BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053309
Article Type:	Protocol
Date Submitted by the Author:	11-May-2021
Complete List of Authors:	Li, Hao; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department Wen, Qian; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department Lu, Lingyun; Sichuan University West China Hospital, Department of Integrated Traditional Chinese and Western Medicine Hu, Hangqi; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department He, Ying; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department Zhou, Yaming; Sichuan University West China Hospital, Gastrointestinal Surgery Wu, Xiaoting; Sichuan University West China Hospital, Gastrointestinal Surgery Li, Ning; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department
Keywords:	COMPLEMENTARY MEDICINE, PAIN MANAGEMENT, GASTROENTEROLOGY

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Transcutaneous electrical acupoint stimulation combined with electroacupuncture for rapid recovery of patients after laparotomy for gastrointestinal surgery: A study protocol for a randomized controlled trial

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ABSTRACT

Introduction: Abdominal surgery is associated with common complications, including decreased or poor appetite, abdominal distension, abdominal pain caused by decreased or absent gastrointestinal motility, anal arrest with flatus and defecation, and nausea and vomiting resulting from the use of anaesthetics and opioid analgesics. These complications seriously affect postoperative recovery, prolong hospital stay, and aggravate patient burden. This study aims to investigate for the first time the efficacy of transcutaneous electrical acupoint stimulation (TEAS) combined with electroacupuncture (EA) therapy for rapid recovery after laparotomy for gastrointestinal surgery. There have been no clinical studies of this combination therapy.

Methods and analysis:This will be a prospective, single-centre, three-arm, randomised controlled trial. A total of 480 patients undergoing abdominal surgery will be stratified according to surgery type (i.e. gastric or colorectal procedure) and randomised into three groups; namely, the EA, TEAS+EA, and control groups. The control group will receive enhanced recovery after surgery (ERAS)-standardised perioperative management, including preoperative education, optimising the anaesthesia scheme, avoiding intraoperative hypothermia, restrictive fluid infusion, and reducing surgical trauma. The EA group will receive electroacupuncture stimulation at L14, PC6, ST36, ST37, and ST39 based on the ERAS-standardised perioperative management. Moreover, the TEAS+EA group will receive ERAS-standardised perioperative management; electroacupuncture stimulation at the L14, PC6, ST36, ST37, and ST39;

and TEAS stimulation at ST21 and SP15. The primary outcome will be the time of the first postoperative spontaneous anal exhaust. Secondary outcomes will include the time of first postoperative voluntary defecation, time to tolerance of a solid diet, time to first ambulation, hospital duration from operation to discharge, pain and nausea vomiting scores on the visual analogue scale (from 0 [no at all] to 10 [the worst]), medication use, incidence of postoperative complications, and evaluation of treatment modality acceptability. All statistical analyses will be performed based on the intention-to-treat principle.

Ethics and dissemination Ethics approval has been granted by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (approval number: 2021; number 52). The results are expected to be published in peer-reviewed journals.

Trial registration number: ChiCTR2100045646 (Chinese Clinical Trial Registry)

Strengths and limitations of this study

- A randomised controlled trial of 480 patients will be conducted to evaluate the efficacy of TEAS combined with EA therapy for rapid recovery after laparotomy for gastrointestinal surgery.
- The trial feasibility has been examined in a pilot randomised trial of 60 patients.
- This trial will be conducted using rigorous methods; for example, the patients will be randomly assigned to three groups; the data will undergo blind statistical analysis; and the interventionists, efficacy evaluators, and statisticians will be separated.

- There is no placebo effect in the control group.

INTRODUCTION

The most common postoperative complications in laparotomy for gastrointestinal surgery include gastrointestinal dysfunction, pain, postoperative nausea and vomiting (PONV), etc. These result from numerous factors, including the intraoperative use of anaesthetic drugs, surgical trauma, peritoneal irritation or inflammatory response, and postoperative use of analgesic drugs[1-3]. Rapid postoperative rehabilitation can prevent or reduce intraperitoneal adhesion; reduce the incidence of complications, including intestinal obstruction and intestinal infection; prevent secondary surgery, reduce opioid usage, and alleviate pain. Moreover, it can promote prompt recovery of the patients' oral diet, reduce the use of parenteral nutrition, shorten the hospitalisation duration, and reduce hospitalisation costs[4-8].

Enhanced recovery after surgery (ERAS) is based on evidence-based medicine and is a standardised, collaborative, and multidisciplinary optimisation management protocol for the perioperative period. It allows a reduction in the physiological and psychological traumatic stress response, as well as postoperative complications; a faster postoperative recovery; a shorter postoperative hospitalisation time; and a reduction in patient costs[9]. This concept was initially proposed by the Danish Medical Scientist Kehlet in 1997[10]. After > 20 years of practice and optimisation, the ERAS concept and pathway have been popularised and rapidly applied worldwide[11]. Although a series of perioperative ERAS measures can accelerate recovery, there remains room for

improvement in the prevention and treatment of postoperative gastrointestinal dysfunction and PONV, as well as in the reduction of opioid use.

Acupuncture exerts therapeutic effects by regulating gastrointestinal dynamics, analgesia, and antiemetics. It is widely considered that a degree of postoperative gastrointestinal dysfunction is an inevitable normal physiological response after abdominal surgery[12]. Several studies have demonstrated that acupuncture can significantly relieve postoperative abdominal pain and distension, promote intestinal ventilation, and promptly restore the patient's diet[13 14]. Acupuncture can enhance gastric dilatation through the sympathetic nerve to promote gastric emptying[15 16]; moreover, the vasoactive intestinal peptide is involved in electroacupuncture-mediated gastric motility regulation.

Additionally, acupuncture can facilitate postoperative multimodal analgesia. Postoperative analgesia is among the core ERAS components. Its principles include sufficient analgesia and minimisation of opioid usage. Adequate postoperative analgesia can reduce excessive stress, help patients get out of bed quickly, and promote recovery. Opioids, which are the main traditional postoperative analgesic drugs, can easily cause postoperative nausea, vomiting, and other complications. Reducing opioid usage allows early recovery of patients. There have been numerous studies on the mechanisms underlying acupuncture analgesia from the perspectives of electrophysiology, neurochemistry, molecular biology, and brain imaging[17-19]. Moreover, numerous clinical studies have shown that acupuncture can significantly reduce postoperative pain and opioid use after total hip replacement, craniotomy,

abdominal surgery, and kidney stone surgery[20-23]. Therefore, based on the ERAS clinical pathway, acupuncture analgesia may better control wound pain and reduce the use of analgesics, including opioids, and therefore accelerate patient recovery.

PONV is a common complication after surgical anaesthesia and analgesia with opioids that can cause dehydration, electrolyte imbalance, wound cracking, and discharge delay. PONV is another important factor that affects the recovery of patients[24]. Studies have shown that Neiguan (PC6) stimulation can effectively prevent PONV[25,26]. Transcutaneous electrical acupoint stimulation (TEAS) is more effective than intravenous ondansetron; additionally, using TEAS combined with drugs can enhance the anti-emetic effects of ondansetron[27].

Numerous studies have supported the application of acupuncture in postoperative rehabilitation; however, there are differences in efficacy across different acupuncture schemes. Currently, EA is the most common acupuncture scheme for rapid postoperative rehabilitation, with TEAS being the second most common scheme. Although TEAS avoids pain resulting from acupuncture needles, its efficacy is slightly worse than that of EA and it has relatively limited clinical application. However, our previous clinical experience and preliminary trials suggested that combining TEAS with EA may have a better curative effect than the conventional electroacupuncture treatment. Moreover, this combination could provide an improved acupuncture treatment protocol for rapid rehabilitation after laparotomy for gastrointestinal surgery. It may promote the recovery of gastrointestinal function more quickly, reduce pain

more obviously, shorten the duration of postoperative hospital stay, and reduce patient hospitalization costs, etc.

Therefore, this prospective, single-centre, three-arm, single-blind, randomised controlled trial (RCT) aims to evaluate the efficacy of TEAS combined with EA therapy for rapid recovery after laparotomy for gastrointestinal surgery.

METHODS AND ANALYSIS

Design

This will be a single-centre, prospective RCT with a three-arm parallel grouping design. The trial protocol version number: 2.0, date 31th March,2021.The study will be conducted at the West China Hospital of Sichuan University (WCHSU) from April 2021 to March 2023. All the participants will be required to provide written informed consent in accordance with the most recent version of the Declaration of Helsinki. Figure 1 presents the study flowchart.

Patient population and setting

A total of 480 Chinese patients undergoing laparotomy for gastrointestinal surgery will be sequentially enrolled at the WCHSU after fulfilling the eligibility criteria and signing informed consent. A clinical assistant with institutional review board training will be in charge of patient enrolment.

Eligibility criteria

The inclusion criteria will be as follows: (1) male and female patients aged 18–70 years; (2) laparotomy tumour resection under general anaesthesia (stomach, colon, and rectum); and (3) volunteering to participate in this study and signing an informed consent form.

The exclusion criteria will be as follows: (1) surgical incision or scar on the meridian of ST21/SP15, (2) local skin infection at acupoints, (3) inability to complete the visual analogue scale (VAS), and (4) allergy to metal or severe needle fear, intolerance of TEAS or EA treatment, (5) uncontrolled diabetes, severe cardiac, central nervous, psychiatric disorders, or coagulopathy; (6) cardiac pacemaker; and (7) participation in other clinical trials.

Withdrawal criteria: Participants meeting any of the following criteria will be withdrawn from the study: (1) occurrence of serious adverse events; (2) participants with serious complications or other serious diseases requiring emergency measures, (3) being required to withdraw during the test, and (4) violation of the test program. Withdrawn patients will not be replaced.

Randomisation and blinding

This study will have a single-blind design. The patient will be blinded to the group allocation; moreover, patients in the same ward will be separated by a bed curtain when receiving acupuncture treatment, with only the research leader and acupuncturist being aware of the treatment allocation. The randomised grouping plan will be designed using SPSS 22.0. According to the plan, 480 patients will be randomly divided into three

groups according to a ratio of 1:1:1: EA, TEAS+EA, and control groups. The group scheme will be kept in a confidential envelope; further, the research leader will randomly distribute the included patients to each group following the distribution plan in the envelope. Additionally, the research leader will only inform the acupuncturist responsible for the operation. Efficacy evaluation will be conducted blinded to the grouping allocation. Blind statistical analysis will be used in the data summary stage. Operators, efficacy evaluators, and statisticians will be separated.

INTERVENTION

All acupoints will be determined based on the National Standard of Location of Acupoints (GB 12346-90). All practitioners performing the treatment must have an acupuncturist qualification certificate with independent clinical experience for > 2 years. The acupuncturists will not be replaced during the experiments.

All patients will receive standardised perioperative management by ERAS, including preoperative education, optimisation of anaesthesia scheme, avoidance of intraoperative hypothermia, restrictive fluid infusion, and reduction of surgical trauma. Regarding the electronic acupuncture treatment instrument (Hwato, SDZ-V, Suzhou Medical Supplies Factory Co., Ltd), the current frequency will be continuous wave 2 Hz, the current intensity will be measured in degrees as tolerated by the patient; moreover, the treatment duration will last 30 min (figure 2). The treatment will be initiated from the first postoperative day, once daily in the morning, until the patient recovered spontaneous flatus from the anus and could tolerate transoral solid food.

In the EA group (electroacupuncture is added at the base of basic treatment), treatment will be bilaterally performed at five acupoint pairs: Hegu (LI4), Neiguan (PC6), Zusanli (ST36), Shangjuxu (ST37), and Xiajuxu (ST39). LI4 is an acupoint of the large intestine meridian and is located on the dorsum of the hand between the first and second metacarpal bones. PC6 belongs to the pericardium meridian and is located between the flexor carpi radialis muscle tendon and the palmaris longus tendon, 2 Cun above the wrist crease. ST36, ST37, and ST39 are acupoints of the stomach meridian. ST36 is located on the lateral side of the lower leg, 3 Cun below the lateral border of the knee and one finger width lateral to the anterior border of the tibia. ST37 is located 3 Cun below ST36. ST39 is located 3 Cun below ST37. After skin disinfection with a disposable disinfecting cotton swab, sterile and disposable stainless steel needles (0.25×40 mm, Suzhou Jiajian, Jiangsu, China) will be quickly and perpendicularly inserted into the skin acupoints at a depth of 25–30 mm. The duration of reinforcing-reducing manipulation of twirling and rotating needles should be used for 1 min to achieve de qi (a composite of sensations including soreness, numbness, distention, heaviness, and other sensations), which significantly contributes to acupuncture efficacy. The ipsilateral Neiguan, Hegu, Zusanli, and Xiajuxu will be separately connected to one electrode set, and therefore yielding four electrode sets (figure 3 a, b).

For the TEAS+EA group, treatment will be based on the EA group with the addition of two pairs of bilateral abdominal acupoints: Liangmen (ST21) and Daheng (SP15). Additionally, ST21 is an acupoint of the stomach meridian that is located 4 Cun

above the umbilicus and 2 Cun open next to the anterior median line. SP15 is an acupoint of the spleen meridian, located 4 Cun beside the umbilicus and lateral to the rectus abdominis muscle. Abdominal acupoints will be stimulated using a self-adhesive electrode pad with electrical conductivity; additionally, the ipsilateral Liangmen will be connected to the Daheng set of electrodes. The ipsilateral Neiguan, Hegu, Zusanli, and Xiajuxu acupoints will be connected to one electrode set to yield a total of six sets of electrodes (figure 3 a, b, c).

The control group will receive ERAS-standardised perioperative management without acupuncture treatment.

OUTCOME MEASURES

Main outcome

The primary outcome will be the time of the first postoperative spontaneous anal exhaust.The observer will be assessments and visits for participants after each treatment.

Secondary outcome

The secondary outcomes include the time of first postoperative voluntary defecation, time to tolerance of a solid diet, time to first ambulation, hospital duration from operation to discharge, pain and nausea vomiting scores on the VAS (from 0 [no at all] to 10 [the worst]), medication use, incidence of postoperative complications, and evaluation of treatment modality acceptability.The observer will be assessments and visits for participants after each treatment.

Safety evaluation

All adverse events will be recorded on the adverse event record sheet by the acupuncturist and participants at any time during the study period. Adverse events to be recorded include fainting during acupuncture treatment, needle breaking, unbearable acupuncture pain, local hematoma, infection, and any other discomfort or accident. The intensity and causality of each adverse event will be evaluated and recorded. If any serious adverse events occur due to an intervention, the intervention will be immediately stopped; further, appropriate corrective action will be taken. Serious adverse events will be promptly reported to the institutional review board within 24 h until 30 days after the end of the trial.

Sample size calculation

The stratification factors will be gastrectomy and colorectal resection, with each layer being divided into three groups: the group ratio will be 1:1:1. The main efficacy indicator will be the time from the laparotomy surgery to the first flatus. Given the lack of reports on TEAS+EA for promoting postoperative recovery, we conducted a preliminary experiment. The preliminary experimental results indicated that the time spent from laparotomy gastrectomy surgery to the first flatus in the control, EA, and TEAS+EA groups was 62.5 ± 26.7 h, 48 ± 24.5 h, and 45.7 ± 28.2 h, respectively, Additionally, in the control group, the time from the laparotomy colorectal surgery to the first flatus was the control, EA, and TEAS+EA groups was 63.6 ± 24.6 h, 50.5 ± 23.6 h, and 47.5±25.2 h, respectively. The sample size was determined using PASS 11 with $\alpha = 0.05$ (two-sided) and $\beta = 0.1$ (90% power). The required sample size will be 72 patients per group. Assuming that 10% of patients will be lost to follow-up, we chose

a sample size of 80 participants for each group, with a total sample size of 480 participants.

Statistical analyses

Statistical analysis will be conducted by independent third-party professional statisticians. All data will be collected by statisticians. Data analysis will be performed using the intention processing principle in SPSS 22.0. Statistical results will be reported using a two-sided test, with statistical significance being set at P-value < 0.05. The results will be expressed as mean ± standard deviation. The t-test will be used for normally distributed homogenous variables, with the hypothesis test of superiority being used for major outcome indicators, the chi-square test for normally distributed data, and the rank-sum test or Fisher's exact probability method for non-normally distributed data.

Patient and public involvement

The patients and the public were not involved in the planning and design of this study. The present trial was developed by acupuncturists based on previous clinical experience and literature. The expected outcomes are commonly used to assess rapid postoperative recovery in clinical practice. The cost of interventions and outcome measurements will be maintained using the study funding; therefore, it was not considered a significant burden and met the patient preferences. The results will be disseminated to the participants via the WCHSU website.

DISCUSSION

Several studies have demonstrated the efficacy of acupuncture in rapid postoperative rehabilitation[28]. Previous clinical experience and studies have shown that acupuncture on the distal limb acupoints is mostly selected for rehabilitation after abdominal surgery, which may be associated with several factors, including the presence of surgical wounds after abdominal surgery, postoperative changes in the structure and state of abdominal organs affecting acupuncture needle manipulation, and safety. However, recent studies have shown that abdominal and limb acupoints facilitate improvement of abdominal pain and the distension degree; moreover, abdominal acupoints have a more optimal effect on improving the degree of abdominal pain[29]. In this study, based on extensive clinical practice, TEAS will be applied to abdominal acupoints, which is safer than electroacupuncture based on acupuncture on the meridians of the distal extremities; moreover, the bilateral beam gate and large transverse acupoints chosen for abdominal surgery are unconventional incision positions that facilitate manipulation. Additionally, they are both antiemetic, promote gastrointestinal motility, and relieve abdominal pain. Therefore, this randomised controlled study will evaluate whether TEAS combined with EA therapy is effective at allowing rapid recovery after laparotomy for gastrointestinal surgery is more effective and beneficial, and therefore further improving patient satisfaction.

ETHICS AND DISSEMINATION

Personal information and study data of all participants will be recorded in case report forms. Moreover, data involving patient privacy will be anonymized, protected by code, and securely kept in a locked cabinet in the WCHSU accessed only by the research team. Upon completion of the trial and data verification, the case report forms will be transferred to the Science and Technology Department of Sichuan Province for safe archival purposes for 10 years before being destroyed. Data for use or analysis following study completion will be available from the corresponding author upon reasonable request. The study results will be presented at national and international scientific conferences and submitted for publication in a peer-reviewed journal.

This study has been approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University in April 2021. The approval number is 2021 (52). The trial protocol strictly adheres to the principles of the latest Declaration of Helsinki. Patient consent for publication is not required.

Authors' contributions: HL and QW contributed equally to this article, participated in the study design, drafted the manuscript, and recruited patients. L-y L and Y-m Z are responsible for the treatment of patients. H-q H and YH are responsible for collecting the data. NL and X-d W are responsible for monitoring this study. All authors contributed to manuscript revision and have read and approved the submitted version.

Funding: This study will be supported by the Sichuan Science and Technology Program (grant number: 2021YFS0254).

Disclaimer: The funding bodies are not involved in study design, data collection, analysis, interpretation of results, and the manuscript.

Competing interests: The authors declare that they have no competing interests.

Provenance and peer review: Not commissioned; externally peer-reviewed.

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Figure Legends

Figure 1: Flowchart of the study protocol.

Figure 2: Instrument and parameter.

Figure 3a: Location and electrode connection of upper limb acupoints.

Figure 3b: Location and electrode connection of lower limb acupoints.

Figure 3c: Location and electrode connection of abdominal acupoints.

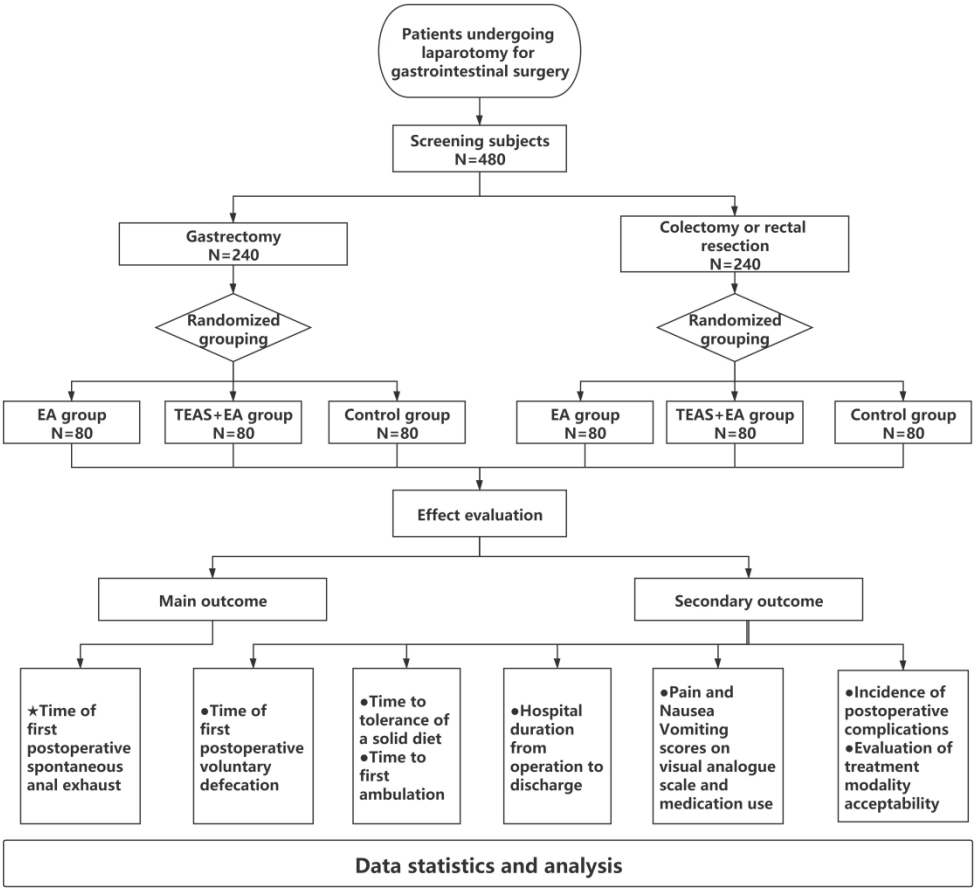

Figure 1: Flowchart of the study protocol.

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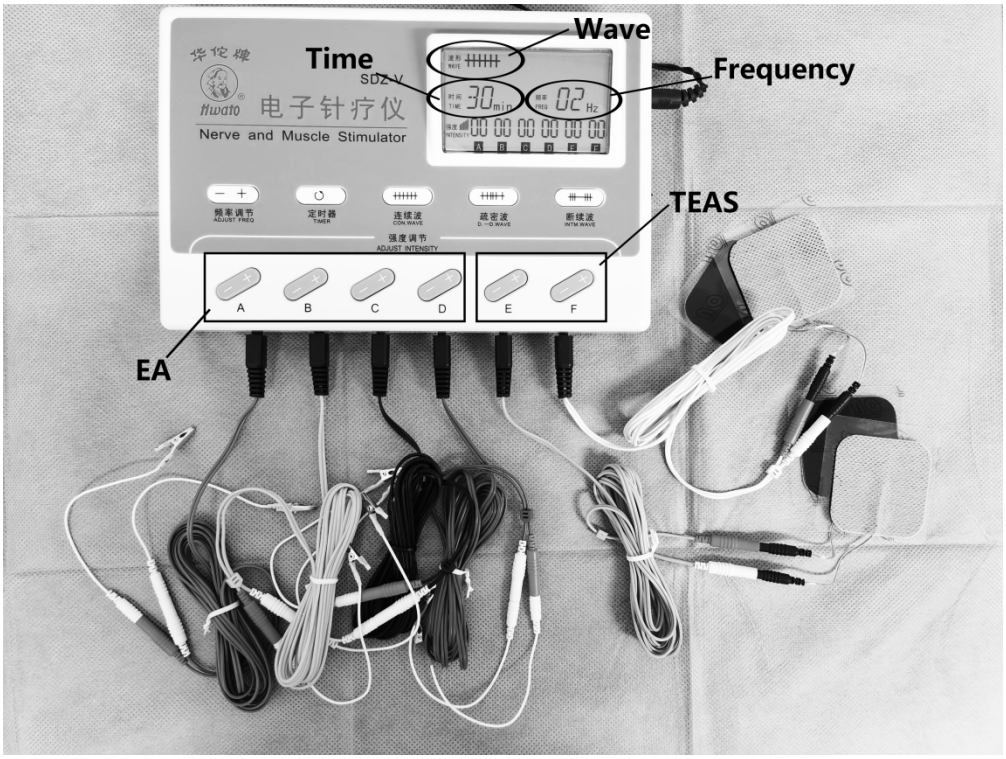

Figure 2: Instrument and parameter.

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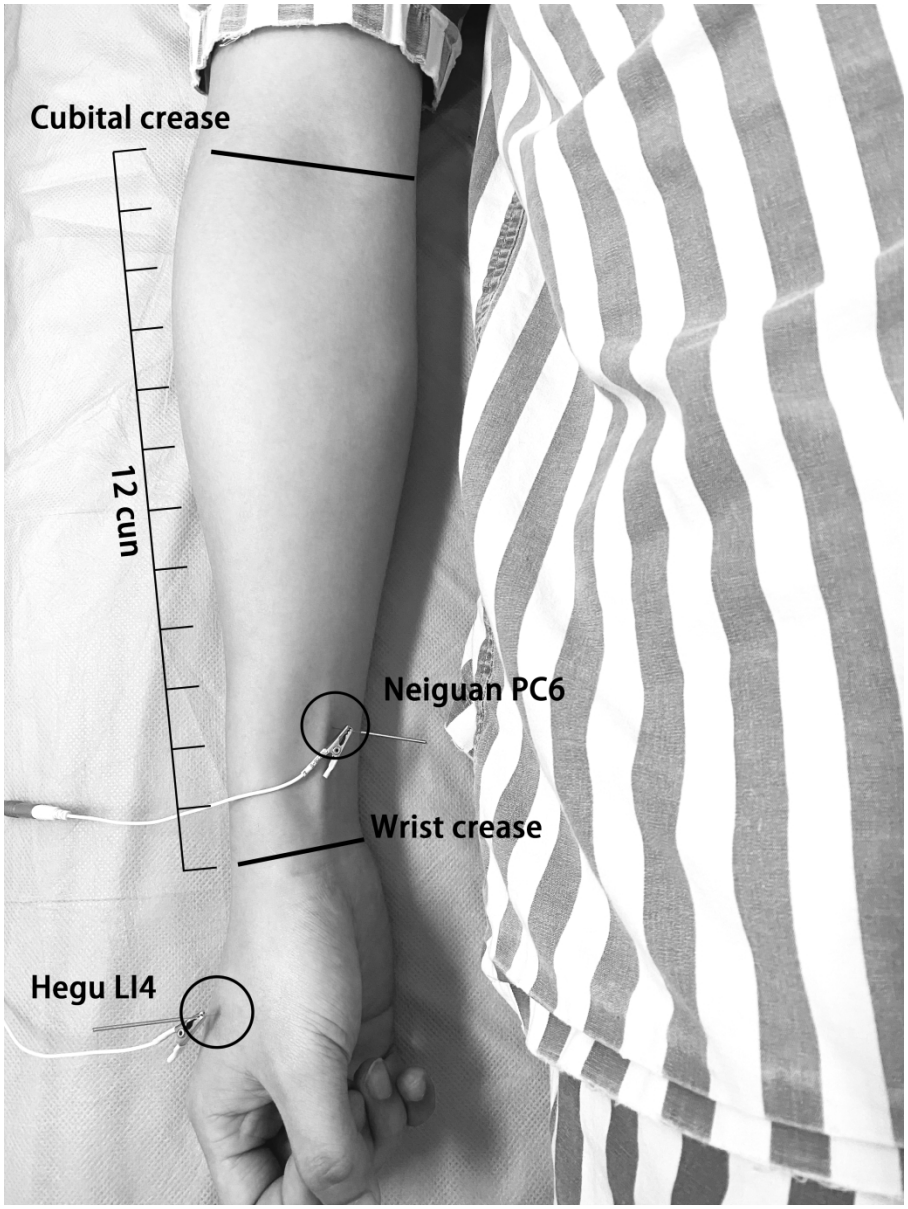

Figure 3a: Location and electrode connection of upper limb acupoints.

1066x1422mm (72 x 72 DPI)

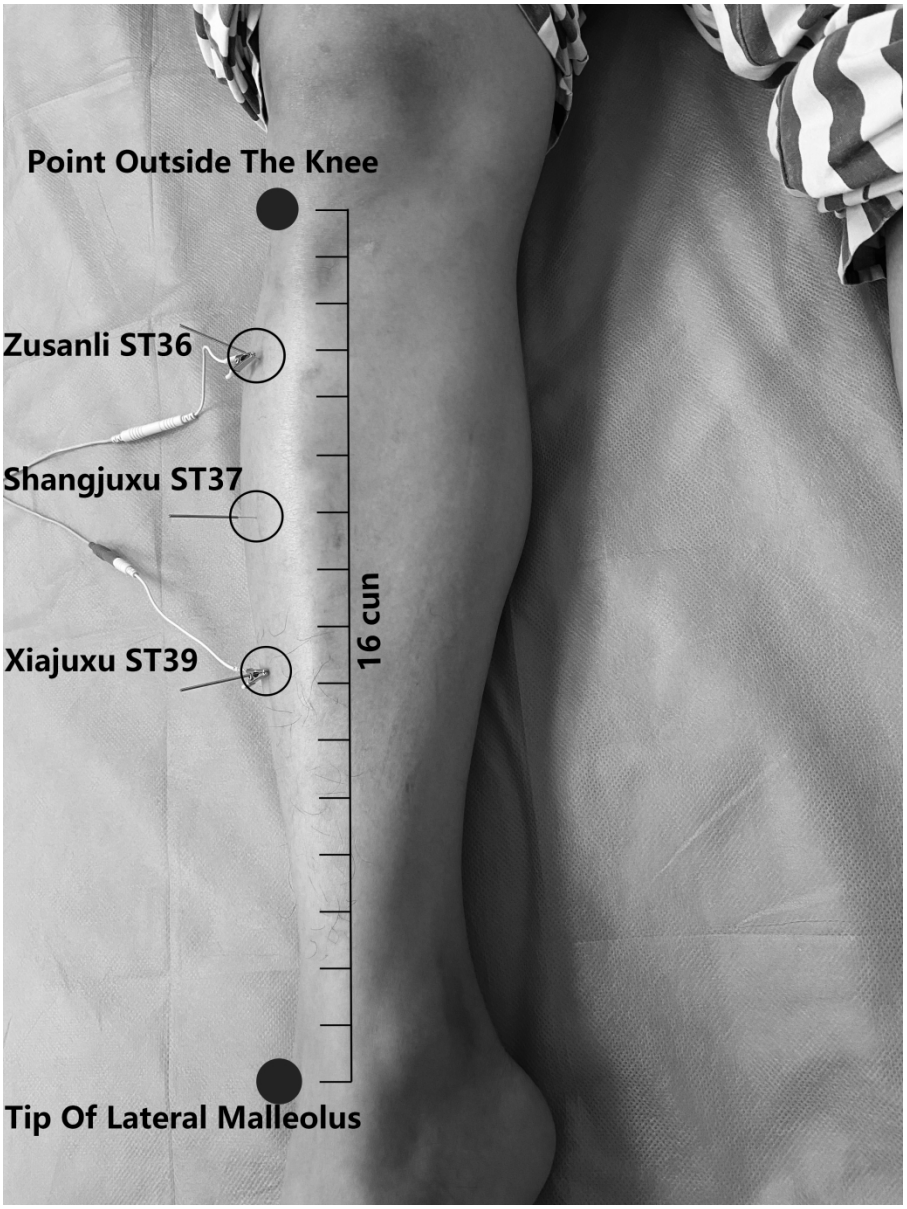

Figure 3b: Location and electrode connection of lower limb acupoints.

1066x1422mm (72 x 72 DPI)

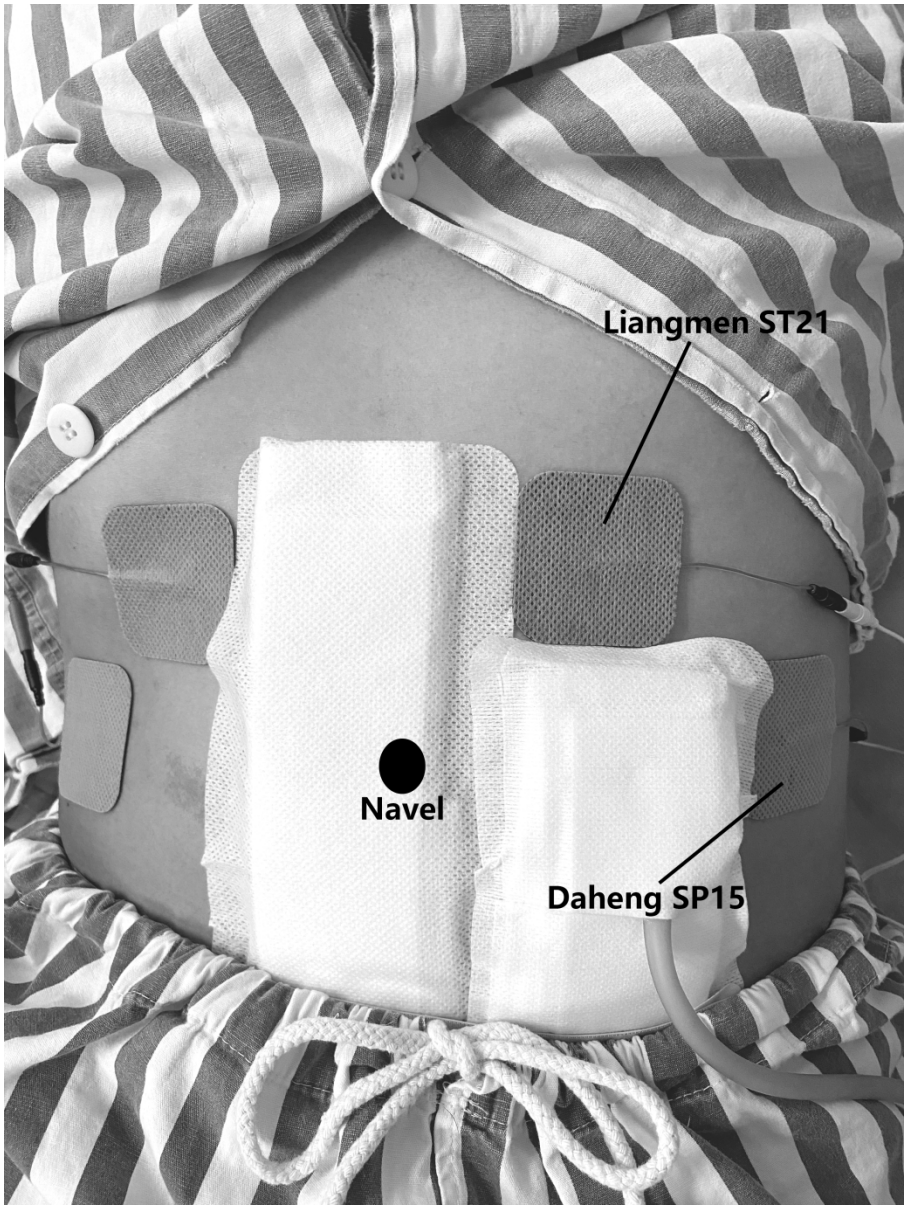

Figure 3c: Location and electrode connection of abdominal acupoints.

1066x1422mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
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	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	15

	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
Introduction			
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	4-7
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	2
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, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
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	7
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	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)	9-11

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11
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)	9-11
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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
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	8-9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
Methods: Data collection, management, and analysis			
Data collection methods	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
	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	15

Statistical methods	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	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	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)	13
Methods: Monitoring			
Data monitoring	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
	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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15

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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
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	13
Dissemination policy	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	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15

Appendices			
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Transcutaneous electrical acupoint stimulation combined with electroacupuncture for rapid recovery of patients after laparotomy for gastrointestinal surgery: A study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053309.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Sep-2021
Complete List of Authors:	Li, Hao; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department Wen, Qian; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department Lu, Lingyun; Sichuan University West China Hospital, Department of Integrated Traditional Chinese and Western Medicine Hu, Hangqi; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department He, Ying; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department Zhou, Yaming; Sichuan University West China Hospital, Gastrointestinal Surgery Wu, Xiaoting; Sichuan University West China Hospital, Gastrointestinal Surgery Li, Ning; Sichuan University West China Hospital, Integrated Traditional and Western Medicine Department
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Gastroenterology and hepatology
Keywords:	COMPLEMENTARY MEDICINE, PAIN MANAGEMENT, GASTROENTEROLOGY

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Transcutaneous electrical acupoint stimulation combined with electroacupuncture for rapid recovery of patients after laparotomy for gastrointestinal surgery: A study protocol for a randomized controlled trial

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# Hao Li and Qian Wen contributed equally to this work.

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ABSTRACT

Introduction: Abdominal surgery is associated with common complications, including decreased or poor appetite, abdominal distension, abdominal pain caused by decreased or absent gastrointestinal motility, anal arrest with flatus and defecation, and nausea and vomiting resulting from the use of anaesthetics and opioid analgesics. These complications seriously affect postoperative recovery, prolong hospital stay, and aggravate patient burden. This study aims to investigate for the first time the efficacy of transcutaneous electrical acupoint stimulation (TEAS) combined with electroacupuncture (EA) therapy for rapid recovery after laparotomy for gastrointestinal surgery. There have been no clinical studies of this combination therapy.

Methods and analysis:This will be a prospective, single-centre, three-arm, randomised controlled trial. A total of 480 patients undergoing abdominal surgery will be stratified according to surgery type (i.e. gastric or colorectal procedure) and randomised into three groups; namely, the EA, TEAS+EA, and control groups. The control group will receive enhanced recovery after surgery (ERAS)-standardised perioperative management, including preoperative education, optimising the anaesthesia scheme, avoiding intraoperative hypothermia, restrictive fluid infusion, and reducing surgical trauma. The EA group will receive electroacupuncture stimulation at LI4, PC6, ST36, ST37, and ST39 based on the ERAS-standardised perioperative management. Moreover, the TEAS+EA group will receive ERAS-standardised perioperative management; electroacupuncture stimulation at the LI4, PC6, ST36, ST37, and ST39;

and TEAS stimulation at ST21 and SP15. The primary outcome will be the GI-2 (composite outcome of time to first defaecation and time to tolerance of a solid diet). Secondary outcomes will include the time of first passage of flatus, time to first defaecation , time to tolerance of a solid diet, time to first ambulation, hospital duration from operation to discharge, pain and nausea vomiting scores on the VAS, medication use, incidence of postoperative complications, and evaluation of treatment modality acceptability. All statistical analyses will be performed based on the intention-to-treat principle.

Ethics and dissemination Ethics approval has been granted by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (approval number: 2021; number 52). The results are expected to be published in peer-reviewed journals.

Trial registration number: ChiCTR2100045646 (Chinese Clinical Trial Registry)

Strengths and limitations of this study

- A randomised controlled trial of 480 patients will be conducted to evaluate the efficacy of TEAS combined with EA therapy for rapid recovery after laparotomy for gastrointestinal surgery.
- The trial feasibility has been examined in a pilot randomised trial of 120 patients，included 60 patients with laparotomy stomach tumor resection and 60 patients with laparotomy colon tumor resection.
- This trial will be conducted using rigorous methods; for example, the patients will be randomly assigned to three groups; the data will undergo blind statistical

analysis; and the interventionists, efficacy evaluators, and statisticians will be separated.

- This trial did not include a sham control arm, the analysis of the placebo response or effect was lacking.

INTRODUCTION

The most common postoperative complications in laparotomy for gastrointestinal surgery include gastrointestinal dysfunction, pain, postoperative nausea and vomiting (PONV), etc. These result from numerous factors, including the intraoperative use of anaesthetic drugs, surgical trauma, peritoneal irritation or inflammatory response, and postoperative use of analgesic drugs[1-3]. Rapid postoperative rehabilitation can prevent or reduce intraperitoneal adhesion; reduce the incidence of complications, including intestinal obstruction and intestinal infection; prevent secondary surgery, reduce opioid usage, and alleviate pain. Moreover, it can promote prompt recovery of the patients' oral diet, reduce the use of parenteral nutrition, shorten the hospitalisation duration, and reduce hospitalisation costs[4-8].

Enhanced recovery after surgery (ERAS) is based on evidence-based medicine and is a standardised, collaborative, and multidisciplinary optimisation management protocol for the perioperative period. It allows a reduction in the physiological and psychological traumatic stress response, as well as postoperative complications; a faster postoperative recovery; a shorter postoperative hospitalisation time; and a reduction in patient costs[9]. This concept was initially proposed by the Danish Medical Scientist Kehlet in 1997[10]. After > 20 years of practice and optimisation, the ERAS concept and pathway have been popularised and rapidly applied

worldwide[11]. Although a series of perioperative ERAS measures can accelerate recovery, there remains room for improvement in the prevention and treatment of postoperative gastrointestinal dysfunction and PONV, as well as in the reduction of opioid use[12].

Acupuncture exerts therapeutic effects by regulating gastrointestinal dynamics, analgesia, and antiemetics. It is widely considered that a degree of postoperative gastrointestinal dysfunction is an inevitable normal physiological response after abdominal surgery[13]. Several studies have demonstrated that acupuncture can significantly relieve postoperative abdominal pain and distension, promote intestinal ventilation, and promptly restore the patient's diet[14 15]. Acupuncture can enhance gastric dilatation through the sympathetic nerve to promote gastric emptying[16 17]; moreover, the vasoactive intestinal peptide is involved in electroacupuncture-mediated gastric motility regulation.

Studies have shown that Zusanli (ST36), Shangjuxu (ST37), and Xiajuxu (ST39) stimulation can effectively improves gastrointestinal transit by reducing local inflammation of the intestinal musculature[18]. Hegu(LI4) is a pair of acupoints belonging to the Large Intestinal meridian, Daheng(SP15) is a pair of acupoints belonging to the Spleen meridian, Liangmen(ST21) is a pair of acupoints belonging to the Stomach meridian. They have the effect of assisting gastrointestinal function recovery, so they are also commonly used in clinical practice[19-21].

Additionally, acupuncture can facilitate postoperative multimodal analgesia. Postoperative analgesia is among the core ERAS components. Its principles include sufficient analgesia and minimisation of opioid usage. Adequate postoperative analgesia can reduce excessive stress, help patients get out of bed quickly, and promote recovery. Opioids, which are the main traditional postoperative analgesic drugs, can easily cause postoperative nausea, vomiting, and other

complications. Reducing opioid usage allows early recovery of patients. There have been numerous studies on the mechanisms underlying acupuncture analgesia from the perspectives of electrophysiology, neurochemistry, molecular biology, and brain imaging[22-24]. Moreover, numerous clinical studies have shown that acupuncture can significantly reduce postoperative pain and opioid use after total hip replacement, craniotomy, abdominal surgery, and kidney stone surgery[25-28]. Therefore, based on the ERAS clinical pathway, acupuncture analgesia may better control wound pain and reduce the use of analgesics, including opioids, and therefore accelerate patient recovery[29].

PONV is a common complication after surgical anaesthesia and analgesia with opioids that can cause dehydration, electrolyte imbalance, wound cracking, and discharge delay. PONV is another important factor that affects the recovery of patients[30]. Studies have shown that Neiguan (PC6) stimulation can effectively prevent PONV[31,32]. Transcutaneous electrical acupoint stimulation (TEAS) is more effective than intravenous ondansetron; additionally, using TEAS combined with drugs can enhance the anti-emetic effects of ondansetron[33].

Numerous studies have supported the application of acupuncture in postoperative rehabilitation; however, there are differences in efficacy across different acupuncture schemes. Currently, EA is the most common acupuncture scheme for rapid postoperative rehabilitation, with TEAS being the second most common scheme. Although TEAS avoids pain resulting from acupuncture needles, its efficacy is slightly worse than that of EA and it has relatively limited clinical application[34]. However, our previous clinical experience and preliminary trials suggested that combining TEAS with EA may have a better curative effect than the conventional electroacupuncture treatment[35-37]. Moreover, this combination could provide an improved acupuncture treatment protocol for rapid rehabilitation after laparotomy for gastrointestinal surgery. It may promote the recovery of gastrointestinal

function more quickly, reduce pain more obviously, shorten the duration of postoperative hospital stay, and reduce patient hospitalization costs, etc.

Therefore, this prospective, single-centre, three-arm, single-blind, randomised controlled trial (RCT) aims to evaluate the efficacy of TEAS combined with EA therapy for rapid recovery after laparotomy for gastrointestinal surgery.

METHODS AND ANALYSIS

Design

This will be a single-centre, prospective RCT with a three-arm parallel grouping design. The trial protocol version number: 2.0, date 31th March,2021.The study will be conducted at the West China Hospital of Sichuan University (WCHSU) from April 2021 to March 2023. All the participants will be required to provide written informed consent in accordance with the most recent version of the Declaration of Helsinki. Figure 1 presents the study flowchart.

Patient population and setting

A total of 480 Chinese patients undergoing laparotomy for gastrointestinal surgery will be sequentially enrolled at the WCHSU after fulfilling the eligibility criteria and signing informed consent. A clinical assistant with institutional review board training will be in charge of patient enrolment.

Eligibility criteria

The inclusion criteria will be as follows: (1) male and female patients aged 18–70 years; (2) laparotomy tumour resection under general anaesthesia (stomach, colon, and rectum); and (3)

volunteering to participate in this study and signing an informed consent form.

The exclusion criteria will be as follows: (1) surgical incision or scar on the meridian of ST21/SP15, (2) local skin infection at acupoints, (3) inability to complete the visual analogue scale (VAS), and (4) allergy to metal or severe needle fear, intolerance of TEAS or EA treatment, (5) uncontrolled diabetes, severe cardiac, central nervous, psychiatric disorders, or coagulopathy; (6) cardiac pacemaker; and (7) participation in other clinical trials.

Withdrawal criteria: Participants meeting any of the following criteria will be withdrawn from the study: (1) occurrence of serious adverse events; (2) participants with serious complications or other serious diseases requiring emergency measures, (3) being required to withdraw during the test, and (4) violation of the test program. Withdrawn patients will not be replaced.

Randomisation and blinding

This study will have a single-blind design. The patient will be blinded to the group allocation; moreover, patients in the same ward will be separated by a bed curtain when receiving acupuncture treatment, with only the research leader and acupuncturist being aware of the treatment allocation. The randomised grouping plan will be designed using SPSS 22.0. According to the plan, 480 patients will be randomly divided into three groups according to a ratio of 1:1:1: EA, TEAS+EA, and control groups. The group scheme will be kept in a confidential envelope; further, the research leader will randomly distribute the included patients to each group following the distribution plan in the envelope. Additionally, the research leader will only inform the acupuncturist responsible for the operation. Efficacy evaluation will be conducted blinded to the grouping allocation. Blind statistical analysis will be used in the data summary stage. Operators, efficacy evaluators, and

statisticians will be separated.

INTERVENTION

All acupoints will be determined based on the National Standard of Nomenclature and Location of Acupuncture Points (GB/T 12346-2006)[38]. All practitioners performing the treatment must have an acupuncturist qualification certificate with independent clinical experience for > 2 years. The acupuncturists will not be replaced during the experiments.

All patients will receive standardised perioperative management by ERAS, including preoperative education, optimisation of anaesthesia scheme, avoidance of intraoperative hypothermia, restrictive fluid infusion, and reduction of surgical trauma. Regarding the electronic acupuncture treatment instrument (Hwato, SDZ-V, Suzhou Medical Supplies Factory Co., Ltd), the current frequency will be continuous wave 2 Hz, the current intensity will be measured in degrees as tolerated by the patient; moreover, the treatment duration will last 30 min (Figure 2). The treatment will be initiated from the first postoperative day, once daily in the morning, until the patient regains defecation and could tolerate transoral solid food.

In the EA group (electroacupuncture is added at the base of basic treatment), treatment will be bilaterally performed at five acupoint pairs: Hegu (LI4), Neiguan (PC6), Zusanli (ST36), Shangjuxu (ST37), and Xiajuxu (ST39). LI4 is an acupoint of the large intestine meridian and is located on the dorsum of the hand between the first and second metacarpal bones. PC6 belongs to the pericardium meridian and is located between the flexor carpi radialis muscle tendon and the palmaris longus tendon, 2 Cun above the wrist crease. ST36, ST37, and ST39 are acupoints of the stomach meridian. ST36 is located on the lateral side of the lower leg, 3 Cun below the lateral border of the knee and

one finger width lateral to the anterior border of the tibia. ST37 is located 3 Cun below ST36. ST39 is located 3 Cun below ST37. After skin disinfection with a disposable disinfecting cotton swab, sterile and disposable stainless steel needles (0.25×40 mm, Suzhou Jiajian, Jiangsu, China) will be quickly and perpendicularly inserted into the skin acupoints at a depth of 25–30 mm. The duration of reinforcing-reducing manipulation of twirling and rotating needles should be used for 1 min to achieve de qi (a composite of sensations including soreness, numbness, distention, heaviness, and other sensations), which significantly contributes to acupuncture efficacy. The ipsilateral Neiguan, Hegu, Zusanli, and Xiajuxu will be separately connected to one electrode set, and therefore yielding four electrode sets (Figure 3 a, b).

For the TEAS+EA group, treatment will be based on the EA group with the addition of two pairs of bilateral abdominal acupoints: Liangmen (ST21) and Daheng (SP15). Additionally, ST21 is an acupoint of the stomach meridian that is located 4 Cun above the umbilicus and 2 Cun open next to the anterior median line. SP15 is an acupoint of the spleen meridian, located 4 Cun beside the umbilicus and lateral to the rectus abdominis muscle. Abdominal acupoints will be stimulated using a self-adhesive electrode pad with electrical conductivity; additionally, the ipsilateral Liangmen will be connected to the Daheng set of electrodes. The ipsilateral Neiguan, Hegu, Zusanli, and Xiajuxu acupoints will be connected to one electrode set to yield a total of six sets of electrodes (Figure 3 a, b, c).

The control group will receive ERAS-standardised perioperative management without acupuncture treatment.

OUTCOME MEASURES

Main outcome

The primary outcome will be the GI-2 (composite outcome of time to first defaecation and time to tolerance of a solid diet). Participants will be visited and evaluated by efficacy evaluators at the end of each treatment.

Secondary outcome

The secondary outcomes include the time of first passage of flatus, time to first defaecation , time to tolerance of a solid diet, time to first ambulation, hospital duration from operation to discharge, pain and nausea vomiting scores on the VAS (from 0 [no at all] to 10 [the worst]), medication use(name, frequency and dosage of analgesic drugs and antiemetic agents), incidence of postoperative complications(include intra-abdominal infection, intestinal ischemia and necrosis, anastomotic leak, pulmonary infection, etc), and evaluation of treatment modality acceptability(classified into five grades: very acceptable, moderately acceptable, somewhat acceptable, moderately unacceptable, and totally unacceptable). Participants will be visited and evaluated by efficacy evaluators at the end of each treatment.

We add GI-2 as a primary outcome outcome to the original protocol after recruitment of the study had already begun. GI-2 is a time indicator, which will be calculated from two existing outcomes (time to first defaecation and time to tolerance of oral diet). There will be no harm to subjects, no additional cost and no more work.

Safety evaluation

All adverse events will be recorded on the adverse event record sheet by the acupuncturist and participants at any time during the study period. Adverse events to be recorded include fainting during acupuncture treatment, needle breaking, unbearable acupuncture pain, local hematoma,

infection, and any other discomfort or accident. The intensity and causality of each adverse event will be evaluated and recorded. If any serious adverse events occur due to an intervention, the intervention will be immediately stopped; further, appropriate corrective action will be taken. Serious adverse events will be promptly reported to the institutional review board within 24 h until 30 days after the end of the trial.

Sample size calculation

The stratification factors will be gastrectomy and colorectal resection, with each layer being divided into three groups: the group ratio will be 1:1:1. The main efficacy indicator will be the GI-2 (composite outcome of time to first postoperativedefaecation and time to tolerance of a solid diet). Given the lack of reports on TEAS+EA for promoting postoperative recovery, we conducted a preliminary experiment. The preliminary experimental results indicated that the GI-2 of laparotomy gastrectomy surgery in the control, EA, and TEAS+EA groups was 113.1±37.5 h, 86.9±36.1 h, and 80.1±33.2 h, respectively, Additionally, in the control group, the GI-2 of laparotomy colorectal surgery in the control, EA, and TEAS+EA groups was 106.2±35.9 h, 85.6±33.1 h, and 78.5±36.3 h, respectively. The sample size was determined using PASS 11 with $\alpha = 0.05$ (two-sided) and $\beta = 0.1$ (90% power). The required sample size will be 60 patients per group. Assuming that 20% of patients will be lost to follow-up, we chose a sample size of 80 participants for each group, with a total sample size of 480 participants.

Statistical analysis

Statistical analysis will be conducted by independent third-party professional statisticians. All data will be collected by efficacy evaluators. Data analysis will be performed using the intention processing principle in SPSS 22.0. Statistical results will be reported using a two-sided test, with

statistical significance being set at P-value < 0.05. Continuous variables will be expressed as: mean (SD), median (interquartile range (IQR)), or minimum and maximum. For comparisons between treatment groups, analyses of variance (ANOVAs) will be used for normally distributed variables, and the Kruskal–Wallis H test will be used for non-normally distributed variables. Categorical variables will be expressed as numbers (%), and will be analyzed via chi-square tests for between-group comparisons.

Patient and public involvement

Patients and/or the public were not involved in study design or conduct of the study.The present trial was developed by acupuncturists based on previous clinical experience and literature. The expected outcomes are commonly used to assess rapid postoperative recovery in clinical practice. The cost of interventions and outcome measurements will be maintained using the study funding; therefore, it was not considered a significant burden and met the patient preferences. The results will be disseminated to the participants via the WCHSU website.

DISCUSSION

Several studies have demonstrated the efficacy of acupuncture in rapid postoperative rehabilitation[39]. Previous clinical experience and studies have shown that acupuncture on the distal limb acupoints is mostly selected for rehabilitation after abdominal surgery, which may be associated with several factors, including the presence of surgical wounds after abdominal surgery, postoperative changes in the structure and state of abdominal organs affecting acupuncture needle manipulation, and safety. However,

recent studies have shown that abdominal and limb acupoints facilitate improvement of abdominal pain and the distension degree; moreover, abdominal acupoints have a more optimal effect on improving the degree of abdominal pain[40]. In this study, based on extensive clinical practice, TEAS will be applied to abdominal acupoints, which is safer than electroacupuncture based on acupuncture on the meridians of the distal extremities; moreover, the SP15 and ST21 chosen for abdominal surgery are unconventional incision positions that facilitate manipulation. Additionally, they are both antiemetic, promote gastrointestinal motility, and relieve abdominal pain. Some previous studies on acupuncture for gastrointestinal symptoms have shown that SA although have some placebo effect, but EA might have greater benefits than SA(Sham-acupuncture)[15 41 42], so we did not include sham control in this study.Therefore, the main purpose of this three-arm randomised controlled study is to evaluate whether TEAS combined with EA therapy is effective at allowing rapid recovery after laparotomy for gastrointestinal surgery is more effective and beneficial, and further improving patient satisfaction.

ETHICS AND DISSEMINATION

Personal information and study data of all participants will be recorded in case report forms. Moreover, data involving patient privacy will be anonymized, protected by code, and securely kept in a locked cabinet in the WCHSU accessed only by the research team. Upon completion of the trial and data verification, the case report forms will be transferred to the Science and Technology Department of Sichuan Province for safe archival purposes for 10 years before being destroyed.

Data for use or analysis following study completion will be available from the corresponding author upon reasonable request. The study results will be presented at national and international scientific conferences and submitted for publication in a peer-reviewed journal.

This study has been approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University in April 2021. The approval number is 2021 (52). The trial protocol strictly adheres to the principles of the latest Declaration of Helsinki. Patient consent for publication is not required.

Authors' contributions: HL and QW contributed equally to this article, participated in the study design, drafted the manuscript, and recruited patients. L-y L and Y-m Z are responsible for the treatment of patients. H-q H and YH are responsible for collecting the data. NL and X-t W are responsible for monitoring this study. All authors contributed to manuscript revision and have read and approved the submitted version.

Funding: This study will be supported by the Sichuan Science and Technology Program (grant number: 2021YFS0254).

Disclaimer: The funding bodies are not involved in study design, data collection, analysis, interpretation of results, and the manuscript.

Competing interests: The authors declare that they have no competing interests.

Provenance and peer review: Not commissioned; externally peer-reviewed.

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Figure Legends

Figure 1: Flowchart of the study protocol.

Figure 2: Instrument and parameter.

Figure 3：Localization of acupoints and electrode connection.

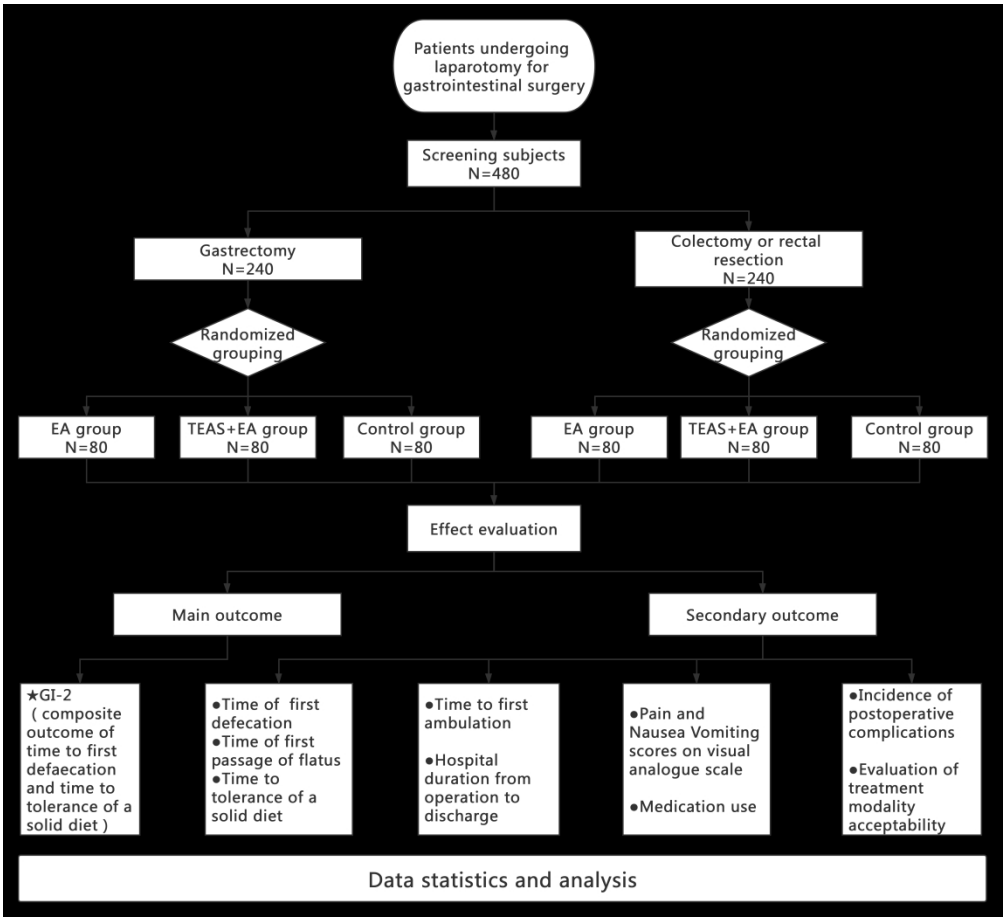

Figure 1: Flowchart of the study protocol.

1711x1560mm (72 x 72 DPI)

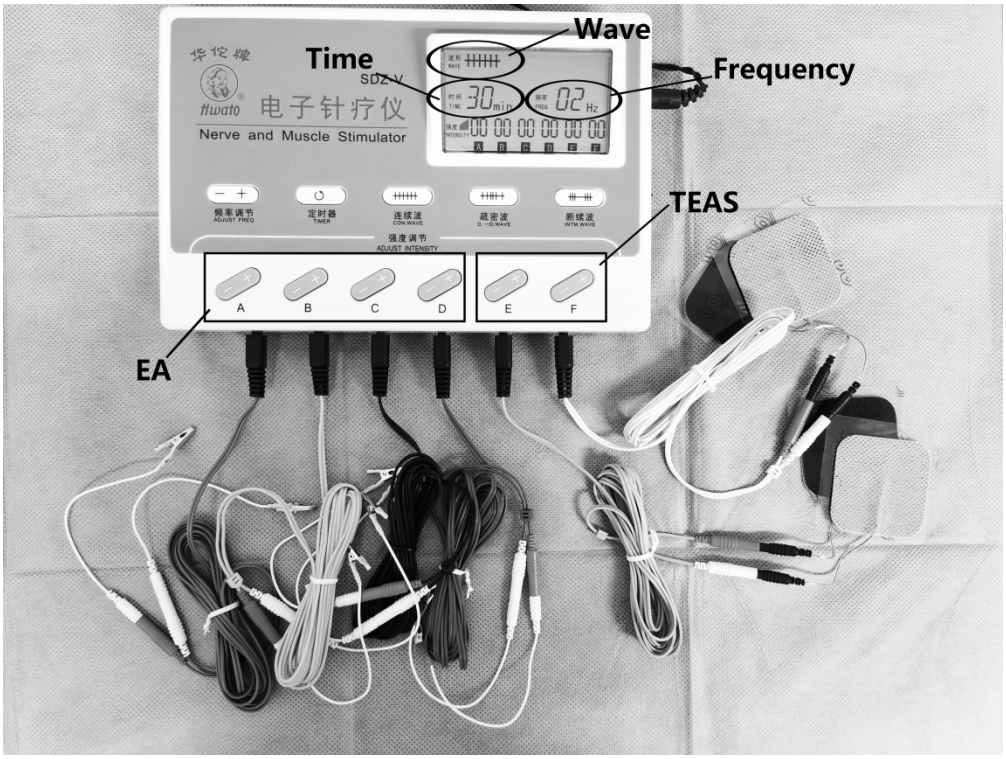

Figure 2: Instrument and parameter.

1286x965mm (72 x 72 DPI)

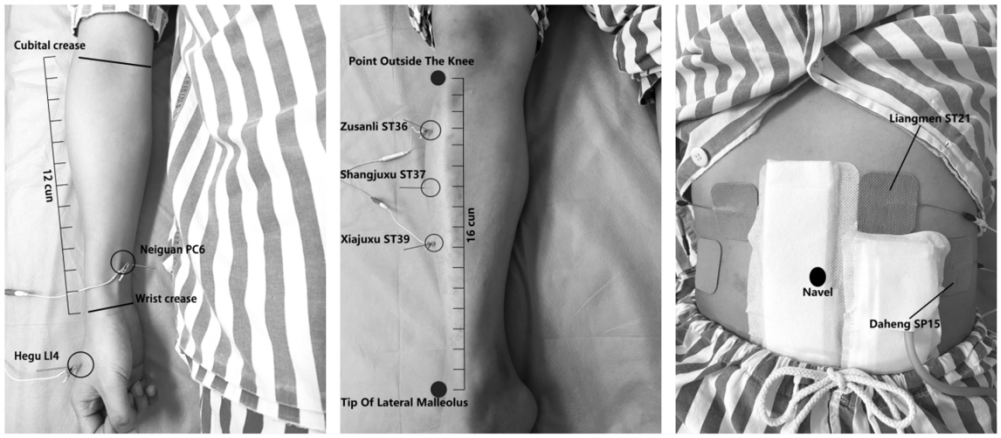

Figure 3: Localization of acupoints and electrode connection.

1492x704mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
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	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	15

	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
Introduction			
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	4-7
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	2
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, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
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	7
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	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)	9-11

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11
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)	9-11
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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
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	8-9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
Methods: Data collection, management, and analysis			
Data collection methods	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
	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	15

Statistical methods	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	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	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)	13
Methods: Monitoring			
Data monitoring	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
	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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15

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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
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	13
Dissemination policy	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	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15

Appendices			
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.