks and less than 12 months
3. significant pain of 50–100 mm on a 100-mm pain visual analogue scale (VAS) during activity (daily life movement or light exercise).
4. restriction of passive ROM more than 25% in two or more motions compared to the healthy side.
5. diagnosis of AC by excluding fracture, dislocation, osteoarthritis, and calcific tendinitis from simple radiography.
6. ability to communicate sufficiently with the researcher and complete the questionnaire.
7. voluntary agreement to participate with written informed consent.

Exclusion Criteria

Participants who meet following characteristics will be excluded:

1. severe pain at rest for more than 70 mm on a 100-mm pain VAS.

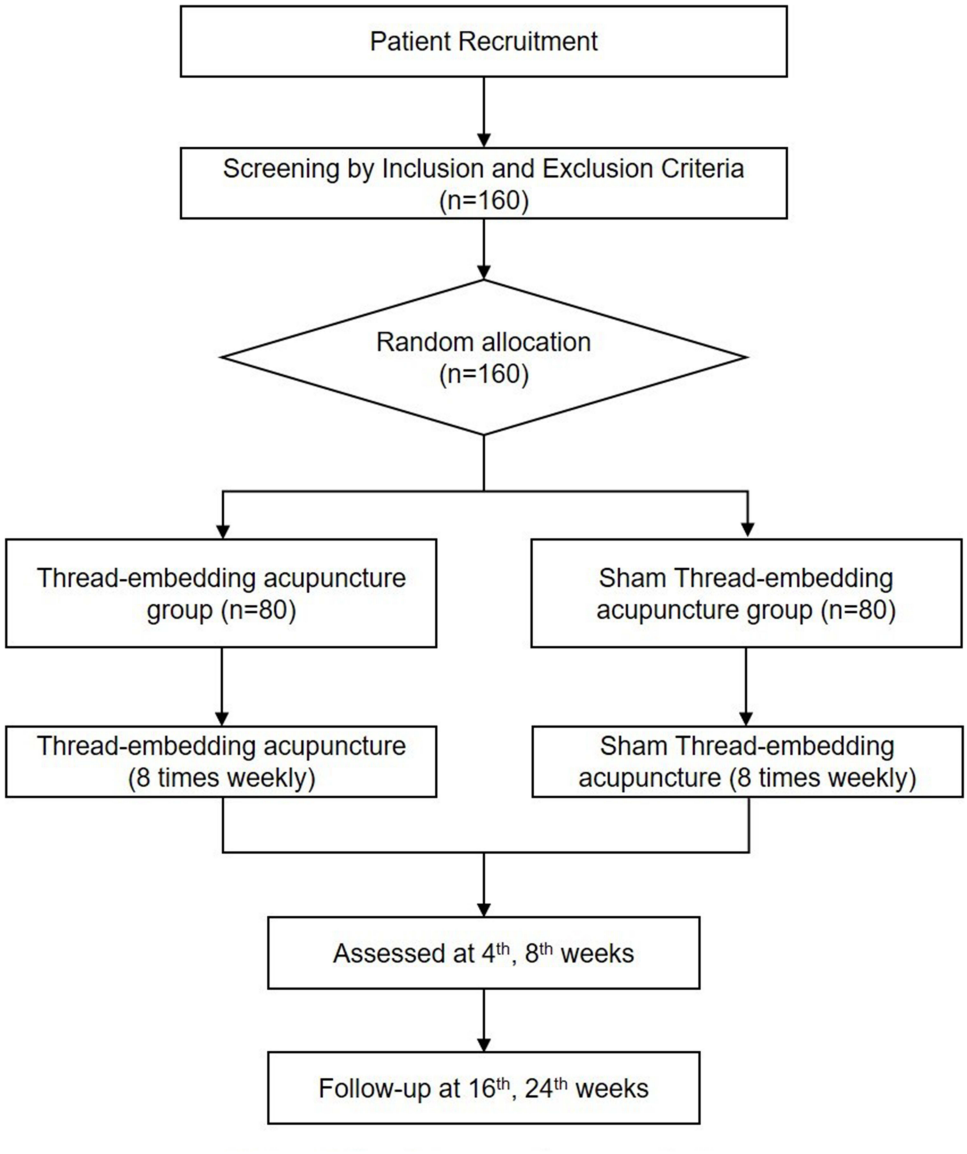

Figure 1 Flow diagram of the study design.

2. restriction of passive ROM of more than 50% in two or more motions compared to the healthy side.
3. a positive drop arm test or empty can test to rule out a rotator cuff tear.
4. Previous history of surgery or significant injury on shoulder.
5. shoulder pain accompanied with stroke, spinal cord injury, or other surgeries.
6. systemic pathology, including inflammatory joint disease or tumor.
7. cervical spine or other upper limb joint disease which significantly affects the shoulder.
8. intra-articular steroid injections within 3 months before participating in the clinical trial.
9. medication history of anti-inflammatory drugs within the previous 2 weeks.
10. musculoskeletal disorders which may affect efficacy evaluation or any joint disease which makes it impossible for the individual to participate in the clinical trial.
11. taking medicine for mental disorders.
12. Women who are pregnant, lactating, or of childbearing age who are unwilling to avoid pregnancy during the trial period.
13. participants who are judged unqualified by the researchers.

Criteria for Elimination

Participants will be dropped out of the study if they meet the following criteria during the trial.

1. if a participant requests discontinuation of treatment during the clinical trial or withdraws consent to participate in the trial.
2. if a serious adverse event (AE) occurs during the trial.
3. if a major violation of the protocol such as not meeting the inclusion/exclusion criteria is newly discovered during the trial.
4. if a participant receives less than six out of the eight treatment sessions.
5. if a participant takes medicines prohibited during the trial.
6. if the researcher in charge concludes that the trial should be terminated.

Procedure

A total of 160 participants who met the eligibility criteria will be recruited competitively at three institutions. All participants will be informed that they can participate voluntarily and withdraw their consent at any stage. They will also be given essential information about the study protocol, which includes the purpose, selection of participants, interventions by random allocation, schedule, expected benefits and risks, alternative treatment options, and confidentiality of the trial. Those who voluntarily agree and sign the informed consent form will be screened through the eligibility criteria. Participants meeting the eligibility criteria will be randomly allocated to either the TEA or STEA group. After random allocation, 10 visit sessions for 24 weeks, including 8 weeks of treatment and 16 weeks of follow-up, will be conducted according to the scheduled appointment (Table 1).

Interventions

The intervention will be carried out once a week for a total of eight weeks using a 29-gauge TEA needle with a 40-mm PDO thread (Hyundae Meditech, Wonju, South Korea) in the TEA group or a thread-removed needle alone in the STEA group. A total of 9 TEA or STEA will be inserted, and the location and technique will be determined by the consensus of the clinical expert group in reference to previous studies.[17,20–22] Details of the intervention are described in the STRICTA checklist (Table 2).

After blinding the participant from seeing the procedure and sterilizing the skin, intervention will be conducted by the practitioners. After inserting the TEA completely to the end of the needle, thread will be left in the body unexposed by removing only the needle. If the thread is exposed, it will be removed safely, and the procedure will be performed again only in the removed location. For the sham control, STEA group will be conducted with thread-removed needles instead of the normal TEA. The thread removal procedure will be performed aseptically and carefully to avoid infection, while maintaining patient blinding. All therapeutic procedures and assessments will be performed by qualified acupuncture specialists with at least 3 years of experience who received a common training program for the uniformity of intervention at each site.

Primary Outcome Measure

The primary outcome measure is an index of shoulder-related pain and dysfunction. All assessments will be performed by an independent researcher who is not related to the intervention process.

Shoulder Pain and Disability Index (SPADI)

Shoulder-related pain and dysfunction will be assessed using the SPADI at visit 1 (baseline), 4, 8 (end of treatment), 9, and 10 (end of follow-up). The SPADI is divided into two subcategories for pain and disability, each with 5 and 8 items. All items are evaluated on a 10-point Likert scale (0 indicating “no pain” or “no difficulty”, 10 indicating “worst imaginable pain” or “so difficult it required help”). The SPADI score is calculated out of 100 (higher score indicating more pain/disability).[23]

Table 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure

	STUDY PERIOD											
	Enroll	Allocation	Intervention								Follow-Up	
TIMEPOINT (WEEK)	**−2~0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**16**	**24**
ENROLLMENT:												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
INTERVENTIONS:												
Thread-embedding acupuncture or sham thread-embedding acupuncture			X	X	X	X	X	X	X	X		
ASSESSMENTS:												
Shoulder pain and disability index		X				X				X	X	X
100-mm pain visual analogue scale	X	X				X				X	X	X
Shoulder range of motion	X	X				X				X	X	X
Rotator cuff quality of life		X				X				X	X	X
European Quality of Life 5-dimension 5-level scale		X				X				X	X	X
Treatment satisfaction score										X	X	X
Economic evaluation		X								X	X	X
SAFETY ASSESSMENTS: Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Blood tests	X									X		
Adverse events	◆———	———	———	———	———	———	———	———	———	———	———◆	

Secondary Outcome Measures

100-mm Pain VAS

The severity of the shoulder pain will be evaluated using the 100-mm pain VAS at visit 1 (baseline), 4, 8 (end of treatment), 9, and 10 (end of follow-up). Participants will be asked about severity of the pain at rest, exercise, and at night.

Shoulder ROM

Shoulder ROM will be measured at visit 1 (baseline), 4, 8 (end of treatment), 9, and 10 (end of follow-up) by using goniometer. The passive ROM will be examined in four motions, including forward flexion, abduction, external rotation at the side, and internal rotation to the posterior.

Rotator Cuff Quality of Life (RC-QoL)

The disease-specific quality of life will be assessed using RC-QoL at visit 1 (baseline), 4, 8 (end of treatment), 9, and 10 (end of follow-up). RC-QoL, which consists of 34 questions and 5 subscales, is a patient-reported questionnaire about "full spectrum of rotator cuff disease", including (1) symptoms and physical complaints; (2) work-related concerns; (3) recreational activities, sports participation, or competition concerns; (4) lifestyle concerns; and (5) social and emotional concerns. The RC-QoL score is calculated out of 100. The highest score is 100, meaning the best quality of life or no symptoms, and the lowest score is 0, meaning the worst quality of life.[24]

Table 2 Details of the Thread-Embedding Acupuncture Treatment Using the STRICTA 2010 Checklist

Item	Detail
1. Acupuncture rationale	1a. Style of acupuncture: thread-embedding acupuncture
	1b. Reasoning for treatment provided (based on historical context, literature sources, and/or consensus methods, with references where appropriate): By the consensus of a group of clinical experts, modified from that used in a previous study[18,23]
	1c. Extent to which treatment was varied: No variation
2. Details of needling	2a. Number of needle insertions per subject per session: Nine acupoints
	2b and 2c. Names of points used and depth of insertion, based on a specified unit of measurement, or on a particular tissue level: 1) Transverse insertion on SI2 toward LI16 and SI13 toward SI12 near supraspinatus muscle 2) Transverse insertion on SI1 toward SI10 and SI11 toward SI12 near infraspinatus muscle 3) Direct insertion on SI9 near the teres minor muscle 4) Transverse insertion on LI15 and TE14 toward lateral deltoid muscle 5) Transverse insertion on HT1 toward TE14 and HT1 toward subscapular fossa near subscapularis muscle
	2d. Response sought: None
	2e. Needle stimulation: No additional stimulation
	2f. Needle retention time: No retention time of needle other than embedding the thread
	2g. Needle type: 29 gauge × 40mm thread-embedding acupuncture (Hyundae Meditech, Wonju, South Korea)
3. Treatment regimen	3a. Number of treatment sessions: Eight sessions
	3b. Frequency and duration of treatment sessions: Once a week for 8 weeks
4. Other components of treatment	4a. Details of other interventions administered to the acupuncture group: None
	4b. Setting and context of treatment, including instructions to practitioners, and information and explanations to patients: Minimized conversation between practitioner and participant
5. Practitioner background	5. Description of participating acupuncturists: Specialists of acupuncture and moxibustion
6. Control or comparator interventions	6a. Rationale for the control or comparator in the context of the research question, with sources that justify this choice: Thread-removed needle will be used as a comparator. In this manner, the specific effect of the thread only will be derived.
	6b. Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used (provide details as for Items 1 to 3 above): All conditions other than the use of the thread-removed needle will be the same as those in the real thread-embedding acupuncture group.

European Quality of Life 5-Dimension 5-Level (EQ 5D-5L) Scale

Korean version of EQ 5D-5L will be used to assess the general health status of participants at visit 1 (baseline), 4, 8 (end of treatment), 9, and 10 (end of follow-up). The EQ-5D-5L consisted of five questions: morbidity, personal care, daily activities, pain/discomfort, and anxiety/depression. Each question is rated from 1 to 5 (1, no problem; 2, slight problems; 3, moderate problems; 4, severe problems; 5, extreme problems). A patient's current health status can be assessed by the EQ 5D-5L. It is a 20-cm scale numbered from 0 to 100 (0, worst health condition imaginable; 100, best health condition imaginable).[25]

Treatment Satisfaction Evaluation

Treatment satisfaction will be evaluated with three questions using a 10-point scale at visit 8 (end of treatment), 9, and 10 (end of follow-up). Three questions consisted of items about satisfaction with the treatment, intention for additional

treatment in the future, and willingness to recommend the treatment to other people. The participants will score each question from 1 (very unsatisfied) to 10 (very satisfied).

Economic Evaluation

Cost-effectiveness analysis of the treatment is based on a trial-based economic evaluation. From a social point of view, direct medical costs, direct non-medical costs, and indirect costs will be investigated at visit 1 (baseline), 8 (end of treatment), 9, and 10 (end of follow-up). Direct medical costs will be collected through data from medical institutions and receipts provided by patients. Direct non-medical costs, including transportation, nursing, and patient time costs, will be derived through the patient questionnaire, and the institute for Medical Technology Assessment productivity costs questionnaire will be used for indirect costs. The wage data of Statistics Korea will be used to calculate patient time costs and indirect costs.

Safety Assessment

At each visit, vital signs such as blood pressure, pulse rate, and temperature will be evaluated. At screening and visit 8 (after 8 weeks), blood tests will be performed that include the following items: erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen, creatinine, alanine transferase, and alanine aminotransferase. For the blood test, 2–3 mL of venous blood will be collected from the forearm and analyzed in the clinical laboratory science department of the hospital. For women of childbearing age (age 25–45 years), except those who have been confirmed as menopause (amenorrhea 12 months or more), a pregnancy test using a urine strip kit will be conducted at the screening visit.

Information about expected AEs and education for reporting to researchers will be provided to the participants along with an informed consent. The researchers will check the occurrence of AEs at each visit and record the details of AEs, including symptoms, date of onset and recovery, outcome, severity, action on intervention and participants, and relevance with intervention in the case report form (CRF). If an AE occurs, researchers will provide appropriate examination and treatment according to compensation rules.

Sample Size

With a 1:1 ratio, medium effect size (Cohen's d = 0.5), 80% power, and a 0.05 significance level, sample size was calculated using G*power program.[26] Considering a 20% dropout rate, we concluded that 80 participants in each group is a reasonable sample size.

Randomization and Allocation Concealment

According to a block randomization procedure with a 1:1 ratio, a total of 160 participants will be randomly allocated to either the TEA group or the STEA group. The randomization sequence, with a block size of four, will be generated by an independent statistician using SAS (SAS Institute Inc., Cary, NC, USA). Random codes will then be sealed in opaque envelopes and managed by an independent blinding manager and principal investigator. After clinical trial participation is confirmed through screening, a random number will be assigned by opening the envelopes.

Blinding

This clinical trial is designed as a patient-assessor blinded study. Participants will be informed that they can be treated with one of two different treatments: TEA or STEA. They will receive treatment using the same standard needle in the same clinic environment, preventing them from recognizing the existence of a thread. Researchers who are not involved in the randomization or intervention will conduct assessment of outcomes. Assessors will simply ask questions for the evaluation and recording of the CRF without knowing which treatment group the participants were allocated.

Blinding information will be placed in a sealed form by the clinical research organization and provided to the principal investigator. If the blinding needs to be removed before the completion of the trial due to a serious AE, the investigator will review and approve the reason for blinding removal. In addition, the date and reason will be recorded in detail on the CRF, and the participants whose blinding has been cancelled will be withdrawn from the trial.

Data Collection and Management

In the data collection and management procedure, information on blinding will be provided only to designated investigators, including clinical research coordinators and practitioners. They will handle and cross-check the trial data. Data collected through blinded participants and assessors will be provided to independent statisticians by masking group information. All data and documents acquired during the study period will be kept confidential and all outputs of this clinical trial must be kept anonymous. Upon completion of the study, all documents will be discarded or preserved according to the management standards of the IRB.

Statistical Method

The statistical significance level will be set at 0.05 (two-sided). A linear mixed model (LMM) will be used to analyze the repeated measured outcome measures related to the effect. If data are missing at random, multiple imputation will be applied. Fixed factors in LMM will be treatment group (TEA versus STEA), time (visit 1, 8, 9, and 10), and the time-by-treatment group interaction.

Cost-effectiveness will be evaluated for the economic evaluation by calculating the incremental cost-utility ratio (ICUR). The quality-adjusted life year (QALY) will be calculated using EQ-5D-5L results based on the report by Jo et al.[27] ICUR will be calculated from the difference in QALY and total costs obtained through this trial between the TEA group and the STEA group. A tornado diagram will be presented by performing a deterministic sensitivity analysis on all possible parameters. Probabilistic sensitivity analysis will be performed using all possible parameters' distribution and representative values. We will present a cost-effectiveness acceptability curve that shows the probability that a treatment intervention will be more cost-effective than a comparative intervention as the willingness-to-pay changes. In addition, bootstrap using individual patient-level data will be performed to present the distribution of economic evaluation effect indicators.

For safety, the incidence of all AEs reported during the study period will be tabulated. The proportion of participants with AEs between each group will be compared using the chi-square test or Fisher's exact test.

Quality Control

To maintain the quality of the trial, the study procedure and documents will be monitored periodically in accordance with Korean Good Clinical Practice.

Discussion

This trial is planned to investigate the clinical effectiveness, safety, and cost-effectiveness of TEA in patients with AC. Among the therapeutic factors of TEA, the hypothesis that the clinical effect of TEA differs depending on the presence or absence of embedded thread is to be verified using STEA with the thread removed. In addition, it is designed to establish comprehensive clinical evidence of TEA for AC through a full-scale design that includes outcome measures for pain, function, quality of life, safety, and economic feasibility.

TEA is a novel method of acupuncture in that an absorbable thread is embedded in the body by inserting an acupuncture needle. The embedded thread has long-term effects through mechanical stimulation and chemical reaction. Based on these differentiated advantages, TEA has been used widely in China and Korea, for various diseases.[28] PDO, which is commonly used for surgical sutures, is safe and has a long absorption time. Due to these characteristics, PDO is generally used for the TEA.[29] In this trial, thread-removed STEA will be used as a control intervention regarding previous studies to confirm the thread-only effect excluding the needle-stimulating effect. Furthermore, to observe the effect of long-term maintenance 16 weeks of follow-up evaluation will be conducted after the completion of 8 intervention sessions.[30–32]

Patients with AC typically complain of nagging pain and global stiffness of the shoulder, which cause significant disability, restricting activities of daily living, leisure and work. It was previously known that AC recovers completely after 1 to 3 years of whole stage; however, according to long-term follow-up studies, 40–50% of patients suffer from

persistent pain and limitation of motion.[33,34] Since there is still no ideal strategy for treatment AC, it is necessary to search for an effective treatment.[35]

The progression of AC is commonly described as going through three or four stages, and the severity of pain and stiffness changes according to the stage.[6,36] In three stage classification, AC is divided into freezing, frozen, and thawing stages. Shoulder pain and limitation of ROM begins and progress gradually in freezing stage for 2 to 9 months. Loss of motion with pain persists in frozen stage for 4 to 12 months. ROM improves and pain subsides in thawing stage for 12 to 42 months.[33,34]

Considering the three-stage classification as the standard, the participants of this study correspond to the second stage with pain and limited ROM. To comprehensively evaluate the multifaceted clinical effect of TEA on AC, pain intensity, physical examination, and questionnaires about function and disease-specific and general quality of life are included as outcome measures in this trial.

This protocol also has one limitation. The calculated sample size may not be precise because there are no pilot studies referred to. Usually, an accurate sample size should be obtained using the standard deviation and mean difference of the pilot study. Future studies will be able to refer to the results of our study to determine the precise sample size of the studies.

The results from this trial will help provide clinical evidence of the efficacy, safety, and economic feasibility of TEA in the treatment of patients with AC during the treatment and long-term follow-up period. Consequently, these findings will aid clinicians in understanding and deciding on TEA as a therapeutic alternative for patients with AC.

Abbreviations

AC, adhesive capsulitis; AE, adverse event; CRF, case report form; EQ 5D-5L, European Quality of Life 5-dimension 5-level; ICUR, incremental cost-utility ratio; IRB, Institutional Review Board; LMM, linear mixed model; PDO, polydioxanone; QALY, quality-adjusted life year; RC-QoL, rotator cuff quality of life; ROM, range of motion; SPADI, shoulder pain and disability index; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; STEA, sham thread-embedding acupuncture; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture; TEA, thread-embedding acupuncture; VAS, visual analogue scale.

Trial Status

Protocol: version 2.3; 18 December 2020. Recruitment for the trial began on 14 September 2021. The trial is expected to be completed in December 2026.

Ethics Approval and Informed Consent

This study protocol of this study has been approved by the IRB of Kyung Hee University Hospital at Gangdong (reference: KHNMCOH 2020-10-013), and written informed consent form will be completed voluntarily prior to screening. Also, this trial will be conducted in compliance with the ethical guidelines of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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