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Acupuncture for Subacute and Chronic Post-thoracotomy Pain in Patients with Traumatic Multiple Rib Fractures: A Study Protocol for a Randomised-controlled, Two-arm, Parallel Design, Pilot Trial

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ABSTRACT

Background: The aim of this study is to assess the feasibility of acupuncture treatment for the management of subacute and chronic post-thoracotomy pain in patients with traumatic multiple rib fractures.
Methods: A total of 30 participants who have undergone thoracotomy after traumatic multiple rib fractures will be recruited. Participants will be invited and equally randomised into acupuncture plus usual care and usual care alone groups. A computer-generated random number sequence will be used and concealed using opaque, sealed, sequentially numbered envelopes. Twelve sessions of manual and electrical acupuncture performed by Korean medicine doctors will be provided over a span of 3 months to participants allocated to the acupuncture group. Participants in the usual care group will continue pain medication, exercise and physical therapy as required. Study feasibility will be measured based on the proportion of patients who complete the measurement of pain at 12 or 24 weeks after baseline. The clinical outcomes will include; the average pain intensity over the recent week at rest, movement and cough, quality of life, patient's global assessment of recovery, respiratory function measured by the pulmonary function test and use of pain medication at 4, 8, 12 and 24 weeks after enrolment. Adverse events will be recorded for all participants. Written informed consent will be obtained from all participants. The local ethics committee has approved the study.
This pilot trial will inform further studies investigating the potential role of acupuncture for subacute and chronic post-thoracotomy pain in patients with traumatic multiple rib fractures.

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Introduction

Patients with traumatic multiple rib fractures who undergo a thoracotomy often present with debilitating chronic pain following surgical intervention, which commonly does not respond well to analgesic treatment [1]. However, there is no standalone intervention to remedy this problem. associated with impaired daily function and diminished quality of life, which may compound patient's post-traumatic recovery.

The prevalence of chronic post-thoracotomy pain varies depending on the study characteristics, and in some cases it has been reported in 50% of patients with multiple rib fractures with or without thoracotomy [2,3]. Surgical incision of muscle fibres, nerve injury due to blunt chest trauma and surgical procedure, bony pain due to rib fractures and removal of fractured bones, have all been suggested as factors that contribute to chronic pain after thoracotomy [1]. However, contributing factors of chronic post-thoracotomy pain remain largely unknown.

Acupuncture is increasingly being used to treat chronic pain and associated symptoms. Cumulative, high-quality evidence supports the benefits of acupuncture for some types of common musculoskeletal chronic pain compared with the usual care alone

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[4]. Several studies have demonstrated pre-clinical evidence of the analgesic effects of acupuncture and shown relevant neurophysiological mechanisms in various experimental settings, which may justify further clinical investigation [5]. However, little is known regarding whether acupuncture would be effective for chronic post-thoracotomy pain after traumatic multiple rib fractures. This condition may differ from the reported treatment of degenerative musculoskeletal conditions where the pathophysiology of pain and symptom manifestation may not be the same.

A case in which a patient with chronic post-thoracotomy pain improved after a series of acupuncture treatments [6] has led to the design of a randomised, two-arm, parallel design, pilot trial to assess the feasibility of conducting further definitive randomised trials. This study specifically aims to investigate whether it is feasible to conduct a parallel group randomised controlled trial of acupuncture for patients with subacute and chronic post-thoracotomy pain after traumatic multiple rib fractures and, there are any barriers to recruitment or participation in the trial.

Materials and Methods

Randomisation and allocation concealment

For the purpose of concealment of allocation, an independent researcher will prepare sequentially numbered, opaque, sealed envelopes containing a random number table that would be generated by the statistical package STATA 14.2 (StataCorp, College Station, Texas, USA). Envelopes will be opened in the presence of the participant by a researcher.

Study context

This study will be a randomised, two-arm, parallel design, pilot trial performed in the outpatient clinic of the Trauma Centre at Pusan National University Hospital, a tertiary hospital, Busan, South Korea. The hospital covers the urban and rural areas of Busan, which had a population of approximately 3,520,306 residents in December 2017 [7]. The annual, surgical volume of thoracotomy for traumatic multiple rib fractures was 117 cases in 2016. Four specialist trauma surgeons, two Korean medicine doctors (KMDs) with more than 10 years of clinical experience in acupuncture treatment, a trauma centre nurse, and a research assistant, will serve as both clinical staff and trial investigators. Acupuncture treatments will be performed in the outpatient clinic.

Participant recruitment process

Patients who have previously undergone a thoracotomy after multiple rib fractures will be recruited. Eligible patients will be recruited either by invitation at the time of outpatient consultation, by the study surgeon or through hospital postings. Written informed consent will be requested from each participant after they have read all the trial information. Those participants who meet the full eligibility criteria and agree to participate, will be allocated to either 1) the acupuncture plus usual care group or 2) the usual care alone group. A trial flowchart and schedule are provided in Figs. 1 and 2.

Eligibility criteria

In this study, traumatic multiple rib fractures are defined as fractures of two or more ribs by any traumatic events (e.g., falling, vehicle accidents or being struck by objects). A thoracotomy is defined as open thoracic surgery to repair fractured ribs. Patients who underwent thoracoscopy will not be eligible.

Inclusion criteria

1) Multiple traumatic rib fractures, treated with a thoracotomy at the Pusan National University Hospital Trauma Centre
2) Patients aged 19 to 80 years
3) A period of more than 1 month since the surgery was performed
4) A pain intensity numeric rating scale (NRS) score of 4 or more during rest, movement, or coughing over the last week
5) An understanding of the research purpose and written informed consent
6) Ability to respond to the study questionnaire with or without assistance.

Exclusion criteria

1) Pregnancy
2) Underlying diseases that may affect postoperative outcomes; such as chronic kidney disease, chronic liver disease, cardiopulmonary insufficiency, or diabetes mellitus with complications.
3) Cognitive impairment that could affect the patient's ability to complete the outcome assessments
4) Previous history of stroke
5) Previous history of sensitivity reaction to acupuncture
6) Unable to cooperate with acupuncture treatments
7) Use of a pacemaker implant
8) Previous history of epilepsy
9) Recent treatment with acupuncture, moxibustion, cupping, or herbal medicine in the last 2 weeks.

Blinding of participants, practitioners, other relevant healthcare staff, outcome assessors and data analysers

This study will not be a placebo-controlled trial. Thus, information on the group allocation cannot be masked to participants, study KMDs and study surgeons. Outcome assessors will be blinded.

Usual care components

For all study participants, there will be no restriction on their usual pain management. Possible components of the usual care

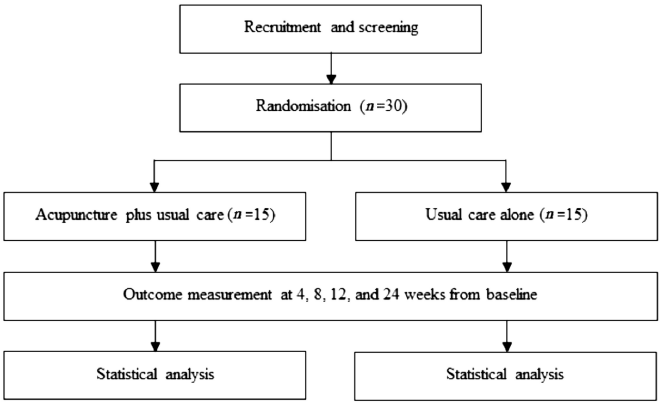

Fig. 1. Trial flowchart.

	STUDY PERIOD								
	Enrolment	Allocation (wk)	Post-allocation (wk)						Close-Out (wk)
TIMEPOINT	*-t_1*	0	*2, 3*	*4*	*5-7*	*8*	*9-11*	*12*	*24*
Enrolment:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
Interventions:									
Acupuncture			X	X	X	X	X	X	
Usual care (both groups)			X	X	X	X	X	X	
Assessments:									
Demographic information	X								
Clinical characteristics	X								
Physical examination	X								
Vital signs	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Pain intensity numeric rating scale	X			X		X		X	X
Quality of life		X						X	X
Use of medications		X		X		X		X	X
Pulmonary function test		X							X
Patient global assessment								X	X

Fig. 2. Schedule for enrollment, interventions, and assessments.

include standard medication (e.g., acetaminophen, non-steroidal anti-inflammatory drugs, anti-convulsant drugs, pregabalin, gabapentin, opioid or other doctor-prescribed medications), paravertebral or epidural injection, physical therapy, exercise (either supervised or self-performed), or other types of interventions to relieve chronic pain. Use of medication or other healthcare resources spent (in the usual care setting) will be documented through participant's self-reporting.

Study acupuncture

Twelve weekly sessions of acupuncture will be provided over a duration of 3 months following enrolment. Stainless-steel disposable acupuncture needles (0.20 x 30 mm, 0.25 x 30 mm, 0.25 x 40 mm or 0.30 x 60 mm, Dongbang, Inc., Ltd.) will be inserted into the body points of Back-shu (BL12 to BL19), ipsilateral peri-segmental areas of the affected dermatomes and paravertebral points located bilaterally on the level of C3 to C7 spinous processes. Optional points on the ipsilateral shoulder and bilateral extremities will be used if necessary. After insertion, manual stimulation of acupuncture needles will be performed to achieve *De-qi* sensation where appropriate. Subsequent electrical stimulation of selected points (e.g., the Back-shu point and the ipsilateral peri-segmental areas of the affected dermatomes or common points for chronic pain management such as LI4 to LI11 or ST36 to LR3) with alternating frequency of 2 to 100 Hz, a biphasic square wave and comfortable intensity as assessed by the patient (ES-160, Ito, Tokyo, Japan) will be performed. Appendix 1 shows further information about the acupuncture treatments.

Concomitant treatments

No restrictions will be placed on the use of non-study concomitant treatments. However, out-of-study Korean medicine (e.g., acupuncture or herbal medicine by non-study KMDs) will be gently discouraged during the intervention period (i.e.,3 months) to avoid potential bias from misclassification of study interventions. Participants will be asked to report the use of healthcare resources outside the trial.

Criteria for discontinuing or modifying interventions

The protocol of acupuncture treatments will be discontinued or modified at the study physician's discretion or by the participant's request to avoid harm or participant discomfort.

Outcomes

Feasibility outcomes

Four feasibility outcomes will be measured.

1) Trial participation index

The proportion of enrolled study participants amongst the eligible study participants who underwent screening.

2) Trial completion index

The proportion of the participants who complete measurements of pain at 12 or 24 weeks after baseline amongst the total participants.

3) Treatment adherence index

The proportion of the participants who completed at least 8 sessions of acupuncture treatments for 3 months amongst the participants in the acupuncture group.

4) Trial attrition index

The proportion of the participants who withdrew from the study amongst the total participants.

Clinical outcomes

1) Pain intensity NRS

The pain scores on a NRS of 0 (no pain at all) to 10 (the worst pain imaginable) during rest, movement, or coughing over the last week will be assessed at baseline, as well as 4, 8, 12, and 24 weeks from baseline.

2) Quality of life

The quality of life will be measured using the validated Korean Short Form-12 health survey (SF-12 v2) at baseline, 12 and 24 weeks. The SF-12 v2 is a shorter version of the SF-36 v2 that uses 12 items, which addresses 8 domains of quality of life, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health [8].

3) Patient global assessment

The global assessment of the recovery will be performed by the participant themselves at 12 and 24 weeks from baseline. Response options during the assessment include "very much improved," "somewhat improved," "no change," "somewhat worsened," and "very much worsened." For the purpose of analyses, the responses of "very much improved" and "somewhat improved" will be categorized into "improved" and the remaining answers will be dichotomized into "not improved".

4) Pulmonary function test

The pulmonary function test will be performed at baseline and at 24 weeks from baseline. Three parameters including the forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and the ratio of FEV1 to FVC (FEV1/FVC) will be measured. For this test, patients will be instructed not to smoke for 4 to 6 hours before the test.

5) Use of medications

The medications used by the patient to control their symptoms will be recorded at baseline, 4, 8, 12, and 24 weeks. These medications include, but are not limited to, acetaminophen, non-opioids and opioids.

Adverse events

All expected and unexpected adverse events (AEs) will be measured during the whole study period. The types and frequencies of AEs will be recorded using both structured items and an open-ended question. Any serious adverse events (SAEs) occurring during the study period will also be investigated.

Sample size calculation

Recruitment of 15 participants into each group will be achievable in the research setting, given the available resources and accounting for a possible drop-out rate of 20%. A formal sample size for this pilot trial was not calculated.

Data management

Double data entry and range checks for data values after completion of final data collection will be performed by trained research assistants. A formal data monitoring committee will not be organised because the study acupuncture treatment is known to be safe in competent hands [9,10]. However, regular data monitoring and auditing for recruitment of participants, outcome collection and reporting of SAEs will be implemented by independent, trained investigators. The final dataset will be anonymised and be available to the first author and an independent statistician.

Confidentiality

Participant information collected from the study will be securely stored in a locked filing cabinet, placed in an area of limited access. A coded identification number for each participant will be used to protect participant confidentiality. Personal information (e.g., participant name, personal identifiers and informed consent forms) will be anonymised. All data and relevant reports will be compiled separately from other study records. We will restrict access to local databases by using password-protected systems. Other reports or materials that can be used as linkage information to participants' personal information to other anonymised data will be locked with limited access.

Statistical data analysis

Primary analyses will be based on the intention-to-treat population, defined as participants initially allocated in the study entry stage. A per-protocol population, defined as participants who complete the measurement of pain by NRS either at 12 or 24 weeks from baseline, will be used for sensitivity analyses. Missing data will be processed using the last observation carried forward (LOCF) method. For continuous outcomes, relative risk for dichotomous outcomes and mean difference with a 95% confidence interval, will be calculated. Chi-squared or Fisher's exact test will be used to test statistical significance where appropriate. Shapiro-Wilk analysis will test whether the data is normally distributed. Analysis of variance (ANOVA) or Kruskal–Wallis test will be used to compare descriptive continuous data amongst groups. Analysis of covariance (ANCOVA) will be performed with the changes in each continuous outcome as a dependent variable, baseline values as a covariate, and group as a fixed factor. The trend of changes in outcomes within each group will be assessed by repeated-measures ANOVA with factors of groups (acupuncture and control group) and time as separate two-level factors. We will regard the two-sided P-value < 0.05 as the level of statistical significance with 90% power. Statistical analysis will be performed by STATA/SE version 14.2 (Stata Corp, College Station, TX, USA).

Dissemination

We will present the trial results at academic conferences, and the completed trial will be submitted for publication in a peer-reviewed journal. The anonymised raw dataset will be available upon request after publication. Study results will be disseminated to relevant stakeholders, including participants, researchers and the hospital staff. Further information with regard to the trial can be requested from the corresponding author.

Written informed consent and study approval

Written informed consent will be obtained from each participant. The local ethics committee of Pusan National University Hospital approved the trial (approval number D-1801-025-063). Changes to the protocol will be notified to the local ethics committee and be transparently reflected in the trial registry and the final publication. A financial reimbursement of 100,000 Korean won (approximately 94 USD) for time spent and participation in the trial will be provided to the participants (Trial registration: Clinical Research Information Service: KCT0002780).

Discussion

This study will be the first to test the feasibility of conducting a randomised, parallel design trial of acupuncture for patients with subacute and chronic post-thoracotomy pain sustained following traumatic multiple rib fractures. It will be carried out in the outpatient clinics of the regional trauma centre at a tertiary hospital. We expect the study results will inform the design of further trials to assess the effectiveness and safety of acupuncture for patients suffering from subacute and chronic pain after trauma and surgery.

Trial status

The trial is currently in the recruitment phase. The first patient was randomised on 06 April 2018. Currently (as of 04 May 2018), 3 patients have been completely enrolled in the trial. The expected date of trial completion is 31 December 2019.

Acknowledgments

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KHK and HMC conceived the study. KHK, HMC, CKL, JPS, SHK, JEK and MKK initiated the study design and drafted the protocol. YKS served as a research assistant. KHK and JEK drafted the study protocol manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript. KHK is the guarantor of this manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Appendix 1. Checklist for Items in STRICTA 2010.

Item	Detail	Description
1. Acupuncture rationale	1a) Style of acupuncture	Manual and electroacupuncture
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	Textbook of acupuncture medicine, Cochrane library, and consensus of Korean medicine experts
	1c) Extent to which treatment was varied	Semi-standardized treatment
2. Details of needling	2a) Number of needle insertions per subject per session	Adjusted according to the participants' condition and the practitioners' judgment
	2b) Names (or location if no standard name) of points used (uni/bilateral)	* Essential acupoints 1) Both sides of 1.5-2.5 cm from the midline at the height of spinous processes of T1-T10 (BL12-BL19) 2) Peridermatomal area of the ipsilateral trunk (most would locate near the thoracotomy scars) 3) Paraspinal points of 1-1.5 cm from the midline at the height of spinous processes of C3-C7. * Optional acupoints are as follows but not necessarily limited to: 1) Points on the extremities that have been commonly used for chronic pain management: LI4, LI11, ST36, LR3, GB39, GB34, TE5 and TE6 2) Points on the trunk and the face that have been commonly used for emotional relief: GV20, EX-HN1, HT7, PC6, EX-HN3 3) Distal points for treating post-thoracotomy ipsilateral shoulder pain: SI11, SI9, SI12, SI13
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	Paravertebral points will be needled within 1.0 to 1.5 cm (cervical region) or 1.5 to 2.0 cm (thoracic region) obliquely toward the vertebral body. Peridermatomal points will be needled parallel to the rib to avoid organ-penetration injury. Other points will be perpendicularly needled within 3.0 cm based on the location.
	2d) Response sought (e.g. de qi or muscle twitch response)	For the myofascial needling on the ipsilateral shoulder region, muscle twitch response would be sought. For needling on paravertebral points and peridermatomal region, de qi response would not be sought. Response for points on the extremities will be sought at the study KMD's discretion.
	2e) Needle stimulation (e.g. manual, electrical)	* Manual stimulation Gentle clockwise and anti-clockwise stimulation will be performed. * Electronic stimulation alternating frequency of 2 to 100 Hz, a biphasic square wave and comfortable intensity by the patient
	2f) Needle retention time	Within 20 minutes
	2g) Needle type (diameter, length, and manufacturer or material)	Sterilized stainless steel needle (0.20×30mm, 0.25×30mm, 0.25×40mm, 0.30✕60mm, DONGBANG Acupuncture Inc., Korea)
3. Treatment regimen	3a) Number of treatment sessions	12 times in total
	3b) Frequency and duration of treatment sessions	Weekly sessions of treatments for three months will be expected.
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice)	* Co-treatments related to the study acupuncture, such as herbal medicine or cupping, will not be provided. If necessary, the wristband for PC6 stimulation will be provided. Enhancing daily physical activity and avoidance of negative lifestyles (such as smoking and alcohol consumption) will be delivered during the clinical encounter between the studyKMDs and the participants.
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	The study KMDs will be instructed to maintain the real-life clinical approach toward the participants although the treatment sessions will be delivered based on the pre-planned protocol. The treatments will be performed in the outpatient clinics of the tertiary hospital.
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Minimal requirements of the study acupuncture practitioners are as follows: 1) Korean medicine doctor 2) at least 3 years of clinical experience of acupuncture
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	Current standard care of the study hospital by the study surgeons as well as the multimodal pain management in the current up-to-date review "Mesbah A, Yeung J, Gao F. Pain after thoracotomy. BJA Education 2016;16:1-7."
	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.	Participants in the control group will continue their management without the study acupuncture. The control group will be assessed via the same methods as the experimental group at 4, 8, 12, and 24 weeks after randomisation.

Note. This checklist, which should be read in conjunction with the explanations of the STRICTA items, is designed to replace CONSORT 2010's item 5 when reporting an acupuncture trial.