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Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Keywords:	electroacupuncture, postoperative pain, total knee arthroplasty, the study protocol

Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Lian-bo Xiao and Yue-lai Chen contributed equally to this paper.

Author Contributions

SZ and LBX conceived the study while HH, JX, LZ, XLS designed the study. The study protocol was drafted by SZ and LBX, and was revised by YLC. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Abstract:

Introduction: The purpose of this study is to assess the efficacy of electroacupuncture to relief pain and promote functional rehabilitation after total knee surgery.

Methods and analysis: We propose a single-blinded, randomised placebo-controlled trial to evaluate the efficacy of electroacupuncture. Osteoarthritis patients (aged 55 to 80 years) undergoing unilateral total knee arthroplasty will be included in the trial. They will be randomised to receive either electroacupuncture or sham-electroacupuncture. A total of 110 patients will receive electroacupuncture and sham-electroacupuncture for three days after TKA. Postoperative pain will be measured using VAS score, and the need for an additional dose of opioid and analgesics will be recorded as the primary outcome. Secondary outcomes include knee function and swelling, postoperative anxiety, postoperative nausea and vomiting among other complications.

Ethics and dissemination: This study has been approved by the ethics committee, and subsequent modifications of the protocol will be reported and approved by it. Written inform content will be obtained from all of the participants or their authorized agents.

Trial registration number: ChiCTR1800016200

Keywords: electroacupuncture, postoperative pain, total knee arthroplasty, the study protocol

Article Summary

Strengths and limitations of this study

The study is the first single-blinded, randomised placebo-controlled trial in China

to assess the efficacy of electroacupuncture to relief pain and promote functional rehabilitation after total knee surgery.

The study will use an efficient sham-electroacupuncture method that makes it hard for patients with acupuncture treatment experience to distinguish between both treatments.

The study is rigorously designed, which includes adequate sample size, proper randomization and allocation concealment, and prospective trial registration to reduce selection and confounding bias.

Yet, the placebo effect cannot be eliminated due to the unblinded surgeons and acupuncturists.

Introduction

Total knee arthroplasty (TKA) is the most frequently performed surgical procedure for end-stage osteoarthritis and rheumatoid arthritis. Moderate to severe postoperative pain is a major complaint in most patients. Acute and subacute postoperative pain is highly associated with persistent post-surgical pain (PPSP), especially when the acute pain is not treated with effective analgesia.[1] A recent study showed that 10%-34% and 7%-23% of patients reported severe pain after TKA and total hip arthroplasty (THA), respectively, which indicates that TKA patients are more likely to develop PPSP.[2] Multimodal analgesia has been used for 20 years and it is considered to be the most effective strategy for PPSP. Abuse of analgesic drugs has increased exposure of the public to the side effects of non-steroidal anti-inflammatory

drugs (NSAIDs) and opioids.[3,4] Drug-free interventions to reduce pain or opioid consumption are more consistent with the principles of enhanced recovery after surgery (ERAS).

According to the theories of Traditional Chinese Medicine (TCM), acupuncture can help dredge the meridians and correct imbalance of flow of energy. Clinical trials and systematic reviews have shown that acupuncture is effective against many different types of acute and chronic pain.[5–7] Electroacupuncture (EA) has been proved to be beneficial for postoperative pain after TKA.[8] Studies on the mechanism of electroacupuncture analgesia indicated that it activates many bioactive chemicals through peripheral, spinal, and supraspinal mechanisms.[9] We hypothesize that EA may active the descending pain regulation of the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM).[10–12] Besides, the placebo effect is highly associated with both areas of the brain.[13] Strict blinding is required to rule out the effects of the placebo effect on outcomes.

The purpose of this study is to assess the efficacy of electroacupuncture on pain relief and promoting functional rehabilitation after total knee surgery. We will use a large sample size and an effective electroacupuncture blind method to ensure a credible conclusion.

Methods and analysis

Study Context

This study will be a parallel randomised controlled trial performed at the inpatient

ward of Shanghai University of Traditional Chinese Medicine Guanghua Hospital, Shanghai, China. The annual surgical number of total knee arthroplasty for osteoarthritis was about 600 in 2017. In this study, there will be 7 investigators, including a chief orthopaedic surgeon (LBX) with 20 years of clinical experience, two orthopaedic physicians (JX and SZ), two Chinese medicine acupuncturists (HH and YLC), and two outcome assessors (LZ, and XLS). ERAS programme will be performed by trained nurses and physiotherapists at the inpatient ward. The schedule and the study flow diagram is shown in Table1 and Figure 1.

Sample size calculation

In a previous meta-analysis study in which pain relief was compared between EA groups and controls, the minimal mean difference of the two groups based on the VAS score was -1.14 (95% CI, -1.90 to -0.38), and the standard deviation was estimated to be 2.[8] Considering a dropout rate of 10%, 110 patients are required to yield a power of 80% with a significance level of 0.05.[14]

Randomisation and allocation concealment

One hundred and ten patients will be divided into EA and Sham-EA groups with a ratio of 1:1. An independent biostatistician will generate a random sequence using the R (version 3.4.4). A sequence of numbers will be prepared and sealed in an opaque envelope. Only the acupuncturist will be allowed to open the envelope to obtain the grouping code.

Single-blinding

The acupuncturist will be blinded to the grouping information in advance, and the

treatment method according to the grouping information contained in envelopes. All participants, orthopaedic surgeons, and relevant healthcare staff will be blinded to the study. The outcome assessor will not be aware of the treatment that patients received and will only instruct the patient to fill in the scales. The independent biostatistician will also be blinded when performing the statistical analyses. To maximize the blinding of patients, an effective sham electroacupuncture method will be applied with adhesive pads, a dull-tipped placebo needle, and a sham electrical stimulation device. Details of the sham operation design are described in the following part.

Eligibility criteria

Eligible

(1) Aged 55 to 80 years; (2) Meet the 1995 American College of Rheumatology (ACR) diagnostic criteria for osteoarthritis; (3) Undergoing unilateral total knee arthroplasty under general anaesthesia without surgical contraindications; (4) American Society of Anesthesiologists (ASA) Grade I or II.

Ineligible

(1) The area of acupuncture points has skin damage and cannot perform acupuncture; (2) Preoperative deep venous thrombosis or swelling of the lower extremities; (3) Severe arrhythmia, heart failure, chronic obstructive pulmonary disease, epilepsy, mental disease; (4) Received treatment of acupuncture in past 1 month.

Study interventions

EA group

Patients will receive early acupuncture analgesia once a day from 24 to 72 hours after surgery. The first session of acupuncture treatment will be performed at 24 hours postoperatively. Firstly, the adhesive pads will be put on the acupoints of bilateral *Futu* (Stomach 32, ST32), *Zusanli* (Stomach 36, ST36), *Yanglingquan* (Gall Bladder 34, GB34), and *Yinlingquan* (Spleen 9, SP9). 1.5 *cun* acupuncture needles (0.25×40mm, Huatuo Inc.) will be manually inserted into the skin through the adhesive pads (Figure. 2). When *De-qi* sensation is achieved, subsequent electrical stimulation with a frequency of 2Hz, a continuous wave and tolerable intensity by the patient will be applied to the four acupoints (GB 34 to ST32 and ST36 to SP9). Needles with electrical stimulation will be retained for 20 minutes in each session. The patients will receive a total of 3 treatments which were given once a day.

Sham-EA group

Similar to the EA group, three sessions of acupuncture will be provided at the same time. An adhesive pad will be put on the sham-acupoint which is 20 mm distal to the real acupoint (Figure. 3). The placebo needle has a blunt-tip and it will be manually inserted into the adhesive pads but without skin penetration to provide participant-blinding effects (Figure. 2). The sham electrical stimulation device will have a connecting cord with a broken inner wire with no actual current output. Needles will also be retained for 20 minutes in each session. The patients will receive a total of 3 sham treatments which were given once a day.This Sham-EA method was proved to be effective in a previous study.[15]

Postoperative analgesia

All patients will receive the same analgesic procedure. Fentanyl patient-controlled analgesia (PCA) will be used at a continuous infusion rate of 0.25 μg/(kg·h) and a bolus of 0.15 μg/kg with a 10-minute lockout time. Patients will be allowed to use Celebrex 200 mg per day. Besides, additional rescue doses of analgesics will be provided upon demand for patients with a VAS score above 60.

Discontinuing criteria

(1) Acupuncture cannot be tolerated after surgery or patients that cannot be implemented according to the protocol; (2) Severe physiological and pathological changes were found during surgery and it is not appropriate to receive acupuncture treatment; (3) Patients in which the trial arrangement cannot be completed or the safety judgment is affected due to surgical factors after the test; (4) Severe adverse reactions, severe complications, and patients with rapid deterioration.

Outcome

Primary outcome

Pain

When the patients are discharged from the operating room, this will be recorded as 0 hours. Outcome assessors will record VAS at 6, 24, 48, and 72 hours after surgery. Patients can use a 100 mm visual analogue scale to assess the pain of their knee (from no symptoms to very severe). Additional PCA dose requirement will be evaluated in this study to reflect the degree of pain. Patients will be trained to adjust the PCA to obtain an additional dose of analgesia depending on the degree of pain. This will be

recorded 48 hours after surgery. Patients will be given an additional dose of analgesia upon demand if the VAS score is above 60. The additional use of analgesics within 2 weeks after surgery will be recorded in the case report forms.

Secondary outcome

Knee function and swelling

Knee function will be measured based on Hospital for Special Surgery Knee Score (HSS score) at one day before surgery and three days after surgery. All patients will first educated about the HSS score by a trained researcher until they fully understand the questionnaire, then asked to complete the form according to their actual conditions. At 24 hours after surgery, the outcome assessor will remove the elastic bandage and measure the circumference of the knee at the superior patellar pole. A second measurement will be performed 72 hours after surgery. According to previous reports, electroacupuncture has the potential to promote functional rehabilitation.

Perioperative anxiety

Perioperative anxiety will be measured by the Hamilton Anxiety Scale (HAMA) at one day before surgery and three days after surgery. HAMA has 14 levels to assess the severity of a patient's anxiety, and it divides anxiety into physical (7~13) and spiritual (1~6 and 14).

Postoperative nausea and vomiting (PONV)

PONV will be measured according to vomiting symptoms scores in 4-time points, including on the day of surgery and 1, 2, 3 days after surgery.[16] Functional Living

Index-Emesis is used to evaluate the effect of PONV on the quality of life, and it will be measured 3 days after surgery.[17]

Postoperative complications and adverse events

All expected and unexpected adverse events will be measured during the allocated intervention process and during the entire study period. Common adverse events are fainting, needle sticking or breaking during acupuncture and acupuncture hematomas. Other postoperative complications including incision infection, urinary retention, deep vein thrombosis, and postoperative persistent pain will be recorded 6 weeks after surgery. All serious adverse events (SAEs) will be reported immediately to the sponsor to allow further investigations into their causes.

Data management

Data entry will be conducted by two independent trained research assistants using paper CRFs to record the research data after completion of final data collection. As acupuncture has known minimal risks, a formal data monitoring committee will not be required.[6,18] Independent investigators of the hospital staff will monitor and audit the data periodically.

Statistical analysis

According to the intention to treat (ITT) principle, full analysis set (FAS) and per-protocol set (PPS) will be used for primary analysis. Safety set (SS) will not be required since acupuncture has minimal risks.[6,18] Sensitivity analysis will be performed to determine the impact of incomplete records on results. Missing data will not be imputed. Statistical analysis will be performed using R (version 3.4.4). The

difference between the two groups will be calculated and compared using the t-test if the Shapiro-Wilk test showed that the data is normally distributed, otherwise the Mann-Whitney U test will be used. A Pearson χ^2 or Fisher's exact test will be used to calculate the differences in the enumeration data. Mixed effects models will be used to analyze the trend of changes in VAS scores with two factors of groups and time.[19]

Ethics and dissemination

This study has been approved by the ethics committee of Shanghai Guanghua Hospital of Integrated Chinese and Western Medicine (approval number AF13v2-2), and any modification of the protocol will be reported and approved by it. Written inform consent will be obtained from all participants or their authorized agents. All electroacupuncture treatments will be free and the research data will be strictly confidential. The result of the trial will be presented on the website of the Chinese Clinical Trial Registry and published in peer-reviewed journals.

Patient and Public Involvement

Patient and public were not involved in the design of this study. The participants will be infomed of the result of this study during the follow-up visit. Besides, we will enlist their help in disseminating the research findings.

Discussion

Multiple evidence-based ERAS strategies for TKA have been shown to reduce postoperative complications and improve the prognosis and patient satisfaction. Postoperative pain after TKA is mostly caused by postoperative functional exercise. Drug-free interventions, especially EA, are highly effective in pain relief and

promoting functional rehabilitation. The minimal clinically important difference (MCID) is a measure that is used to evaluate the clinical significance of an intervention. In the case of standardized multimodal analgesia, the MCID for VAS of postoperative pain after TKA is -2.26, and the MCID can be used to evaluate the effect of Sham-EA.[20] Further research is required to determine whether a single EA without multimodal analgesia may provide enough analgesia for the patients after TKA. We suggest incorporation of EA as a routine treatment in ERAS strategies for TKA. EA may also be used as a new analgesia to replace opioids usage.

Reference

1 Veal FC, Bereznicki LRE, Thompson AJ, *et al.* Subacute Pain as a Predictor of Long-Term Pain Following Orthopedic Surgery: An Australian Prospective 12 Month Observational Cohort Study. *Medicine (Baltimore)* 2015;**94**:e1498. doi:10.1097/MD.0000000000001498

2 Beswick AD, Wylde V, Gooberman-Hill R, *et al.* What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012;**2**:e000435. doi:10.1136/bmjopen-2011-000435

3 Han C, Li X, Jiang H, *et al.* The use of gabapentin in the management of postoperative pain after total knee arthroplasty. *Medicine (Baltimore)* 2016;**95**:e3883. doi:10.1097/MD.0000000000003883

4 Katz J, Buis T, Cohen L. Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. *Can J Anesth Can d'anesthésie* 2008;**55**:88–99. doi:10.1007/BF03016320

5 Ntritsou V, Mavrommatis C, Kostoglou C, *et al.* Effect of perioperative electroacupuncture as an adjunctive therapy on postoperative analgesia with tramadol and ketamine in prostatectomy: a randomised sham-controlled single-blind trial. *Acupunct Med* 2014;**32**:215–22. doi:10.1136/acupmed-2013-010498

6 Manheimer E, Cheng K, Linde K, *et al.* Acupuncture for peripheral joint osteoarthritis. *Cochrane Database Syst Rev* Published Online First: 20 January 2010. doi:10.1002/14651858.CD001977.pub2

7 Ju ZY, Wang K, Cui HS, *et al.* Acupuncture for neuropathic pain in adults. *Cochrane Database Syst Rev* Published Online First: 2 December 2017. doi:10.1002/14651858.CD012057.pub2

8 Tedesco D, Gori D, Desai KR, *et al.* Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty. *JAMA Surg* 2017;**152**:e172872. doi:10.1001/jamasurg.2017.2872

9 Zhang R, Lao L, Ren K, *et al. Mechanisms of acupuncture-electroacupuncture on persistent pain*. 2014. doi:10.1097/ALN.0000000000000101

10 Tinnermann A, Geuter S, Sprenger C, *et al.* Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science (80-)* 2017;**358**:105–8. doi:10.1126/science.aan1221

11 Bliss TVP, Collingridge GL, Kaang B-K, *et al.* Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nat Rev Neurosci* 2016;**17**:485–96. doi:10.1038/nrn.2016.68

12 Pogatzki-zahn EM, Segelcke D, Schug SA. Postoperative pain — from mechanisms to treatment. *PAIN Reports* 2017;**2**:e588. doi:10.1097/PR9.0000000000000588

13 Grahl A, Onat S, Büchel C. The periaqueductal gray and Bayesian integration in placebo analgesia. *Elife* 2018;**7**. doi:10.7554/eLife.32930

14 Chow SC, Wang H, Shao J. *Sample Size Calculations in Clinical Research, Second Edition*. Taylor & Francis 2007.

15 Liu Z, Liu Y, Xu H, *et al.* Effect of Electroacupuncture on Urinary Leakage Among Women With Stress Urinary Incontinence. *Jama* 2017;**317**:2493. doi:10.1001/jama.2017.7220

16 Hesketh PJ, Kris MG, Grunberg SM, *et al.* Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;**15**:103–9. doi:10.1200/JCO.1997.15.1.103

17 Lindley CM, Hirsch JD, O'Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

18 Witt CM, Pach D, Brinkhaus B, *et al.* Safety of Acupuncture: Results of a Prospective Observational Study with 229,230 Patients and Introduction of a Medical Information and Consent Form. *Complement Med Res* 2009;**16**:91–7. doi:10.1159/000209315

19 Detry M, Ma Y. Analyzing repeated measurements using mixed models. *Jama* 2016;**315**:407–8. doi:10.1001/jama.2015

20 Danoff JR, Goel R, Sutton R, *et al.* How Much Pain Is Significant? Defining the Minimal Clinically Important Difference for the Visual Analog Scale for Pain After Total Joint Arthroplasty. *J Arthroplasty* 2018;**33**:S71–S75.e2. doi:10.1016/j.arth.2018.02.029

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Table 1. The schedule of trial enrolment, interventions and assessments

	Enrolment	Intervention period			
	Pre-OP	6 hours	24 hours	48 hours	72 hours
Enrolment					
Informed consent	●				
Assessment of eligibility	●				
Randomisation	●				
Interventions		●	●	●	●
EA	●				
Sham-EA	●				
Assessments	●			●	
VAS	●	●	●	●	●
Additional dose released by PCA				●	
HSS score	●				●
HAMA score	●				●
PONV		●	●	●	●
COK			●		●
Additional use of analgesics	●				●
Postoperative complications and adverse events		●	●	●	●

OP, operation; EA, electroacupuncture; VAS, Visual Analogue Score; PCA, patient controlled analgesia; HSS, hospital for special surgery; HAMA, Hamilton Anxiety Scale; PONV, post-operative nausea and vomiting; COK, circumference of knee

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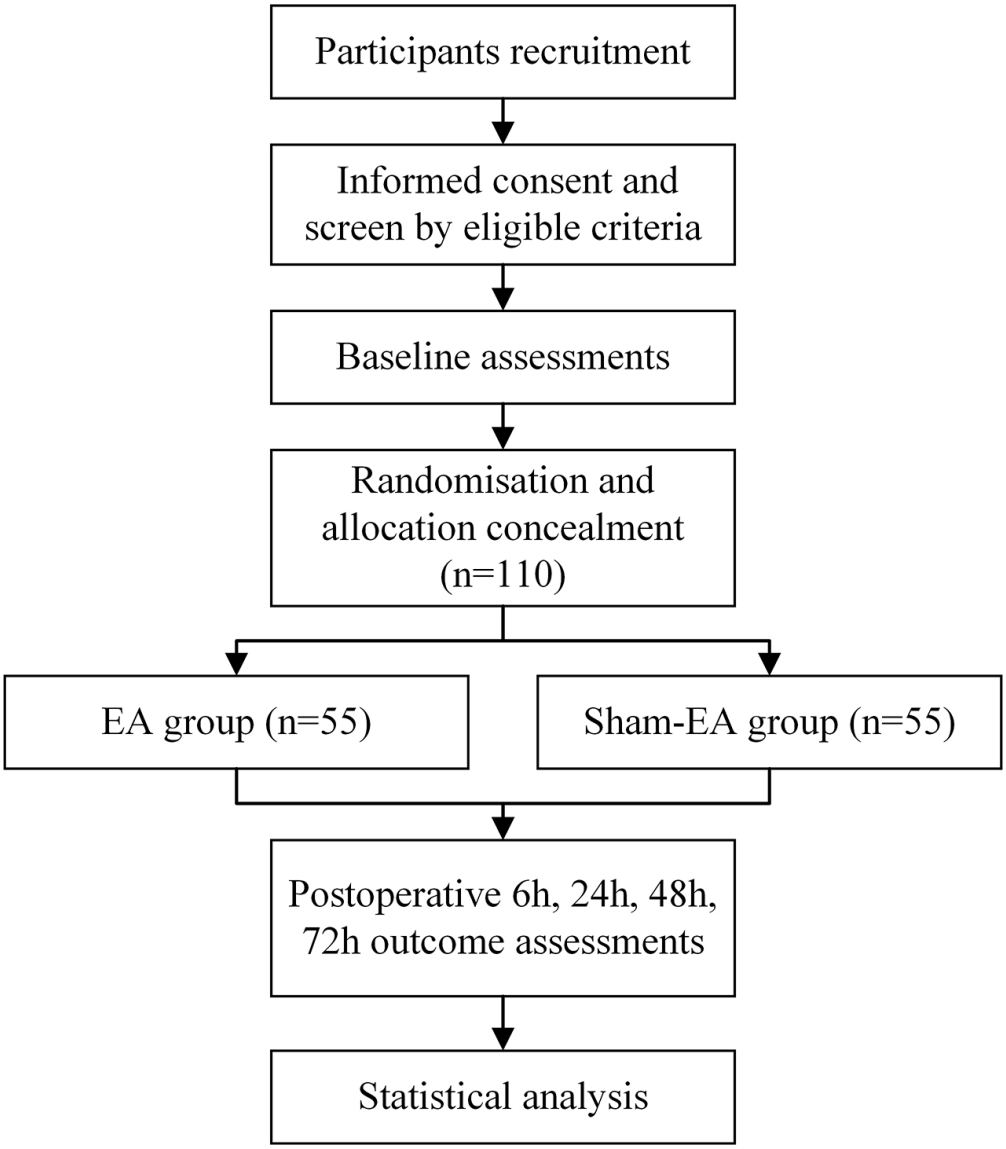

Figure 1. Study flow diagram, including participants recruitment, eligibility, screening, randomization, allocation concealment, and outcome assessments. EA, electroacupuncture.

107x122mm (300 x 300 DPI)

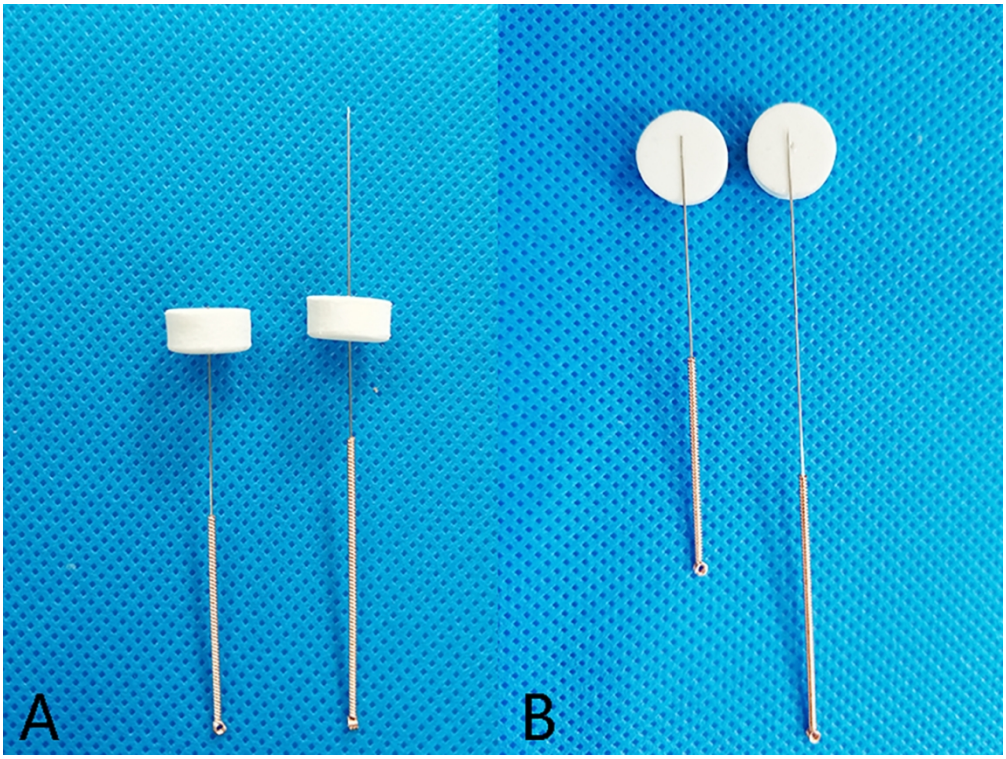

Figure 2. The difference between acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

119x90mm (300 x 300 DPI)

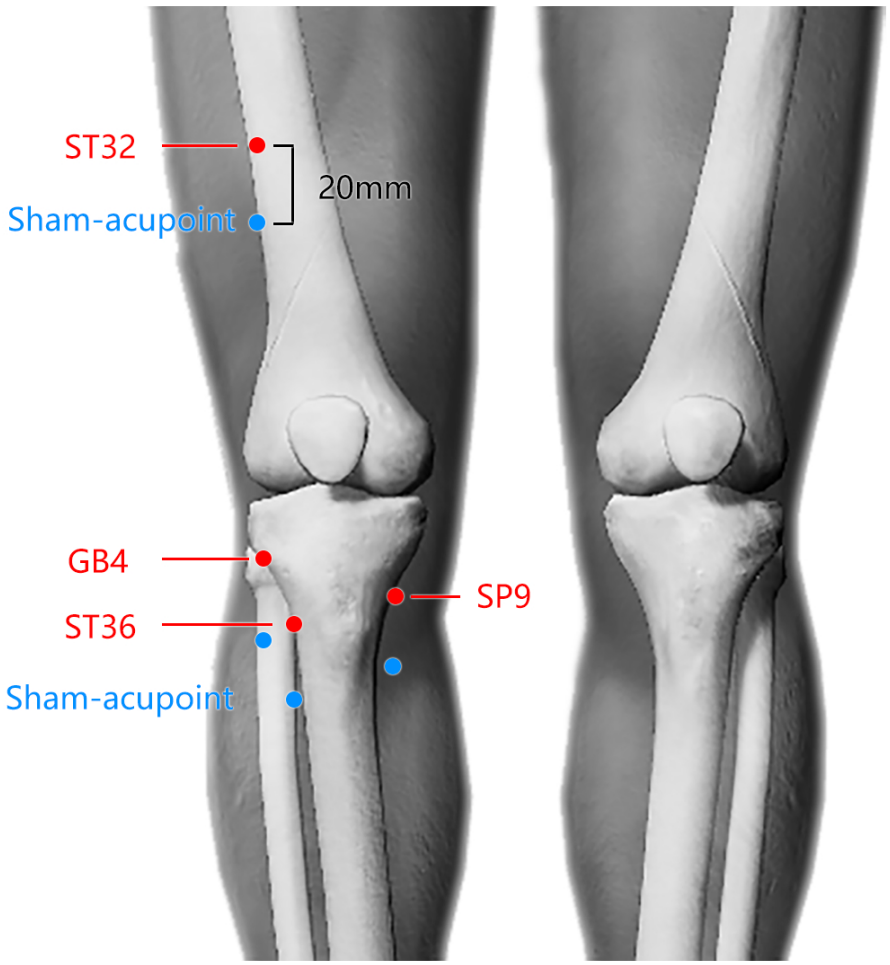

Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

94x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	6

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6-7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Data access	#29	Statement of who will have access to the final trial dataset,	12

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Author Contributions

SZ and LBX conceived the study while HH, JX, LZ, XLS designed the study. The study protocol was drafted by SZ and LBX, and was revised by YLC. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Abstract:

Introduction: The purpose of this study is to assess the efficacy of electroacupuncture to relieve pain and promote functional rehabilitation after total knee surgery.

Methods and analysis: We propose a single-blinded, randomised placebo-controlled trial to evaluate the efficacy of electroacupuncture. Patients with osteoarthritis (aged 55 to 80 years) undergoing unilateral total knee arthroplasty will be included in the trial. They will be randomised to receive either electroacupuncture or sham-electroacupuncture. A total of 110 patients will receive electroacupuncture and sham-electroacupuncture for three days after TKA. Postoperative pain will be measured using VAS score, and the need for an additional dose of opioid and analgesics will be recorded as the primary outcome. Secondary outcomes include knee function and swelling, postoperative anxiety, postoperative nausea and vomiting among other complications.

Ethics and dissemination: This study has been approved by the ethics committee, and subsequent modifications of the protocol will be reported and approved by it. Written inform content will be obtained from all of the participants or their authorized agents.

Trial registration number: ChiCTR1800016200

Keywords: electroacupuncture, postoperative pain, total knee arthroplasty, study protocol

Article Summary

Strengths and limitations of this study

1. The study is the first single-blinded, randomised placebo-controlled trial in China

to assess the efficacy of electroacupuncture to relieve pain and promote functional rehabilitation after total knee surgery.

2. The study will use an efficient sham-electroacupuncture method that makes it hard for patients with electroacupuncture treatment experience to distinguish between both treatments.

3. The study is rigorously designed, which includes adequate sample size, proper randomization and allocation concealment, and prospective trial registration to reduce selection and confounding bias.

4. There is still bias in the implementation of blind method due to the unblinded acupuncturists.

Introduction

Total knee arthroplasty (TKA) is the most frequently performed surgical procedure for end-stage osteoarthritis and rheumatoid arthritis. Moderate to severe postoperative pain is a major complaint in most patients. Acute and subacute postoperative pain is highly associated with persistent post-surgical pain (PPSP), especially when the acute pain is not treated with effective analgesia.[1] A recent study showed that 10%-34% and 7%-23% of patients reported severe pain after TKA and total hip arthroplasty (THA), respectively, which indicates that TKA patients are more likely to develop PPSP.[2] Multimodal analgesia has been used for 20 years and it is considered to be the most effective strategy for PPSP. Abuse of analgesic drugs has increased exposure of the public to the side effects of non-steroidal anti-inflammatory

drugs (NSAIDs) and opioids.[3,4] Drug-free interventions to reduce pain or opioid consumption are more consistent with the principles of Enhanced Recovery After Surgery (ERAS).

Clinical trials and systematic reviews have shown that the efficacy of electroacupuncture or acupuncture analgesia is controversial.[5–8] Electrotherapy and acupuncture have been proved to be potentially beneficial for postoperative pain after TKA.[9] Studies on the mechanism of electroacupuncture analgesia indicated that it activates many bioactive chemicals through peripheral, spinal, and supraspinal mechanisms.[10] The supraspinal mechanisms showed EA analgesia is highly associated with descending pain regulation of the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM).[10,11] The PAG-RVM system is recognized as the central site of action of analgesic agents including opioids, cyclooxygenase inhibitors, and cannabinoids.[12–14] We hypothesize that EA may exert an analgesic effect by activating the PAG-RVM system. Besides, the placebo effect is highly associated with both areas of the brain.[15,16] Strict blinding is required to rule out the effects of the placebo effect on outcomes.

The purpose of this study is to assess the efficacy of electroacupuncture on pain relief and promoting functional rehabilitation after total knee surgery. We will use a large sample size and a reliable blind method of electroacupuncture to ensure a credible conclusion.

Methods and analysis

Study Context

This study will be a single-blinded, randomised placebo-controlled trial performed at the inpatient ward of Shanghai University of Traditional Chinese Medicine Guanghua Hospital, Shanghai, China. The annual surgical number of total knee arthroplasty for osteoarthritis was about 600 in 2017. We planned to begin recruiting patients from June 2018 and patients preparing for unilateral TKA will be recruited. In this study, there will be 7 investigators, including a chief orthopaedic surgeon (LBX) with 20 years of clinical experience, two orthopaedic physicians (JX and SZ), two Chinese medicine acupuncturists (HH and YLC), and two outcome assessors (LZ, and XLS). ERAS programme (Table 1) will be performed by trained nurses and physiotherapists at the inpatient ward. The ERAS programme is routinely applied, but electroacupuncture has been added to analgesia. The schedule and the study flow diagram is shown in Table 2 and Figure 1.

Sample size calculation

In a previous meta-analysis study in which pain relief was compared between EA groups and controls, the minimal mean difference of the two groups based on the VAS score (on a scale of 0-10) was -1.14 (95% CI, -1.90 to -0.38), and the standard deviation was estimated to be 2.[9] Considering a dropout rate of 10%, 110 patients are required to yield a power of 80% with a significance level of 0.05.[17]

Randomisation and allocation concealment

One hundred and ten patients will be divided into EA and Sham-EA groups with a ratio of 1:1. An independent biostatistician will generate a random sequence using

the R (version 3.4.4). A sequence of numbers will be prepared and sealed in an opaque envelope. Only the acupuncturist will be allowed to open the envelope to obtain the grouping code.

Single-blinding

The acupuncturist will be blinded to the grouping information in advance, and the treatment method according to the grouping information contained in envelopes. All participants, orthopaedic surgeons, and relevant healthcare staff will be blinded to the study. The outcome assessor will not be aware of the treatment that patients received and will only instruct the patient to fill in the scales. The independent biostatistician will also be blinded when performing the statistical analyses. To maximize the blinding of patients, an effective sham electroacupuncture method will be applied with adhesive pads, a dull-tipped placebo needle, and a sham electrical stimulation device. Details of the sham operation design are described in the following part.

Eligibility criteria

Eligible

(1) Aged 55 to 80 years; (2) Meet the 1995 American College of Rheumatology (ACR) diagnostic criteria for osteoarthritis; (3) Undergoing unilateral total knee arthroplasty under general anaesthesia without surgical contraindications; (4) American Society of Anesthesiologists (ASA) Grade I or II.

Ineligible

(1) The area of acupuncture points has skin damage and cannot perform acupuncture; (2) Preoperative deep venous thrombosis or swelling of the lower

extremities; (3) Severe arrhythmia, heart failure, chronic obstructive pulmonary disease, epilepsy, mental disease; (4) Received treatment of acupuncture in past 1 month.

Study interventions

EA group

Patients will receive early acupuncture analgesia once a day from 24 to 72 hours after surgery. The first session of acupuncture treatment will be performed at 24 hours postoperatively. Firstly, the adhesive pads will be put on the acupoints of bilateral *Futu* (Stomach 32, ST32), *Zusanli* (Stomach 36, ST36), *Yanglingquan* (Gall Bladder 34, GB34), and *Yinlingquan* (Spleen 9, SP9). 1.5 *cun* acupuncture needles (0.25×40mm, Huatuo Inc.) will be manually inserted into the skin through the adhesive pads (Figure. 2). When *De-qi* sensation is achieved, subsequent electrical stimulation with a frequency of 2Hz, a continuous wave and tolerable intensity by the patient will be applied to the four acupoints (GB 34 to ST32 and ST36 to SP9) using a Hwato SDZ-V electrical stimulation device (Suzhou Medical Appliance Factory, Suzhou, China). Needles with electrical stimulation will be retained for 20 minutes in each session. The patients will receive a total of 3 treatments which were given once a day.

Sham-EA group

Similar to the EA group, three sessions of acupuncture will be provided at the same time. An adhesive pad will be put on the sham-acupoint which is 20 mm distal to the real acupoint (Figure. 3). The placebo needle has a blunt-tip and it will be

manually inserted into the adhesive pads but without skin penetration to provide participant-blinding effects (Figure. 2). The sham electrical stimulation device will have a connecting cord with a broken inner wire with no actual current output. Needles will also be retained for 20 minutes in each session. The patients will receive a total of 3 sham treatments which were given once a day. This Sham-EA method was proved to be effective in a previous study.[18]

Postoperative analgesia

All patients will receive the same analgesic procedure. Fentanyl patient-controlled analgesia (PCA) will be used at a continuous infusion rate of 0.25 μg/(kg·h) and a bolus of 0.15 μg/kg with a 10-minute lockout time. Patients will be allowed to use Celebrex 200 mg per day. Besides, additional rescue doses of analgesics will be provided upon demand for patients with a VAS score above 60.

Discontinuing criteria

(1) Acupuncture cannot be tolerated after surgery or patients that cannot be implemented according to the protocol; (2) Severe physiological and pathological changes were found during surgery and it is not appropriate to receive acupuncture treatment, such as anaesthesia accidents, cardiac-cerebrovascular accidents, nerve or vascular injury during surgery; (3) Patients in which the trial arrangement cannot be completed or the safety judgment is affected due to surgical factors after the test; (4) Severe adverse reactions, severe complications, such as deep vein thrombosis, pulmonary embolism and severe allergic reactions.

Outcome

Primary outcome

Pain

When the patients are discharged from the operating room, this will be recorded as 0 hours. Patients will put a mark on a 100 mm visual analogue scale to assess the pain of their knee (from no pain to very severe) at 6, 24, 48, and 72 hours after surgery, then assessors record it. Additional PCA dose requirement will be evaluated in this study to reflect the degree of pain. Patients will be trained to adjust the PCA to obtain an additional dose of analgesia depending on the degree of pain. This will be recorded 48 hours after surgery. Patients will be given an additional dose of analgesia upon demand if the VAS score is above 60. The additional use of analgesics within 2 weeks after surgery will be recorded in the case report forms.

Secondary outcome

Knee function and swelling

Knee function will be measured based on Hospital for Special Surgery Knee-Rating Scale [19] (HSS scale) (Supplemental file) at one day before surgery and three days after surgery. All patients will first be educated about the HSS scale by a trained researcher until they fully understand the questionnaire, then asked to complete the form according to their actual conditions. At 24 hours after surgery, the outcome assessor will remove the elastic bandage and measure the circumference of the knee at the superior patellar pole. A second measurement will be performed 72 hours after surgery.

Perioperative anxiety

Perioperative anxiety will be measured by the Hamilton Anxiety Scale (HAMA)[20] (Supplemental file) at one day before surgery and three days after surgery. HAMA has 14 levels to assess the severity of a patient's anxiety, and it divides anxiety into physical (7~13) and spiritual (1~6 and 14).

Postoperative nausea and vomiting (PONV)

PONV will be measured according to vomiting symptoms scores in 4-time points, including on the day of surgery and 1, 2, 3 days after surgery.[21] Functional Living Index-Emesis (FLIE) [22] (Supplemental file) is used to evaluate the effect of PONV on the quality of life, and it will be measured 3 days after surgery.

Postoperative complications and adverse events

All expected and unexpected adverse events will be measured during the allocated intervention process and during the entire study period. Acupuncture-related adverse events are hematoma and syncope during acupuncture. Other postoperative complications including incision infection, urinary retention, deep vein thrombosis, and postoperative persistent pain will be recorded 6 weeks after surgery. All serious adverse events (SAEs) will be reported immediately to the sponsor to allow further investigations into their causes.

Data management

Data entry will be conducted by two independent trained research assistants using paper CRFs to record the research data after completion of final data collection. As acupuncture has known minimal risks, a formal data monitoring committee will not

be required.[8,23] Independent investigators of the hospital staff will monitor and audit the data periodically.

Statistical analysis

According to the intention to treat (ITT) principle, full analysis set (FAS) and per-protocol set (PPS) will be used for primary analysis. Safety set (SS) will not be required since acupuncture has minimal risks.[8,23] Sensitivity analysis will be performed to determine the impact of incomplete records on results. Missing data will not be imputed. Statistical analysis will be performed using R (version 3.4.4). The difference between the two groups will be calculated and compared using the t-test if the Shapiro-Wilk test showed that the data is normally distributed, otherwise the Mann-Whitney U test will be used. A Pearson χ^2 or Fisher's exact test will be used to calculate the differences in the count data. Mixed effects models will be used to analyze the trend of changes in VAS scores with two factors of groups and time.[24]

Ethics and dissemination

This study has been approved by the ethics committee of Shanghai Guanghua Hospital of Integrated Chinese and Western Medicine (approval number AF13v2-2), and any modification of the protocol will be reported and approved by it. Written inform consent will be obtained from all participants or their authorized agents. All electroacupuncture treatments will be free and the research data will be strictly confidential. The result of the trial will be presented on the website of the Chinese Clinical Trial Registry and published in peer-reviewed journals.

Patient and Public Involvement

Patient and public were not involved in the design of this study. The participants will be informed of the result of this study during the follow-up visit. Besides, we will enlist their help in disseminating the research findings.

Discussion

Drug-free interventions, especially EA, have been proven effective in pain relief and promoting functional rehabilitation,[25,26] and they will have good prospects for relieving opioid abuse or overuse of NSAIDs. However, the effect and mechanism of acupuncture analgesia are not clear, and the placebo effect is considered to play an important role.[8] This study has enough samples to obtain reliable results and we have improved the implementation of blinding to reduce the placebo effect. We hope that the results of the study will provide new evidence for electroacupuncture treatment of postoperative pain in TKA. Another question is to determine if the statistical difference between the two groups is clinically conscious. The minimal clinically important difference (MCID) is a measure that is used to evaluate the clinical significance of an intervention. In the case of standardized multimodal analgesia, the MCID for VAS of postoperative pain after TKA is -22.6 (on a scale of 0-100), and the MCID can be also used to evaluate the difference of EA and sham.[27]

Multiple evidence-based ERAS strategies for TKA have been shown to reduce postoperative complications and improve prognosis and patient satisfaction. Postoperative analgesia is an important part of ERAS. This study is based on add-on design, electroacupuncture and sham are applied to two groups of patients who used standard multimodal analgesia to evaluate the benefits of electroacupuncture on

postoperative pain in TKA. We recommend EA and more non-drug therapies as a routine treatment in ERAS programme of TKA if results of the study prove that it really works.

Reference

1 Veal FC, Bereznicki LRE, Thompson AJ, *et al.* Subacute Pain as a Predictor of Long-Term Pain Following Orthopedic Surgery: An Australian Prospective 12 Month Observational Cohort Study. *Medicine (Baltimore)* 2015;**94**:e1498. doi:10.1097/MD.0000000000001498

2 Beswick AD, Wylde V, Gooberman-Hill R, *et al.* What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012;**2**:e000435. doi:10.1136/bmjopen-2011-000435

3 Han C, Li X, Jiang H, *et al.* The use of gabapentin in the management of postoperative pain after total knee arthroplasty. *Medicine (Baltimore)* 2016;**95**:e3883. doi:10.1097/MD.0000000000003883

4 Katz J, Buis T, Cohen L. Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. *Can J Anesth Can d'anesthésie* 2008;**55**:88–99. doi:10.1007/BF03016320

5 Li X, Wang R, Xing X, *et al.* Acupuncture for Myofascial Pain Syndrome: A Network Meta-Analysis of 33 Randomized Controlled Trials. *Pain Physician* 2017;**20**:E883–902.

6 Peng L, Zhang C, Zhou L, *et al.* Traditional manual acupuncture combined with rehabilitation therapy for shoulder hand syndrome after stroke within the Chinese healthcare system: a systematic review and meta-analysis. *Clin Rehabil* 2018;**32**:429–39. doi:10.1177/0269215517729528

7 Ju ZY, Wang K, Cui HS, *et al.* Acupuncture for neuropathic pain in adults. *Cochrane Database Syst Rev* Published Online First: 2 December 2017. doi:10.1002/14651858.CD012057.pub2

8 Manheimer E, Cheng K, Linde K, *et al.* Acupuncture for peripheral joint osteoarthritis. *Cochrane Database Syst Rev* Published Online First: 20 January 2010. doi:10.1002/14651858.CD001977.pub2

9 Tedesco D, Gori D, Desai KR, *et al.* Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty. *JAMA Surg* 2017;**152**:e172872. doi:10.1001/jamasurg.2017.2872

10 Zhang R, Lao L, Ren K, *et al. Mechanisms of acupuncture-electroacupuncture on persistent pain*. 2014. doi:10.1097/ALN.0000000000000101

11 Zhao Z-Q. Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol* 2008;**85**:355–75. doi:10.1016/j.pneurobio.2008.05.004

12 Pogatzki-zahn EM, Segelcke D, Schug SA. Postoperative pain — from mechanisms to treatment. *PAIN Reports* 2017;**2**:e588. doi:10.1097/PR9.0000000000000588

13 Heinricher MM, Tavares I, Leith JL, *et al.* Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res Rev* 2009;**60**:214–25.

doi:10.1016/j.brainresrev.2008.12.009

14 Leith JL, Wilson AW, Donaldson LF, *et al.* Cyclooxygenase-1-derived prostaglandins in the periaqueductal gray differentially control C- versus A-fiber-evoked spinal nociception. *J Neurosci* 2007;**27**:11296–305. doi:10.1523/JNEUROSCI.2586-07.2007

15 Tinnermann A, Geuter S, Sprenger C, *et al.* Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science* 2017;**358**:105–8. doi:10.1126/science.aan1221

16 Grahl A, Onat S, Büchel C. The periaqueductal gray and Bayesian integration in placebo analgesia. *Elife* 2018;**7**. doi:10.7554/eLife.32930

17 Chow SC, Wang H, Shao J. *Sample Size Calculations in Clinical Research, Second Edition*. Taylor & Francis 2007.

18 Liu Z, Liu Y, Xu H, *et al.* Effect of Electroacupuncture on Urinary Leakage Among Women With Stress Urinary Incontinence. *Jama* 2017;**317**:2493. doi:10.1001/jama.2017.7220

19 Bach CM, Nogler M, Steingruber IE, *et al.* Scoring Systems in Total Knee Arthroplasty. 2002;:184–96.

20 HAMILTON M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50–5. doi:10.1145/363332.363339

21 Hesketh PJ, Kris MG, Grunberg SM, *et al.* Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;**15**:103–9. doi:10.1200/JCO.1997.15.1.103

22 Lindley CM, Hirsch JD, O'Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

23 Witt CM, Pach D, Brinkhaus B, *et al.* Safety of Acupuncture: Results of a Prospective Observational Study with 229,230 Patients and Introduction of a Medical Information and Consent Form. *Complement Med Res* 2009;**16**:91–7. doi:10.1159/000209315

24 Detry M, Ma Y. Analyzing repeated measurements using mixed models. *Jama* 2016;**315**:407–8. doi:10.1001/jama.2015

25 Chen G, Gu R-X, Xu D-D. [The application of electroacupuncture to postoperative rehabilitation of total knee replacement]. *Zhongguo Zhen Jiu* 2012;**32**:309–12.

26 Yue C, Zhang X, Zhu Y, *et al.* Systematic Review of Three Electrical Stimulation Techniques for Rehabilitation After Total Knee Arthroplasty. *J Arthroplasty* 2018;**33**:2330–7. doi:10.1016/j.arth.2018.01.070

27 Danoff JR, Goel R, Sutton R, *et al.* How Much Pain Is Significant? Defining the Minimal Clinically Important Difference for the Visual Analog Scale for Pain After Total Joint Arthroplasty. *J Arthroplasty* 2018;**33**:S71–S75.e2. doi:10.1016/j.arth.2018.02.029

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Table 1. Enhanced Recovery After Surgery Programme

Preoperative	
1	Preoperative education
2	Carbohydrate loading preoperatively and avoidance of prolonged starving
3	Use of preoperative probiotics
4	No mechanical bowel preparation
5	No premedication
6	Preemptive analgesia
Intraoperative	
7	Maintenance of normothermia
8	Goal-directed perioperative fluid administration
9	Minimally invasive incision
10	Avoidance of nasogastric tubes and deep vein catheterization
11	Avoidance of bladder catheter, if necessary early removal of bladder catheter
12	Use of tranexamic acid
13	Periarticular local injection analgesia
Postoperative	
14	Multimodal analgesia: PCA analgesia, NSAIDs; Avoidance of opioid analgesia
15	Use of postoperative antiemetic and laxatives
16	Enforced early mobilisation
17	Enforced early postoperative oral feeding

PCA, patient controlled analgesia; NSAIDs, non-steroidal antiinflammatory drugs

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Table 2. The schedule of trial enrolment, interventions and assessments

	Enrolment	Intervention period			
	Pre-OP	6 hours	24 hours	48 hours	72 hours
Enrolment					
Informed consent	●				
Assessment of eligibility	●				
Randomisation	●				
Interventions					
EA		●	●	●	●
Sham-EA		●	●	●	●
Assessments					
VAS	●	●	●	●	●
Additional dose released by PCA				●	
HSS scale	●				●
HAMA score	●				●
PONV		●	●	●	●
COK			●		●
Additional use of analgesics	●				●
Postoperative complications and adverse events		●	●	●	●

OP, operation; EA, electroacupuncture; VAS, Visual Analogue Score; PCA, patient-controlled analgesia; HSS, hospital for special surgery; HAMA, Hamilton Anxiety Scale; PONV, post-operative nausea and vomiting; COK, circumference of knee

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Figure Legend

Figure 1. The study flow diagram, including participants recruitment, eligibility, screening, randomization, allocation concealment, and outcome assessments. EA, electroacupuncture.

Figure 2. The difference between the acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

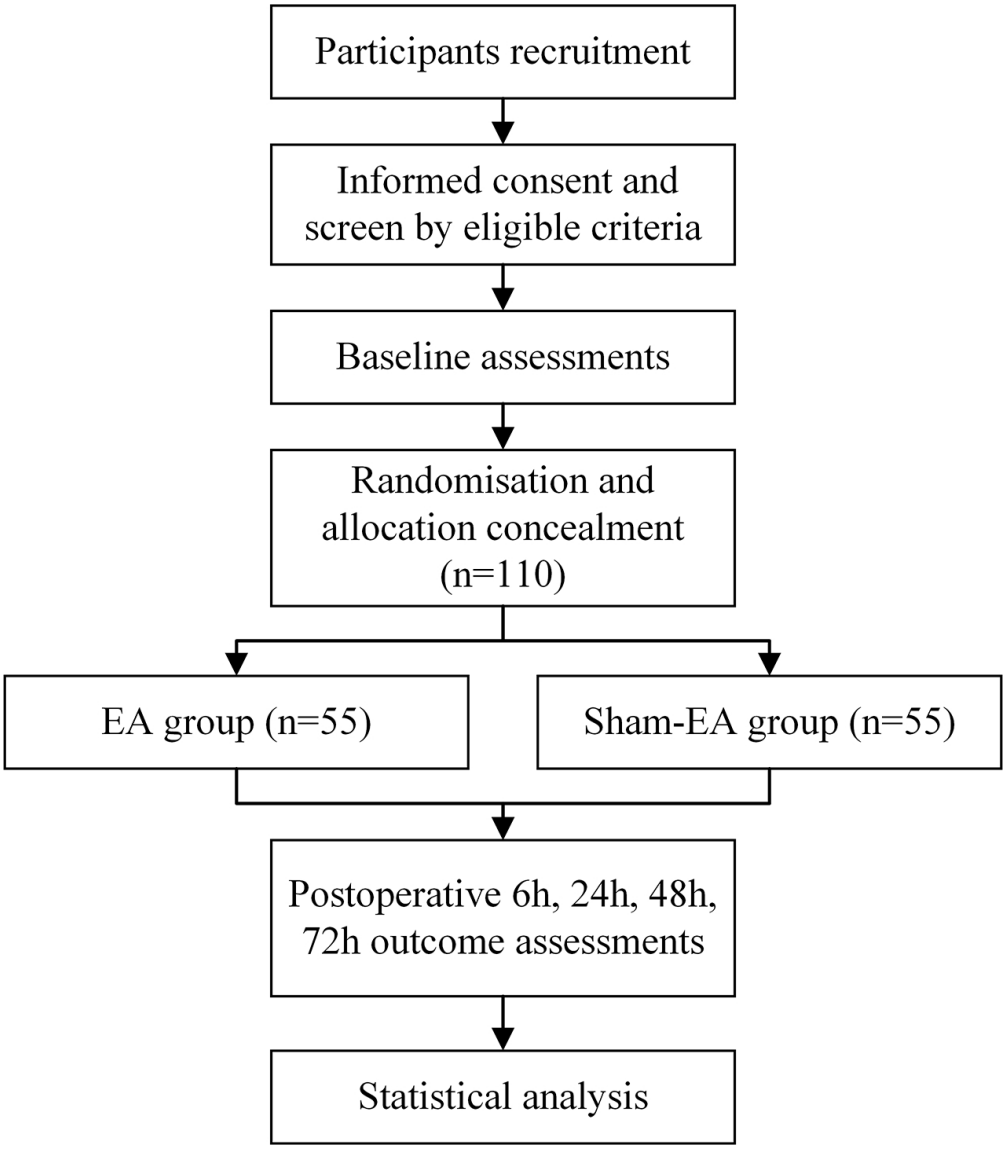


Figure 1. Study flow diagram, including participants recruitment, eligibility, screening, randomization, allocation concealment, and outcome assessments. EA, electroacupuncture.

107x122mm (300 x 300 DPI)

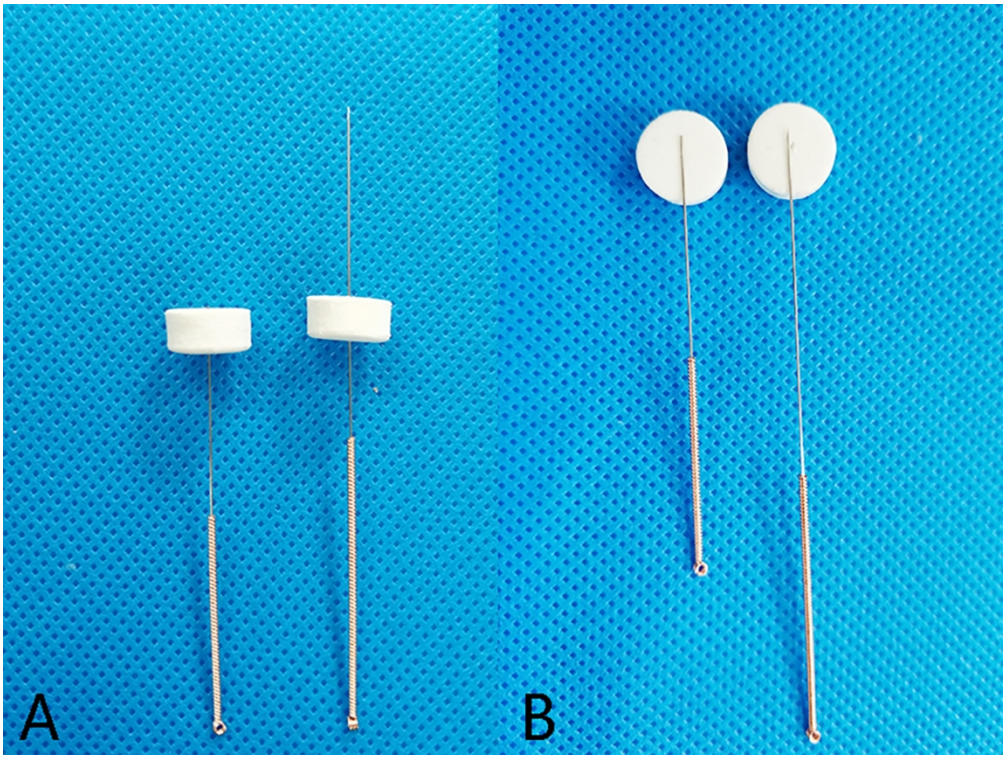


Figure 2. The difference between acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

119x90mm (300 x 300 DPI)

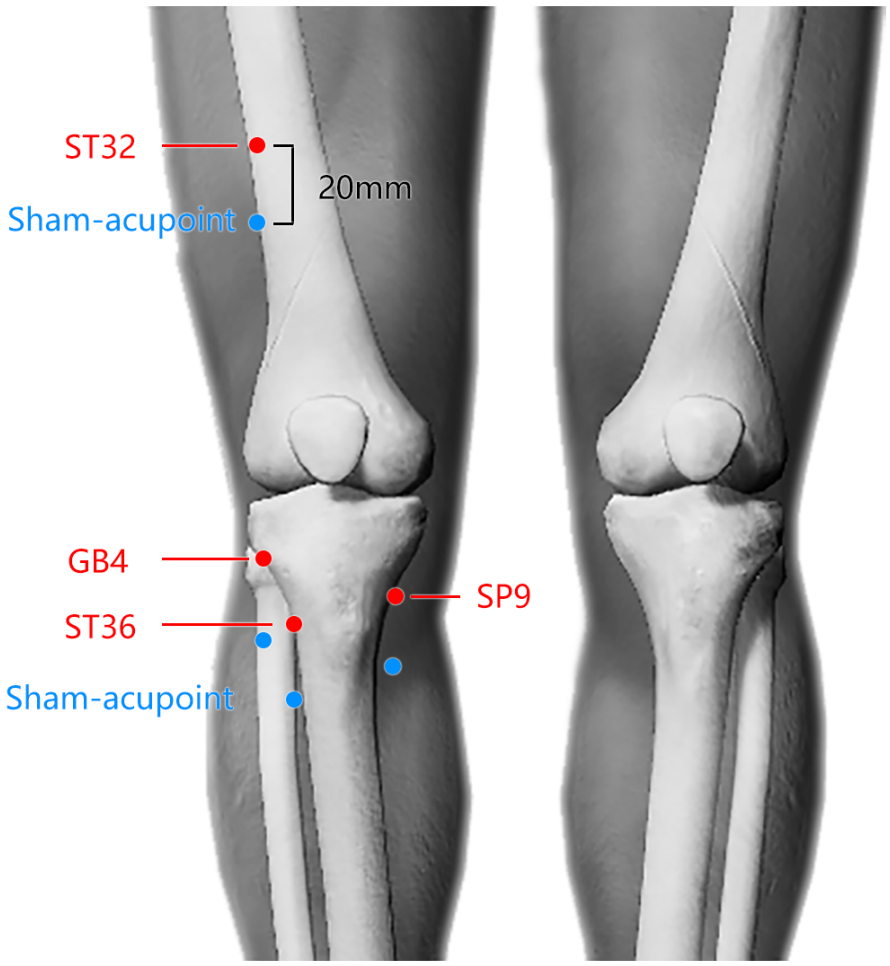


Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

94x90mm (300 x 300 DPI)

Supplemental file

1. Hospital for Special Surgery Knee-Rating Scale[1]

Hospital for Special Surgery Knee-Rating Scale (HSS)

Criteria	Points
Pain (30 points)	
No pain at any time	30
No pain on walking	15
Mild pain on walking	10
Moderate pain on waling	5
Severe pain on walking	0
No pain at rest	15
Mild pain at rest	10
Moderate pain at rest	5
Severe pain at rest	0
Function (22 points)	
Walking and standing unlimited	12
Walking distance of 5-10 blocks and standing ability intermittent >1/2hr	10
Walking 1-5 blocks and standing up < 1/2hr	8
Walking less than 1 block	4
Cannot walk	0
Climbing stairs	5
Climbing stairs with support	2
Transfer activity	5
Transfer activity with support	2
Range of Motion (18 points)	
1 point for each 8 degrees (max 18 points)	18
Muscle Strength (10 points)	
Excellent: cannot break quadriceps power	10
Good: can break the quadriceps power	8
Fair: move through the arc of motion	4
Poor: cannot move through arc of motion	0
Flexion Deformity (10 points)	
No deformity	10
Less than 5 degrees	8
5-10 degrees	5
> 10 degrees	0
Instability (10 points)	
None	10

Mild: 0-5 degrees	8
Moderate: 5-15 degrees	5
Severe: > 15degrees	0
Subtraction	
One cane	-1
One crutch	-2
Two crutches	-3
Extension lag of 5 degrees	-2
Extension lag of 10 degrees	-3
Extension lag of 15 degrees	-5
Each 5 degrees of varus	-1
Each 5 degrees of valgus	-1

Excellent ≥ 85
Good = 70-84
Fair = 60-69
Poor ≤ 60

2. Hamilton Anxiety Rating Scale (HAMA)[2]

Hamilton Anxiety Rating Scale (HAMA)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 Anxious mood
Worries, anticipation of the worst, fearful anticipation, irritability. 0 1 2 3 4

2 Tension
Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax. 0 1 2 3 4

3 Fears
Of dark, of strangers, of being left alone, of animals, of traffic, of crowds. 0 1 2 3 4

4 Insomnia
Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors 0 1 2 3 4

5 Intellectual
Difficulty in concentration, poor memory. 0 1 2 3 4

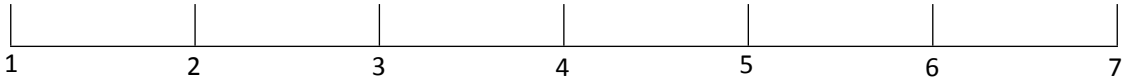
6 Depressed mood Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.	0 1 2 3 4
7 Somatic (muscular) Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.	0 1 2 3 4
8 Somatic (sensory) Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.	0 1 2 3 4
9 Cardiovascular symptoms Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat	0 1 2 3 4
10 Respiratory symptoms Pressure or constriction in chest, choking feelings, sighing, dyspnea.	0 1 2 3 4
11 Gastrointestinal symptoms Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.	0 1 2 3 4
12 Genitourinary symptoms Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence	0 1 2 3 4
13 Autonomic symptoms Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.	0 1 2 3 4
14 Behavior at interview Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.	0 1 2 3 4

0 ~ 7: No anxiety
8~14: Possible anxiety
15~21: Mild anxiety
22~29: Obvious anxiety
>29: Severe anxiety

3. Functional Living Index Emesis (FLIE)[3]

Functional Living Index Emesis (FLIE)

1. How much nausea have you had in the past 3 days?



None A Great Deal

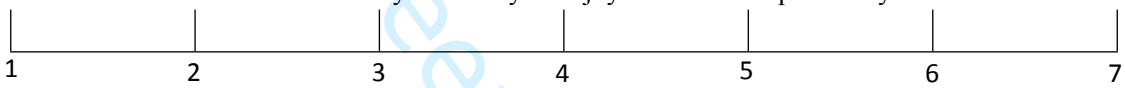
2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?

Not at all A Great Deal

3. Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?

A Great Deal Not at all

4. How much has nausea affected your ability to enjoy a meal in the past 3 days?

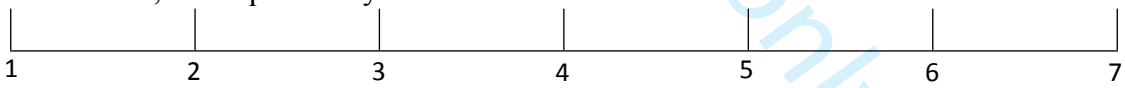


Not at all A Great Deal

5. How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?

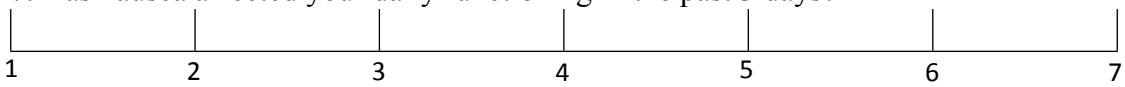
Not at all A Great Deal

6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?



A Great Deal Not at all

7. Has nausea affected your daily functioning in the past 3 days?

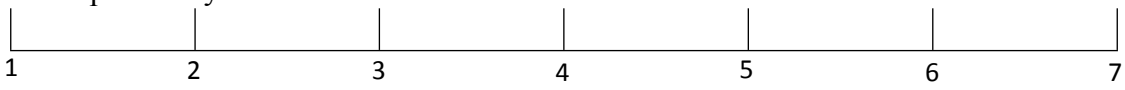


Not at all A Great Deal

8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days.

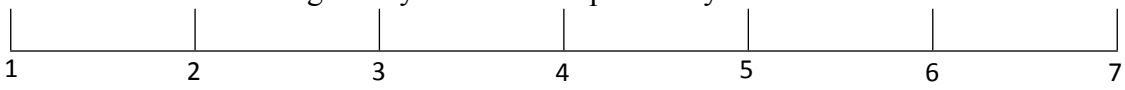
Not at all A Great Deal

9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days.



Not at all A Great Deal

10. How much vomiting have you had in the past 3 days?



None A Great Deal

11. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?

A Great Deal Not at all

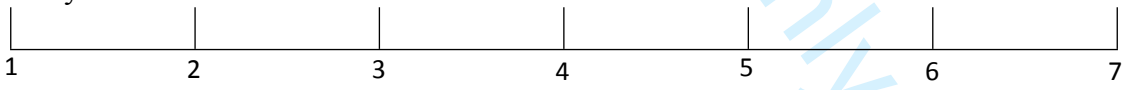
12. Has vomiting affected your ability to complete your usual household tasks during the past 3 days?

Not at all A Great Deal

13. How much has vomiting affected your ability to enjoy a meal in the past 3 days?

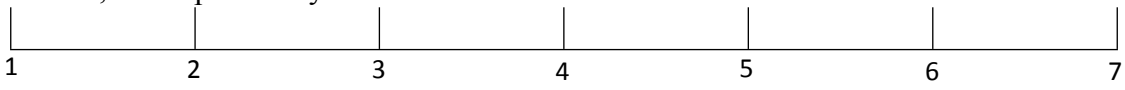
Not at all A Great Deal

14. How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?



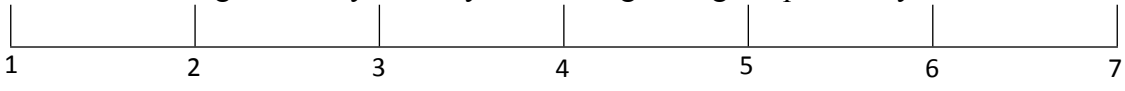
Not at all A Great Deal

15. How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?



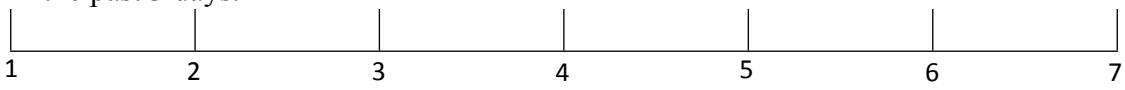
A Great Deal Not at all

16. Has vomiting affected your daily functioning during the past 3 days?



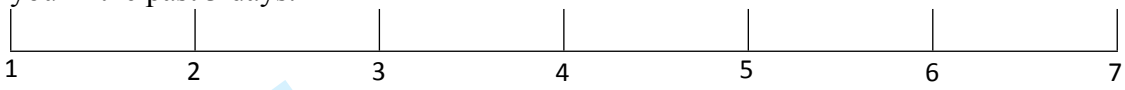
Not at all A Great Deal

17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.



Not at all A Great Deal

18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.



A Great Deal Not at all

References:

1 Bach CM, Nogler M, Steingruber IE, *et al.* Scoring Systems in Total Knee Arthroplasty. 2002;:184–96.

2 HAMILTON M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50–5.http://www.ncbi.nlm.nih.gov/pubmed/13638508

3 Lindley CM, Hirsch JD, O'Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	6

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6-7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Data access	#29	Statement of who will have access to the final trial dataset,	12

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Research methods
Keywords:	electroacupuncture, postoperative pain, total knee arthroplasty, the study protocol

Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Lian-bo Xiao and Yue-lai Chen contributed equally to this paper.

Author Contributions

SZ and LBX conceived the study while HH, JX, LZ, XLS designed the study. The study protocol was drafted by SZ and LBX, and was revised by YLC. All authors approved the final manuscript of this study protocol.

Word Count:2190

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Conflicts of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Abstract:

Introduction: The purpose of this study is to assess the efficacy of electroacupuncture to relieve pain and promote functional rehabilitation after total knee surgery.

Methods and analysis: We propose a single-blinded, randomised placebo-controlled trial to evaluate the efficacy of electroacupuncture. Patients with osteoarthritis (aged 55 to 80 years) undergoing unilateral total knee arthroplasty will be included in the trial. They will be randomised to receive either electroacupuncture or sham-electroacupuncture. A total of 110 patients will receive electroacupuncture and sham-electroacupuncture for three days after TKA. Postoperative pain will be measured using VAS score, and the need for an additional dose of opioid and analgesics will be recorded as the primary outcome. Secondary outcomes include knee function and swelling, postoperative anxiety, postoperative nausea and vomiting among other complications.

Ethics and dissemination: This study has been approved by the ethics committee, and subsequent modifications of the protocol will be reported and approved by it. Written inform content will be obtained from all of the participants or their authorized agents.

Trial registration number: ChiCTR1800016200

Keywords: electroacupuncture, postoperative pain, total knee arthroplasty, study protocol

Article Summary

Strengths and limitations of this study

1. The study is the first single-blinded, randomised placebo-controlled trial in China

to assess the efficacy of electroacupuncture to relieve pain and promote functional rehabilitation after total knee surgery.

2. The study will use an efficient sham-electroacupuncture method that makes it hard for patients with electroacupuncture treatment experience to distinguish between both treatments.

3. The study is rigorously designed, which includes adequate sample size, proper randomization and allocation concealment, and prospective trial registration to reduce selection and confounding bias.

4. There is still bias in the implementation of blind method due to the unblinded acupuncturists.

Introduction

Total knee arthroplasty (TKA) is the most frequently performed surgical procedure for end-stage osteoarthritis and rheumatoid arthritis. Moderate to severe postoperative pain is a major complaint in most patients. Acute and subacute postoperative pain is highly associated with persistent post-surgical pain (PPSP), especially when the acute pain is not treated with effective analgesia.[1] A recent study showed that 10%-34% and 7%-23% of patients reported severe pain after TKA and total hip arthroplasty (THA), respectively, which indicates that TKA patients are more likely to develop PPSP.[2] Multimodal analgesia has been used for 20 years and it is considered to be the most effective strategy for PPSP. Abuse of analgesic drugs has increased exposure of the public to the side effects of non-steroidal anti-inflammatory

drugs (NSAIDs) and opioids.[3,4] Drug-free interventions to reduce pain or opioid consumption are more consistent with the principles of Enhanced Recovery After Surgery (ERAS).

Clinical trials and systematic reviews have shown that the efficacy of electroacupuncture or acupuncture analgesia is controversial.[5–8] Electrotherapy and acupuncture have been proved to be potentially beneficial for postoperative pain after TKA.[9] Studies on the mechanism of electroacupuncture analgesia indicated that it activates many bioactive chemicals through peripheral, spinal, and supraspinal mechanisms.[10] The supraspinal mechanisms showed EA analgesia is highly associated with descending pain regulation of the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM).[10,11] The PAG-RVM system is recognized as the central site of action of analgesic agents including opioids, cyclooxygenase inhibitors, and cannabinoids.[12,13] We hypothesize that EA may exert an analgesic effect by activating the PAG-RVM system. Because the mechanism of electroacupuncture analgesia is not clear, there are also opinions that pain relief may be due to expectation or placebo effects.[8] Besides, placebo analgesia is highly associated with both areas of the brain.[14–16] Strict blinding and placebo-controlled is required to rule out the effects of the placebo effect on outcomes.

The purpose of this study is to assess the efficacy of electroacupuncture on pain relief and promoting functional rehabilitation after total knee surgery. We will use a large sample size and a reliable blind method of electroacupuncture to ensure a credible conclusion.

Methods and analysis

Study Context

This study will be a single-blinded, randomised placebo-controlled trial performed at the inpatient ward of Shanghai University of Traditional Chinese Medicine Guanghua Hospital, Shanghai, China. The annual surgical number of total knee arthroplasty for osteoarthritis was about 600 in 2017. We planned to begin recruiting patients from June 2018 and patients preparing for unilateral TKA will be recruited. In this study, there will be 7 investigators, including a chief orthopaedic surgeon (LBX) with 20 years of clinical experience, two orthopaedic physicians (JX and SZ), two Chinese medicine acupuncturists (HH and YLC), and two outcome assessors (LZ, and XLS). Sheng Zhong (SZ) and Hai Huang (HH) will recruit patients who meet the inclusion criteria in the hospital and introduce the patient to the trial process, possible benefits and risks to obtain their informed consent. ERAS programme (Table 1) will be performed by trained nurses and physiotherapists at the inpatient ward. The ERAS programme is routinely applied, but electroacupuncture has been added to analgesia. The schedule and the study flow diagram is shown in Table 2 and Figure 1.

Sample size calculation

In a previous meta-analysis study in which pain relief was compared between EA groups and controls, the minimal mean difference of the two groups based on the VAS score (on a scale of 0-10) was -1.14 (95% CI, -1.90 to -0.38), and the standard

deviation was estimated to be 2.[9] Considering a dropout rate of 10%, 110 patients are required to yield a power of 80% with a significance level of 0.05.[17]

Randomisation and allocation concealment

One hundred and ten patients will be divided into EA and Sham-EA groups with a ratio of 1:1. An independent biostatistician will generate a random sequence using the R (version 3.4.4). A sequence of numbers will be prepared and sealed in an opaque envelope. Only the acupuncturist will be allowed to open the envelope to obtain the grouping code.

Single-blinding

The acupuncturist will be blinded to the grouping information in advance, and the treatment method according to the grouping information contained in envelopes. All participants, orthopaedic surgeons, and relevant healthcare staff will be blinded to the study. The outcome assessor will not be aware of the treatment that patients received and will only instruct the patient to fill in the scales. The independent biostatistician will also be blinded when performing the statistical analyses. To maximize the blinding of patients, an effective sham electroacupuncture method will be applied with adhesive pads, a dull-tipped placebo needle, and a sham electrical stimulation device. Details of the sham operation design are described in the following part.

Eligibility criteria

Eligible

(1) Aged 55 to 80 years; (2) Meet the 1995 American College of Rheumatology (ACR) diagnostic criteria for osteoarthritis; (3) Undergoing unilateral total knee

arthroplasty under general anaesthesia without surgical contraindications; (4) American Society of Anesthesiologists (ASA) Grade I or II.

Ineligible

(1) The area of acupuncture points has skin damage and cannot perform acupuncture; (2) Preoperative deep venous thrombosis or swelling of the lower extremities; (3) Severe arrhythmia, heart failure, chronic obstructive pulmonary disease, epilepsy, mental disease; (4) Received treatment of acupuncture in past 1 month.

Study interventions

EA group

Patients will receive early acupuncture analgesia once a day from 24 to 72 hours after surgery. The first session of acupuncture treatment will be performed at 24 hours postoperatively. Firstly, the adhesive pads will be put on the acupoints of bilateral *Futu* (Stomach 32, ST32), *Zusanli* (Stomach 36, ST36), *Yanglingquan* (Gall Bladder 34, GB34), and *Yinlingquan* (Spleen 9, SP9). 1.5 *cun* acupuncture needles (0.25×40mm, Huatuo Inc.) will be manually inserted into the skin through the adhesive pads (Figure. 2). When *De-qi* sensation is achieved, subsequent electrical stimulation with a frequency of 2Hz, a continuous wave and tolerable intensity by the patient will be applied to the four acupoints (GB 34 to ST32 and ST36 to SP9) using a Hwato SDZ-V electrical stimulation device (Suzhou Medical Appliance Factory, Suzhou, China). Needles with electrical stimulation will be retained for 20 minutes in each session. The patients will receive a total of 3 treatments which were given once a

day.

Sham-EA group

Similar to the EA group, three sessions of acupuncture will be provided at the same time. An adhesive pad will be put on the sham-acupoint which is 20 mm distal to the real acupoint (Figure. 3). The placebo needle has a blunt-tip and it will be manually inserted into the adhesive pads but without skin penetration to provide participant-blinding effects (Figure. 2). The sham electrical stimulation device will have a connecting cord with a broken inner wire with no actual current output. Needles will also be retained for 20 minutes in each session. The patients will receive a total of 3 sham treatments which were given once a day. This Sham-EA method was proved to be effective in a previous study.[18]

Postoperative analgesia

All patients will receive the same analgesic procedure. Fentanyl patient-controlled analgesia (PCA) will be used at a continuous infusion rate of 0.25 μg/(kg·h) and a bolus of 0.15 μg/kg with a 10-minute lockout time. Patients will be allowed to use Celebrex 200 mg per day. Besides, additional rescue doses of analgesics will be provided upon demand for patients with a VAS score above 60.

Discontinuing criteria

(1) Acupuncture cannot be tolerated after surgery or patients that cannot be implemented according to the protocol; (2) Severe physiological and pathological changes were found during surgery and it is not appropriate to receive acupuncture treatment, such as anaesthesia accidents, cardiac-cerebrovascular accidents, nerve or

vascular injury during surgery; (3) Patients in which the trial arrangement cannot be completed or the safety judgment is affected due to surgical factors after the test; (4) Severe adverse reactions, severe complications, such as deep vein thrombosis, pulmonary embolism and severe allergic reactions.

Outcome

Primary outcome

Pain

When the patients are discharged from the operating room, this will be recorded as 0 hours. Patients will put a mark on a 100 mm visual analogue scale to assess the pain of their knee (from no pain to very severe) at 6, 24, 48, and 72 hours after surgery, then assessors record it. Additional PCA dose requirement will be evaluated in this study to reflect the degree of pain. Patients will be trained to adjust the PCA to obtain an additional dose of analgesia depending on the degree of pain. This will be recorded 48 hours after surgery. Patients will be given an additional dose of analgesia upon demand if the VAS score is above 60. The additional use of analgesics within 2 weeks after surgery will be recorded in the case report forms.

Secondary outcome

Knee function and swelling

Knee function will be measured based on Hospital for Special Surgery Knee-Rating Scale [19] (HSS scale) (Supplemental file) at one day before surgery and three days after surgery. All patients will first be educated about the HSS scale by a

trained researcher until they fully understand the questionnaire, then asked to complete the form according to their actual conditions. At 24 hours after surgery, the outcome assessor will remove the elastic bandage and measure the circumference of the knee at the superior patellar pole. A second measurement will be performed 72 hours after surgery.

Perioperative anxiety

Perioperative anxiety will be measured by the Hamilton Anxiety Scale (HAMA)[20] (Supplemental file) at one day before surgery and three days after surgery. HAMA has 14 levels to assess the severity of a patient's anxiety, and it divides anxiety into physical (7~13) and spiritual (1~6 and 14).

Postoperative nausea and vomiting (PONV)

PONV will be measured according to vomiting symptoms scores in 4-time points, including on the day of surgery and 1, 2, 3 days after surgery.[21] Functional Living Index-Emesis (FLIE) [22] (Supplemental file) is used to evaluate the effect of PONV on the quality of life, and it will be measured 3 days after surgery.

Postoperative complications and adverse events

All expected and unexpected adverse events will be measured during the allocated intervention process and during the entire study period. Acupuncture-related adverse events are hematoma and syncope during acupuncture. Other postoperative complications including incision infection, urinary retention, deep vein thrombosis, and postoperative persistent pain will be recorded 6 weeks after surgery. All serious adverse events (SAEs) will be reported immediately to the sponsor to allow further

investigations into their causes.

Data management

Data entry will be conducted by two independent trained research assistants using paper CRFs to record the research data after completion of final data collection. As acupuncture has known minimal risks, a formal data monitoring committee will not be required.[8,23] Independent investigators of the hospital staff will monitor and audit the data periodically.

Statistical analysis

According to the intention to treat (ITT) principle, full analysis set (FAS) and per-protocol set (PPS) will be used for primary analysis. Safety set (SS) will not be required since acupuncture has minimal risks.[8,23] Sensitivity analysis will be performed to determine the impact of incomplete records on results. Missing data will not be imputed. Statistical analysis will be performed using R (version 3.4.4). The difference between the two groups will be calculated and compared using the t-test if the Shapiro-Wilk test showed that the data is normally distributed, otherwise the Mann-Whitney U test will be used. A Pearson χ^2 or Fisher's exact test will be used to calculate the differences in the count data. Mixed effects models will be used to analyze the trend of changes in VAS scores with two factors of groups and time.[24]

Ethics and dissemination

This study has been approved by the ethics committee of Shanghai Guanghua Hospital of Integrated Chinese and Western Medicine (approval number AF13v2-2), and any modification of the protocol will be reported and approved by it. Written

inform consent will be obtained from all participants or their authorized agents. All electroacupuncture treatments will be free and the research data will be strictly confidential. The result of the trial will be presented on the website of the Chinese Clinical Trial Registry and published in peer-reviewed journals.

Patient and Public Involvement

Patient and public were not involved in the design of this study. The participants will be informed of the result of this study during the follow-up visit. Besides, we will enlist their help in disseminating the research findings.

Discussion

Drug-free interventions, especially EA, have been proven effective in pain relief and promoting functional rehabilitation,[25,26] and they will have good prospects for relieving opioid abuse or overuse of NSAIDs. However, the effect and mechanism of acupuncture analgesia are not clear, and the placebo effect is considered to play an important role.[8] This study has enough samples to obtain reliable results and we have improved the implementation of blinding to adequately characterize the placebo effect. We hope that the results of the study will provide new evidence for electroacupuncture treatment of postoperative pain in TKA. Another question is to determine if the statistical difference between the two groups is clinically relevant. The minimal clinically important difference (MCID) is a measure that is used to evaluate the clinical significance of an intervention. In the case of standardized multimodal analgesia, the MCID for VAS of postoperative pain after TKA is -22.6 (on a scale of 0-100), and the MCID can be also used to evaluate the difference of EA

and sham.[27]

Multiple evidence-based ERAS strategies for TKA have been shown to reduce postoperative complications and improve prognosis and patient satisfaction. Postoperative analgesia is an important part of ERAS. This study is based on add-on design, electroacupuncture and sham are applied to two groups of patients who used standard multimodal analgesia to evaluate the benefits of electroacupuncture on postoperative pain in TKA. We recommend EA and more non-drug therapies as a routine treatment in ERAS programme of TKA if the results indicate effectiveness over placebo.

Reference

1 Veal FC, Bereznicki LRE, Thompson AJ, *et al.* Subacute Pain as a Predictor of Long-Term Pain Following Orthopedic Surgery: An Australian Prospective 12 Month Observational Cohort Study. *Medicine (Baltimore)* 2015;**94**:e1498. doi:10.1097/MD.0000000000001498

2 Beswick AD, Wylde V, Gooberman-Hill R, *et al.* What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012;**2**:e000435. doi:10.1136/bmjopen-2011-000435

3 Han C, Li X, Jiang H, *et al.* The use of gabapentin in the management of postoperative pain after total knee arthroplasty. *Medicine (Baltimore)* 2016;**95**:e3883. doi:10.1097/MD.0000000000003883

4 Katz J, Buis T, Cohen L. Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. *Can J Anesth Can d'anesthésie* 2008;**55**:88–99. doi:10.1007/BF03016320

5 Li X, Wang R, Xing X, *et al.* Acupuncture for Myofascial Pain Syndrome: A Network Meta-Analysis of 33 Randomized Controlled Trials. *Pain Physician* 2017;**20**:E883–902.

6 Peng L, Zhang C, Zhou L, *et al.* Traditional manual acupuncture combined with rehabilitation therapy for shoulder hand syndrome after stroke within the Chinese healthcare system: a systematic review and meta-analysis. *Clin Rehabil* 2018;**32**:429–39. doi:10.1177/0269215517729528

7 Ju ZY, Wang K, Cui HS, *et al.* Acupuncture for neuropathic pain in adults. *Cochrane Database Syst Rev* Published Online First: 2 December 2017. doi:10.1002/14651858.CD012057.pub2

8 Manheimer E, Cheng K, Linde K, *et al.* Acupuncture for peripheral joint osteoarthritis. *Cochrane Database Syst Rev* Published Online First: 20 January 2010. doi:10.1002/14651858.CD001977.pub2

9 Tedesco D, Gori D, Desai KR, *et al.* Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty. *JAMA Surg* 2017;**152**:e172872. doi:10.1001/jamasurg.2017.2872

10 Zhang R, Lao L, Ren K, *et al. Mechanisms of acupuncture-electroacupuncture on persistent pain*. 2014. doi:10.1097/ALN.0000000000000101

11 Zhao Z-Q. Neural mechanism underlying acupuncture analgesia. *Prog*

Neurobiol 2008;**85**:355–75. doi:10.1016/j.pneurobio.2008.05.004

12 Pogatzki-zahn EM, Segelcke D, Schug SA. Postoperative pain — from mechanisms to treatment. *PAIN Reports* 2017;**2**:e588. doi:10.1097/PR9.0000000000000588

13 Leith JL, Wilson AW, Donaldson LF, *et al.* Cyclooxygenase-1-derived prostaglandins in the periaqueductal gray differentially control C- versus A-fiber-evoked spinal nociception. *J Neurosci* 2007;**27**:11296–305. doi:10.1523/JNEUROSCI.2586-07.2007

14 Tinnermann A, Geuter S, Sprenger C, *et al.* Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science* 2017;**358**:105–8. doi:10.1126/science.aan1221

15 Grahl A, Onat S, Büchel C. The periaqueductal gray and Bayesian integration in placebo analgesia. *Elife* 2018;**7**. doi:10.7554/eLife.32930

16 Eippert F, Bingel U, Schoell ED, *et al.* Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* 2009;**63**:533–43. doi:10.1016/j.neuron.2009.07.014

17 Chow SC, Wang H, Shao J. *Sample Size Calculations in Clinical Research, Second Edition*. Taylor & Francis 2007.

18 Liu Z, Liu Y, Xu H, *et al.* Effect of Electroacupuncture on Urinary Leakage Among Women With Stress Urinary Incontinence. *Jama* 2017;**317**:2493. doi:10.1001/jama.2017.7220

19 Bach CM, Nogler M, Steingruber IE, *et al.* Scoring Systems in Total Knee

Arthroplasty. 2002;:184–96.

20 HAMILTON M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50–5. doi:10.1145/363332.363339

21 Hesketh PJ, Kris MG, Grunberg SM, *et al.* Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;**15**:103–9. doi:10.1200/JCO.1997.15.1.103

22 Lindley CM, Hirsch JD, O'Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

23 Witt CM, Pach D, Brinkhaus B, *et al.* Safety of Acupuncture: Results of a Prospective Observational Study with 229,230 Patients and Introduction of a Medical Information and Consent Form. *Complement Med Res* 2009;**16**:91–7. doi:10.1159/000209315

24 Detry M, Ma Y. Analyzing repeated measurements using mixed models. *Jama* 2016;**315**:407–8. doi:10.1001/jama.2015

25 Chen G, Gu R-X, Xu D-D. [The application of electroacupuncture to postoperative rehabilitation of total knee replacement]. *Zhongguo Zhen Jiu* 2012;**32**:309–12.

26 Yue C, Zhang X, Zhu Y, *et al.* Systematic Review of Three Electrical Stimulation Techniques for Rehabilitation After Total Knee Arthroplasty. *J Arthroplasty* 2018;**33**:2330–7. doi:10.1016/j.arth.2018.01.070

27 Danoff JR, Goel R, Sutton R, *et al.* How Much Pain Is Significant? Defining the Minimal Clinically Important Difference for the Visual Analog Scale for

Pain After Total Joint Arthroplasty. *J Arthroplasty* 2018;**33**:S71–S75.e2.

doi:10.1016/j.arth.2018.02.029

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Table 1. Enhanced Recovery After Surgery Programme

Preoperative	
1	Preoperative education
2	Carbohydrate loading preoperatively and avoidance of prolonged starving
3	Use of preoperative probiotics
4	No mechanical bowel preparation
5	No premedication
6	Preemptive analgesia
Intraoperative	
7	Maintenance of normothermia
8	Goal-directed perioperative fluid administration
9	Minimally invasive incision
10	Avoidance of nasogastric tubes and deep vein catheterization
11	Avoidance of bladder catheters, if necessary early removal of bladder catheters
12	Use of tranexamic acid
13	Periarticular local injection analgesia
Postoperative	
14	Multimodal analgesia: PCA analgesia, NSAIDs; Avoidance of opioid analgesia
15	Use of postoperative antiemetic and laxatives
16	Enforced early mobilisation
17	Enforced early postoperative oral feeding

PCA, patient controlled analgesia; NSAIDs, non-steroidal antiinflammatory drugs

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Table 2. The schedule of trial enrolment, interventions and assessments

	Enrolment	Intervention period			
	Pre-OP	6 hours	24 hours	48 hours	72 hours
Enrolment					
Informed consent	●				
Assessment of eligibility	●				
Randomisation	●				
Interventions					
EA		●	●	●	●
Sham-EA		●	●	●	●
Assessments					
VAS	●	●	●	●	●
Additional dose released by PCA				●	
HSS scale	●				●
HAMA score	●				●
PONV		●	●	●	●
COK			●		●
Additional use of analgesics	●				●
Postoperative complications and adverse events		●	●	●	●

OP, operation; EA, electroacupuncture; VAS, Visual Analogue Score; PCA, patient-controlled analgesia; HSS, hospital for special surgery; HAMA, Hamilton Anxiety Scale; PONV, post-operative nausea and vomiting; COK, circumference of knee

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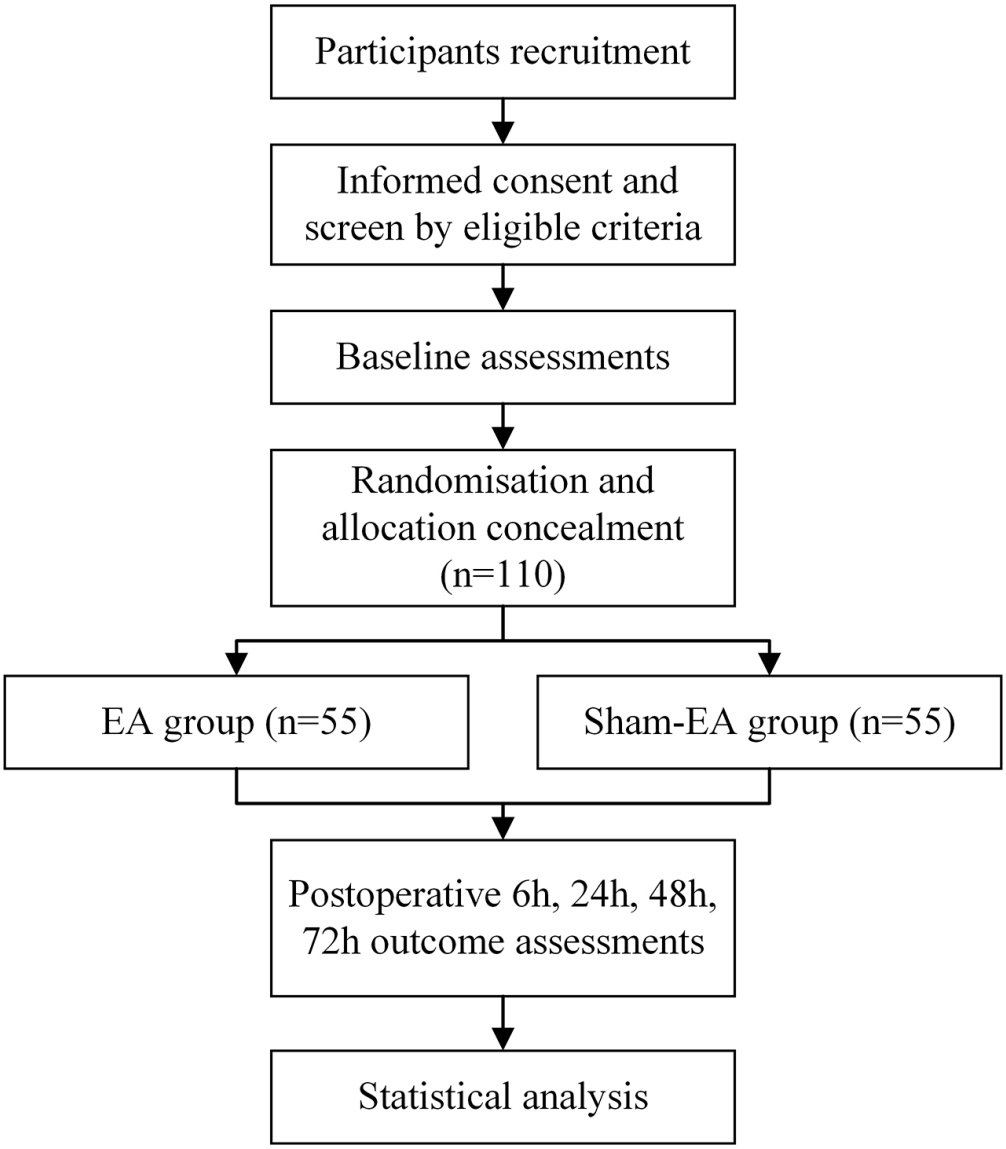
Figure Legend

Figure 1. The study flow diagram, including participants recruitment, eligibility, screening, randomization, allocation concealment, and outcome assessments. EA, electroacupuncture.

Figure 2. The difference between the acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.



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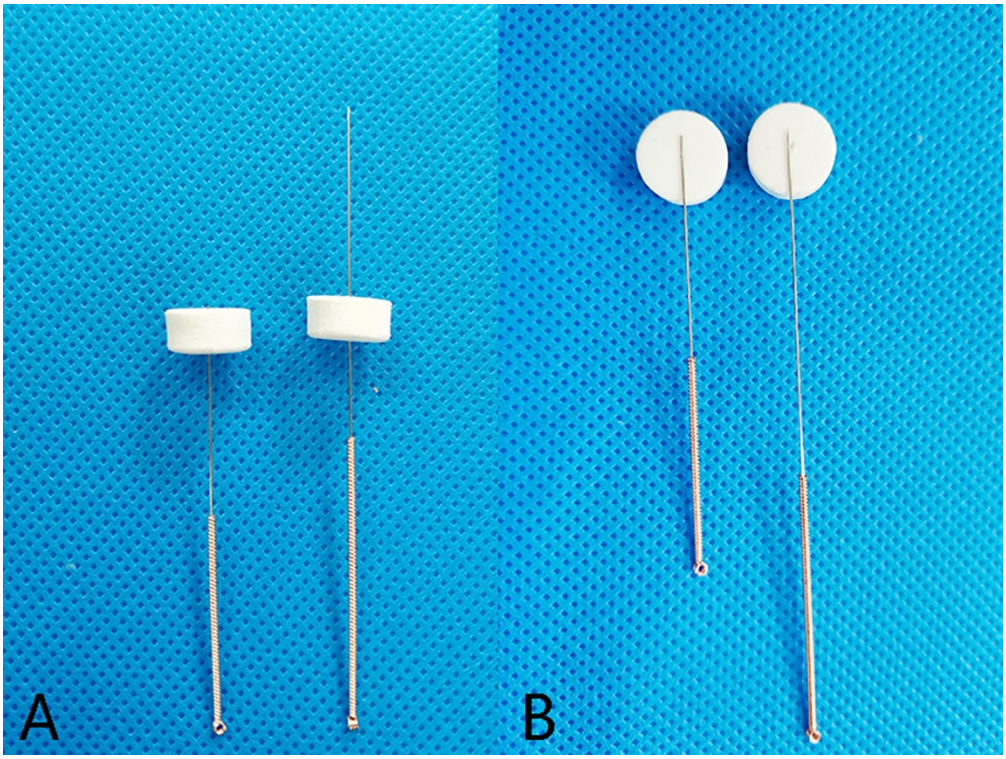


Figure 2. The difference between acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

119x90mm (300 x 300 DPI)

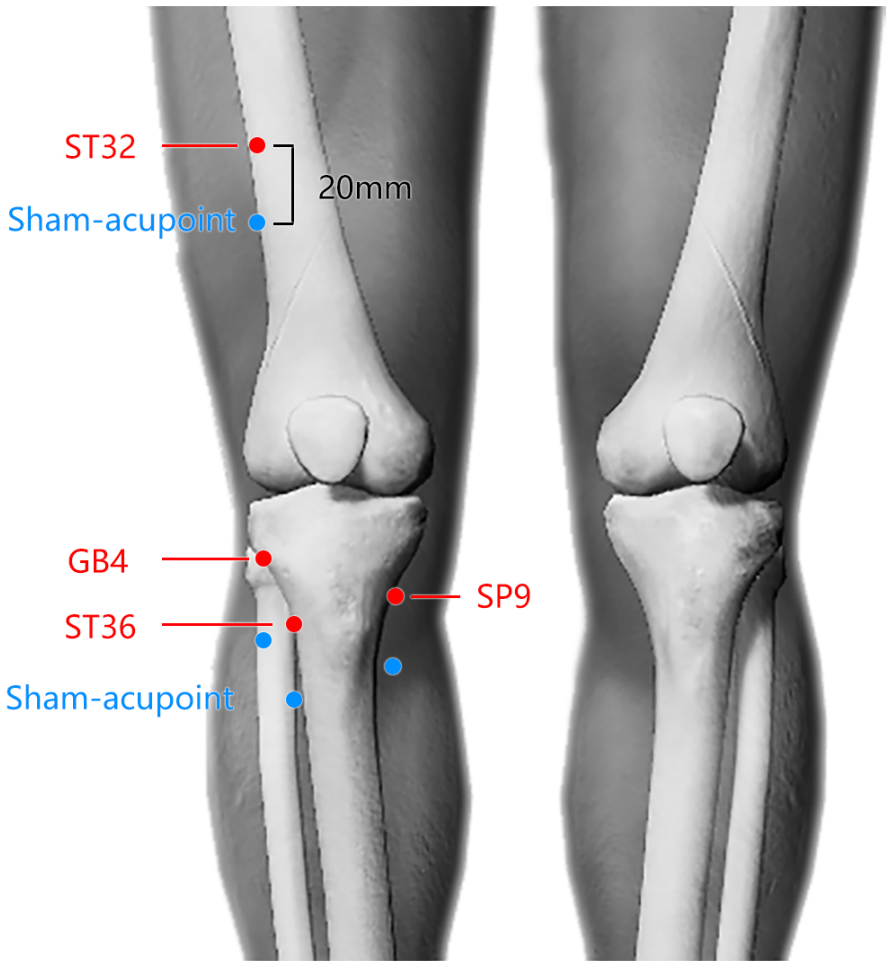


Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

94x90mm (300 x 300 DPI)

Supplemental file

1. Hospital for Special Surgery Knee-Rating Scale[1]

Hospital for Special Surgery Knee-Rating Scale (HSS)

Criteria	Points
Pain (30 points)	
No pain at any time	30
No pain on walking	15
Mild pain on walking	10
Moderate pain on waling	5
Severe pain on walking	0
No pain at rest	15
Mild pain at rest	10
Moderate pain at rest	5
Severe pain at rest	0
Function (22 points)	
Walking and standing unlimited	12
Walking distance of 5-10 blocks and standing ability intermittent >1/2hr	10
Walking 1-5 blocks and standing up < 1/2hr	8
Walking less than 1 block	4
Cannot walk	0
Climbing stairs	5
Climbing stairs with support	2
Transfer activity	5
Transfer activity with support	2
Range of Motion (18 points)	
1 point for each 8 degrees (max 18 points)	18
Muscle Strength (10 points)	
Excellent: cannot break quadriceps power	10
Good: can break the quadriceps power	8
Fair: move through the arc of motion	4
Poor: cannot move through arc of motion	0
Flexion Deformity (10 points)	
No deformity	10
Less than 5 degrees	8
5-10 degrees	5
> 10 degrees	0
Instability (10 points)	
None	10

Mild: 0-5 degrees	8
Moderate: 5-15 degrees	5
Severe: > 15degrees	0
Subtraction	
One cane	-1
One crutch	-2
Two crutches	-3
Extension lag of 5 degrees	-2
Extension lag of 10 degrees	-3
Extension lag of 15 degrees	-5
Each 5 degrees of varus	-1
Each 5 degrees of valgus	-1

Excellent ≥ 85
Good = 70-84
Fair = 60-69
Poor ≤ 60

2. Hamilton Anxiety Rating Scale (HAMA)[2]

Hamilton Anxiety Rating Scale (HAMA)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 Anxious mood
Worries, anticipation of the worst, fearful anticipation, irritability. 0 1 2 3 4

2 Tension
Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax. 0 1 2 3 4

3 Fears
Of dark, of strangers, of being left alone, of animals, of traffic, of crowds. 0 1 2 3 4

4 Insomnia
Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors 0 1 2 3 4

5 Intellectual
Difficulty in concentration, poor memory. 0 1 2 3 4

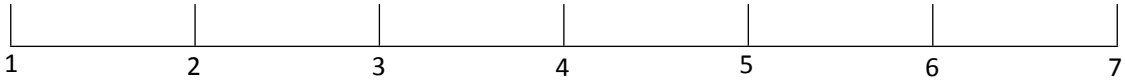
6 Depressed mood Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.	0 1 2 3 4
7 Somatic (muscular) Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.	0 1 2 3 4
8 Somatic (sensory) Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.	0 1 2 3 4
9 Cardiovascular symptoms Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat	0 1 2 3 4
10 Respiratory symptoms Pressure or constriction in chest, choking feelings, sighing, dyspnea.	0 1 2 3 4
11 Gastrointestinal symptoms Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.	0 1 2 3 4
12 Genitourinary symptoms Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence	0 1 2 3 4
13 Autonomic symptoms Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.	0 1 2 3 4
14 Behavior at interview Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.	0 1 2 3 4

0 ~ 7: No anxiety
8~14: Possible anxiety
15~21: Mild anxiety
22~29: Obvious anxiety
>29: Severe anxiety

3. Functional Living Index Emesis (FLIE)[3]

Functional Living Index Emesis (FLIE)

1. How much nausea have you had in the past 3 days?



None A Great Deal

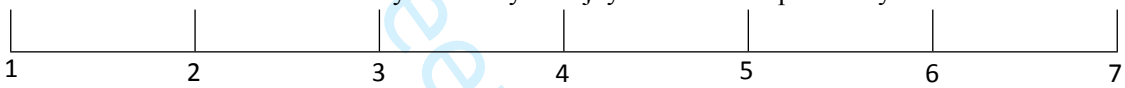
2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?

Not at all A Great Deal

3. Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?

A Great Deal Not at all

4. How much has nausea affected your ability to enjoy a meal in the past 3 days?

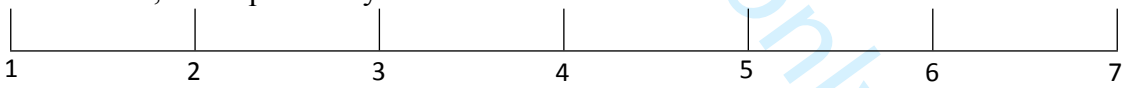


Not at all A Great Deal

5. How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?

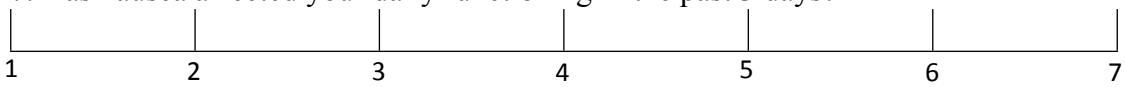
Not at all A Great Deal

6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?



A Great Deal Not at all

7. Has nausea affected your daily functioning in the past 3 days?

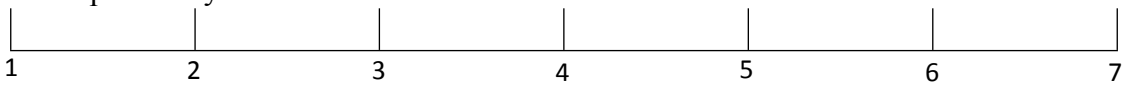


Not at all A Great Deal

8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days.

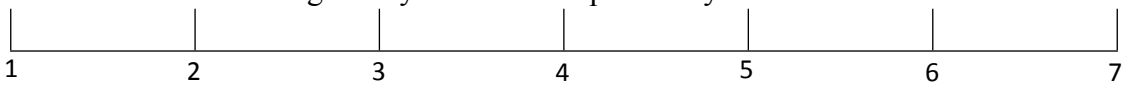
Not at all A Great Deal

9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days.



Not at all A Great Deal

10. How much vomiting have you had in the past 3 days?



None A Great Deal

11. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?

A Great Deal Not at all

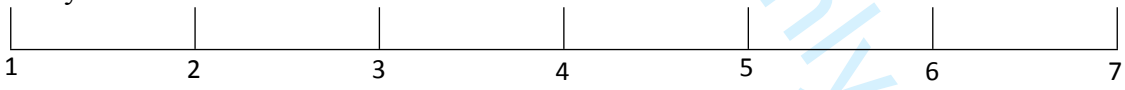
12. Has vomiting affected your ability to complete your usual household tasks during the past 3 days?

Not at all A Great Deal

13. How much has vomiting affected your ability to enjoy a meal in the past 3 days?

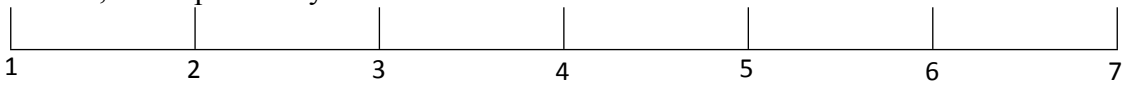
Not at all A Great Deal

14. How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?



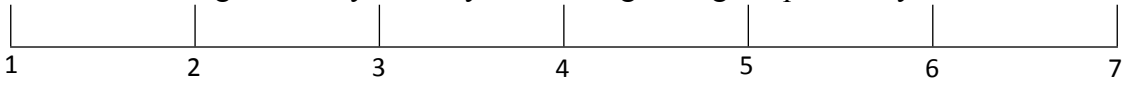
Not at all A Great Deal

15. How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?



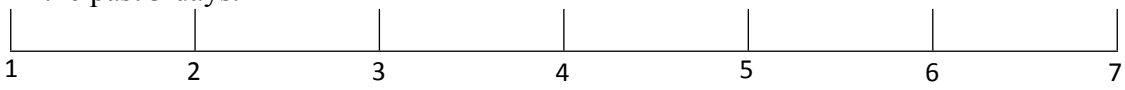
A Great Deal Not at all

16. Has vomiting affected your daily functioning during the past 3 days?



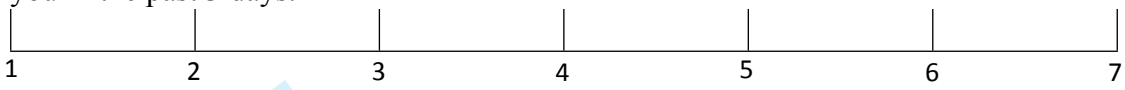
Not at all A Great Deal

17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.



Not at all A Great Deal

18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.



A Great Deal Not at all

References:

1 Bach CM, Nogler M, Steingruber IE, *et al.* Scoring Systems in Total Knee Arthroplasty. 2002;:184–96.

2 HAMILTON M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50–5.http://www.ncbi.nlm.nih.gov/pubmed/13638508

3 Lindley CM, Hirsch JD, O'Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

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Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	6

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6-7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Data access	#29	Statement of who will have access to the final trial dataset,	12

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a