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Keywords:	Transcutaneous electrical acupoint stimulation (TEAS), postoperative ileus (POI), Pretreatment

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Transcutaneous electrical acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing laparoscopic colon surgery: Study protocol for a randomized controlled trial

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Abstract

Introduction: Postoperative ileus (POI) is a common complication after surgery, which severely affects postoperative recovery. It is not clear whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can improve recovery of POI. This trial will evaluate the effects of TEAS pretreatment for POI.

Methods and analysis: This will be a prospective, randomized, controlled trial. ASA I-II level patients aged 18-65 years and scheduled for laparoscopic colon surgery will be included. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS (STEAS) groups underwent 2 sessions of TEAS/STEAS treatment daily for 3 days before surgery and a last TEAS/STEAS treatment for 30 minutes before anesthesia. The primary endpoint is the first defecation time. The secondary endpoints include postoperative anal exhaust time, time for dieting, time beginning to walk alone, length of hospital stay, postoperative pain VAS score of the first 3 days after operation, analgesic requirements, complications, inflammatory mediators in blood including IFN-β, IFN -γ, IL-6, IL-1.

Ethics and dissemination: This study has been approved by the Chinese registered clinical trial ethics review committee (NO.ChiECRCT-20170084). The result of the trial will be published in an internationally peer-reviewed journal.

Trial registration: This study has been registered with the Chinese clinical trial register (NO. ChiCTR-INR-17013184).

Trial status: The study was in the recruitment phase at the time of manuscript submission.

Abbreviations: POI = Postoperative ileus, TCM = traditional Chinese medicine, EA = electro-acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index, PACU = post anaesthesia care unit, ERAS= Enhanced Recovery After Surgery.

Key words: Transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI); Pretreatment.

Strengths and limitations of the study

- This study aims to evaluate the influence of pretreatment with transcutaneous electrical acupoint stimulation (TEAS) in preventing of postoperative ileus (POI) after surgery.
- The intervention is simple, non-invasive and easy acceptance therapy.
- This study will be possible to verify the mechanism of inflammatory response reduction by TEAS pretreatment in preventing postoperative ileus.
- It is a single-center study, the generalization and application may be limited. To reduce this potential bias, large sample, multicenter, multiracial studies are still needed.

Introduction

Postoperative ileus (POI) is a transient gastrointestinal propulsion disfunction following surgery. It often occurs after abdominal surgery and may also occur following surgery at other sites [1]. The main symptom is abdominal pain, abdominal distention, nausea, vomiting, stop exhaust defecation, intolerance to solid food, etc. Postoperative ileus is usually temporary, but if it prolonged, may lead to surgical incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection, intestinal ischemia, aspiration pneumonia and other serious complications [2-4]. A retrospective cohort study involving nearly 500 U.S. hospitals has shown that postoperative ileus is a key reason for prolonged hospitalization and increased medical costs for patients with abdominal surgery [1]. The United States spends more than $1.46 billion on POI treatments every year [5]. At present, methods used in treatment of postoperative ileus mainly include: perioperative rational use of narcotic drugs and opioids, eating as soon as possible, avoidance to use nasogastric tube after operation, early ambulation, postoperative epidural analgesia, restrict fluid intake, the minimally invasive surgery (such as laparoscopic), drug therapy, chewing gum, etc. However, despite the numerous treatment strategies, the current clinical treatment effect is still not ideal. POI is still a difficult clinical problem that affects the rapid recovery of postoperative patients. It is necessary to find more effective, convenient and economical treatment methods [6-10].

The main mechanism that causes POI may be the activation of macrophages in the external muscular layer during surgical operation [11]. Intestinal manipulation during operation can activate the macrophages cells outside layer muscle of small intestine, the cells can release inflammatory factors (IL-6, IL-1β) and chemokine (MIP-1α), and increase the expression of adhesion molecules (ICAM-1) on the endothelial cells, induction of neutrophils and monocytes in the circulation into the small intestine muscle layer. These cells and activating macrophages can release a large amount of the inducible nitric oxide synthase（iNOS）and prostaglandin, inhibits the movement and contraction of the gastrointestinal tract in the end[12, 13]. Further, the inflammatory mediators were migrated with the blood flow, and further activation of macrophages in the distal gastrointestinal tract caused the whole gastrointestinal paralysis [14].

It was confirmed by a large number of animal experiments that the reduction of inflammatory response was effective for POI treatment [15-17].

Clinical doctors of traditional Chinese medicine (TCM) have long history using acupuncture to treat functional gastrointestinal disease. In recent years, doctors around the world have also been increasingly concerned about the significant effect of acupuncture on POI. Therefore, the effect of EA on postoperative ileus is clear and promising. Ng, S.S*., et al.* applied electro-acupuncture (EA) in the treatment postoperative intestinal paralysis of patients under laparoscopic colon surgery [18]. The results showed that compared with patients without electro-acupuncture treatment, the defecation time, length of hospital stay were significantly shortened in the EA group. You, X.M., et al. found that significant reduction of the incidence of POI in patients with hepatic resection by acupuncture combined with Chinese herbal medicine, and the time of hospitalization was also significantly shortened (14.0±4.9d vs 16.5±6.8d, P=0.014) [19].

Our previous studies proved that the pretreatment of acupuncture could regulate the excessive activation of the innate immune system, and inhibit inflammatory response. This effect may be achieved by activating the vagus nerve system [20, 21]. Studies have shown that transcutaneous electrical acupoint stimulation and EA therapy have similar effects in pain treatment and alleviating inflammatory response [22, 23].

Traditional Chinese medicine holds that the best treatment for disease is precaution. Based on all of the above studies, we hypothesize that using transcutaneous electrical acupoint stimulation (TEAS) as pretreatment, before the operation, may reduce the incidence of postoperative ileus. Until now, there is no research report on this.

We design this randomized, controlled trial, which intends to find whether the pretreatment of transcutaneous electrical acupoint stimulation can reduce the incidence of postoperative ileus in laparoscopic colon resection patients. Further to verify that this anti-inflammatory effect is associated with the immunomodulation function of TEAS.

Methods and analysis

Study objective

The primary objective is to investigate whether the pretreatment of percutaneous acupuncture can improve gastrointestinal motor function after laparoscopic colon surgery. The secondary objective is to verify the suppression of overactivation of innate immune system and reduction of inflammatory response as the mechanism of pretreatment of percutaneous acupuncture to prevent POI.

Study location

A prospecive, single-centre, single-blinded, randomized, controlled trial will be conducted at Shuguang hospital affiliated to Shanghai university of traditional Chinese medicine, China.

Study population

Participants will be recruited according to the following inclusion and exclusion criteria.

Inclusion criteria

1. Aged 18 ~ 75 years old male and female patients.
2. Patients undergoing laparoscopic descending colon and rectal cancer surgery.
3. Weight index BMI 18 to 31 kg/m^2.
4. The ASA is I-II level.
5. Patients signed informed consent.

Exclusion criteria

1. The middle and lower segment rectal cancer, the whole colon, complete rectal resection, or need of a complex endoscopic surgery.
2. It is necessary for abdominal wall fistula, gastrointestinal fistula or fistula surgery.
3. Operation history of abdominal, pelvic or complication.
4. Patients to receive epidural or epidural analgesic.
5. Patients with skin infections, surgical incision or scar on the point.
6. Patients with limbs, spinal surgery or nerve injury.
7. Patients participated in other clinical trials or received other acupuncture therapy in the near four weeks.

8. Patients with cardiac pacemakers.
9. Patients with preoperative combined pain, patients with central analgesic drugs, opioid addiction, dependents, or patients with a history of alcoholism.
10. Patients with preoperative combination of severe central nervous system disease and severe mental illness.

Endpoints

Primary endpoint

The first defecation time (h): the time to observe the first anal defecation after laparoscopic surgery.

Secondary endpoints

Postoperative anal exhaust time (h), time that the patients tolerated a solid diet (h), time to walk independently (h), length of hospital stay (d), postoperative pain VAS score day1,day2,day3 (0 to 10, 0 points represent entirely painless, 10 points represent the worst pain intensity), postoperative analgesic requirements, postoperative complications, detected inflammatory mediators IFN-β, IFN-γ, IL-6, IL-1 in blood before TEAS/STEAS intervention and 1d, 3d, 5d after operation respectively.

Randomization and blinding

Patients were randomized to receive either TEAS or STEAS treatment by stratified randomization according to sex, in a 1:1 ratio (Figure1). According to the computer-generated random sequence, a sealed nonopaque envelope would be opened to determine the group of entry. The acupuncturist was aware of treatment allocation. A nurse anaesthetist as outcome investigator was blinded to the treatment allocation.

Current sample size justification

According to our previous pilot study, mean time to first defecation in the laparoscopic colon surgery was 62±19h. With assumption that the clinically meaningful difference in mean time to first defecation between TEAS and STEAS groups is 1 day or 24 hours, 66 patients in each group were needed to reach a power of 80% and 5% Type I error rate. Suppose the drop-out rate is 10%, a sample size of 146 patients for 2 groups was needed in this study.

Statistical analysis

All data will be analysed using SPSS17.0 or other statistical software packages as needed. The statistical methods will include descriptive statistics, the t-test, χ^2 test, analysis of variance, univariate logistic regression analysis and multivariate linear regression analysis. The significance level will be set at 5%.

Pretreatment

The patients randomized to TEAS and STEAS groups underwent 2 sessions of TEAS/STEAS treatment daily for three consecutive days before surgery. And the patients were administered a last TEAS/STEAS treatment for 30 minutes before anesthesia.

The perioperative management of all patients was standardized. Early ambulation was encouraged. Oral feeding was resumed as early as possible. All patients will be followed up until discharge from the hospital.

In TEAS group, the acupoints including Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4), and Neiguan (P-6), were identified before electrical stimulation with surface electrodes (Figure 2). Selection of these acupoints was based on a consensus between the acupuncturists of the study. No electrical stimulation sensation was performed in STEAS group. Electric stimulation was used in TEAS group with the Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China). Frequency of the electric stimulation was set at 100 Hz. In STEAS group, pseudo-stimulation was provided by deliberately connecting the electrodes to the incorrect output socket of EA device, and thus there was no flow of electric current. Patients could see the output light flashing but no current was transmitted throughout

the procedure. Patients were told that the stimulation frequency selected was not perceivable by human beings. Each session of EA treatment last for 30 minutes.

All operations were under general anesthesia, according to standardized anesthesia procedures. Patients would be fasting for 12 hours before operation. Right upper extremity venous access would be established before the patients entering the operation room. 8ml/kg of lactate ringer's was intravenous infusion for compensatory expansion before induction. Patients would then intravenously receive midazolam (0.04 mg/kg), fentanyl (3 mu g/kg), vecuronium bromide (0.1 mg/kg), propofol (1.5-2.0mg/kg) for anesthesia induction. Maintaining anesthesia used CP-600 anaesthesia delivery system (Slgo medical technology co., LTD, Beijing, china). Adjustment of propofol was performed in order to maintain the bispectral index (BIS) reaching 40 ~ 60. After operation, all patients would be remained in the post anaesthesia care unit (PACU) and would return to the ward for recovery procedure until discharge.

Adverse events

All adverse reactions would be recorded and closely monitored through spontaneous reports by patients or direct observation by clinicians or by non-inducing methods to ask patients about their adverse events. Taking appropriate treatment if necessary. Serious adverse events should be reported to the ethics committee.

Data collection and management

Demographic variables and clinical data will be collected from all patients. Furthermore, during the procedure, blood pressure, heart rate and oxygen saturation will be monitored. Any adverse events will be recorded. Data will be collected throughout the study and will be securely managed under conditions of confidentiality. Data collection will be performed by a nurse anaesthetist. The participants will be referred to by their participant number rather than their name throughout the study unless otherwise specified. All relevant documents and files will be archived for 5 years. Data can be only accessed by the investigators who sign the confidential disclosure agreement and by institutional or governmental auditors during the study. Data without patient identifiers will be publicly accessible after the study. The process will be monitored by the Institutional Ethics Committee for Clinical Research of Shuguang Hospital.

Patient and public involvement

Patient and Public Involvement (PPI) has been considered over the course of the trial design. we organized a Clinical Experience Advisory Panel (CEAP). Our CEAP is made up of staff with expertise in management of complications after abdominal surgery and nursing. CEAP staff will meet twice a year and track the progress of the study and offer advice to the research team. The relationship of CEAP and our research team is coordinated by our hospital clinical trial management committee. Patients will be invited to request study results if interested.

Discussion

Prevention of postoperative bowel paralysis is of great importance to reduce perioperative complications and reduce hospitalization costs. It has been proved that acupuncture and EA can effectively treat postoperative bowel paralysis and shorten the time of POI. However, there are few studies on whether the pretreatment of TEAS can prevent POI. Previous studies have shown that TEAS are similar to handle acupuncture and EA in pain treatment, reducing inflammation and so on.

It is necessary to verify the efficacy and effectiveness of POI prevention by using TEAS through clinical trial. This study will evaluate on the occurrence of POI for patients after using pretreatment with TEAS. There are still some limitations to this study. This study is a single-centre trial, and therapeutic effect of TEAS may be ethnic and regional, so it is necessary to conduct multi-center and large sample study in future. In addition, it is difficult to apply the blind method to the treatment of TEAS, which is hard to distinguish the psychological factors and placebo effect of the patients, and more methodological improvements are needed.

TEAS is treatment that combines percutaneous neurostimulation therapy and acupuncture point together. In comparison with EA or acupuncture, it has the advantages of non-invasive, simple operation and easy acceptance. The successful implementation of our clinical trial will help provide an effective technical means for improving gastrointestinal function recovery in patients undergoing laparoscopic surgery. It can provide optimized option for postoperative rehabilitation treatment such as Enhanced Recovery After Surgery (ERAS). In particular, it can also decrease the economic burden of intensive care units as well as recovery institutions.

Acknowledgements

We thank Dr. Stanley Tao from Shanghai Ruihui Biotech for his valuable assistance in the statistical design of this study.

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Availability of data and materials

The dataset to be generated during the present designed study will be available from the corresponding author on reasonable request via email.

Authors' contributions

Jian Wang conceived of the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated in its design and coordination. Wen-ting Chen, Yue Yong and Jun Guo collected references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistics analysis. Rui Feng will follow up patients and record data. Jian Wang, Li-hua Fan and Jian-gang Song drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure Legend

Figure 1. Flow chart of the study

Figure 2. Acupoints selected in this trial. (a) shows he gu (IL-4), neiguan(P-6). (b) shows zu sanli(ST-36), Shang juxu(ST-37). (c) Han's acupoint nerve stimulator.

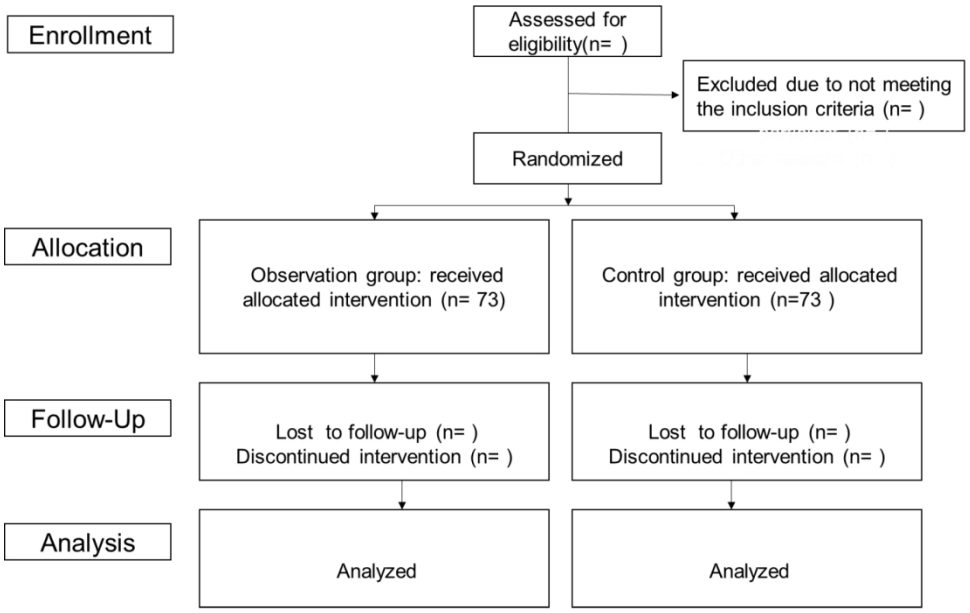

Figure 1. Flow chart of the study

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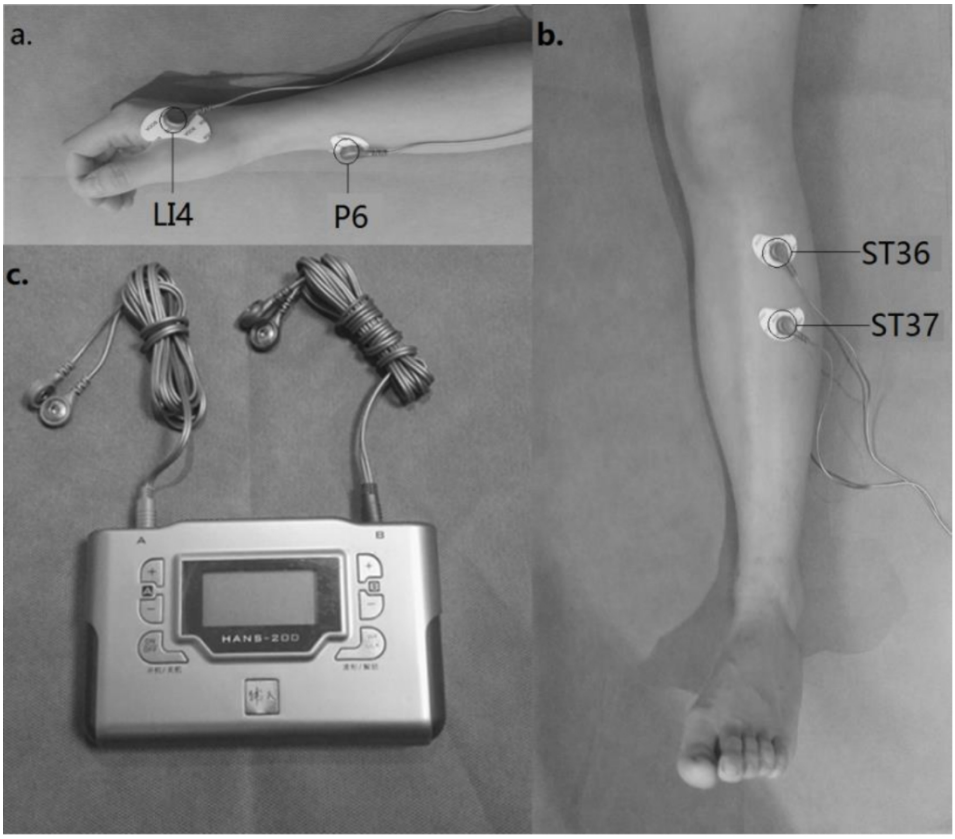

Figure 2. Acupoints selected in this trial. (a) shows he gu (IL-4), neiguan(P-6). (b) shows zu sanli(ST-36), Shang juxu(ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&11
	5b	Name and contact information for the trial sponsor	11
	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	11
	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)	9

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&5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5
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)	5
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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8&9
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	7
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)	7

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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	9
	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	9

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	9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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)	8
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	9
	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	9
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
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)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	9
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	9
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	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.

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Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

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Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

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Abstract

Introduction: Postoperative ileus (POI), a common complication after surgery, severely affects postoperative recovery. It is unclear whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can improve recovery from POI. This trial will evaluate the effects of pretreatment with TEAS on POI.

Methods and analysis: This will be a prospective, randomized, controlled trial. ASA I–III level patients, aged 18–75 years and scheduled for laparoscopic colon surgery, will be included in the study. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS (STEAS) groups. The groups will undergo two sessions of TEAS/STEAS daily for three days before surgery, with a final TEAS/STEAS treatment 30 minutes before anesthesia. The primary endpoint of the study will be time to first defecation. Secondary endpoints will include time to first flatus, time to tolerance of oral diet, GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to independent walking , length of hospital stay, postoperative pain VAS score on the first three days after surgery, analgesic requirements, complications, and plasma concentrations of IFN-β, IFN-γ, IL-6 and IL-1β. Multiple linear regression will be used to identify independent predictors of outcome measures.

Ethics and dissemination: This study has been approved by the Chinese Registered Clinical Trial Ethics Review Committee (NO.ChiECRCT-20170084). The results of the trial will be published in an international peer-reviewed journal.

Trial registration: This study has been registered with the Chinese Clinical Trial Registry (NO. ChiCTR-INR-17013184).

Trial status: The study was in the recruitment phase at the time of manuscript submission.

Abbreviations: POI = postoperative ileus, TCM = traditional Chinese medicine, EA = electro-acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index, PACU = post anesthesia care unit, ERAS= enhanced recovery after surgery.

Key words: transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI); pretreatment.

Strengths and limitations of the study

- This study aims to evaluate whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can prevent postoperative ileus (POI).
- TEAS is a safe, noninvasive and easily accepted adjunctive intervention.
- This study will provide deeper insights into the mechanism by which TEAS pretreatment reduces the inflammatory response.
- This is a single-center study, which is a potential limitation.

Introduction

Postoperative ileus (POI) is a transient dysfunction of gastrointestinal propulsion that often occurs after abdominal surgery and may also occur following surgery at other sites[1]. The main symptoms of POI include abdominal pain and distention, nausea, vomiting, difficult defecation and intolerance to solid food. POI is usually temporary, but if prolonged, may lead to surgical incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection, intestinal ischemia, aspiration pneumonia and other serious complications[2-4]. A retrospective cohort study involving nearly 500 hospitals in the United States showed that POI is a key reason for prolonged hospitalization and increased medical costs for patients undergoing abdominal surgery[1]. The United States spends more than $1.46 billion treating POI every year[5]. At present, the most common methods used to treat POI include: rational perioperative use of narcotic drugs and opioids, eating as soon as possible after surgery, avoidance of nasogastric tubes after the operation, early ambulation, postoperative epidural analgesia, restriction of fluid intake, the use of minimally invasive surgery (such as laparoscopic), drug therapy and the use of chewing gum. Despite the numerous treatment strategies, POI remains a difficult clinical challenge that compromises the rapid recovery of postoperative patients. It is, therefore, necessary to find more effective, convenient and economical treatment methods[6-10].

The main mechanism underlying POI may be activation of macrophages in the external muscular layer during the surgical procedure[11]. Intestinal manipulation during surgery can activate macrophages in the outer muscle layer of the small intestine, leading to release of inflammatory factors (IL-6, IL-1β) and the chemokine MIP-1α, together with increased expression of the adhesion molecule ICAM-1 on endothelial cells and induction of neutrophils and monocytes in the circulation into the small intestine muscle layer. These cells, and activated macrophages, can release a large amount of inducible nitric oxide synthase (iNOS) and prostaglandin, which inhibit the movement and contraction of the gastrointestinal tract[12,13]. Transport of these inflammatory mediators in the blood stream causes activation of macrophages in the distal gastrointestinal tract, leading to total gastrointestinal paralysis[14]. It

has been confirmed by a large number of animal experiments that reducing the inflammatory response is an effective way to treat POI[15-17].

There is a long history in traditional Chinese medicine (TCM) of using acupuncture to treat functional gastrointestinal diseases and, in recent years, there has been significant global interest in the beneficial effects of acupuncture on POI. The positive effect of electroacupuncture (EA) on POI has been clearly demonstrated. Ng *et al.* used EA to treat postoperative intestinal paralysis in patients undergoing laparoscopic colon surgery[18]. Defecation time and length of hospital stay were significantly shortened in patients who received EA compared with those who did not receive the treatment. In patients undergoing hepatic resection, You *et al*. found a significant reduction in the incidence of POI in patients treated with a combination of acupuncture and Chinese herbal medicine. The length of hospitalization was also significantly shortened in the treated group (14.0 ± 4.9 d vs 16.5 ± 6.8 d, $P = 0.014$)[19].

In previous studies, we proved that pretreatment with acupuncture could reduce excessive activation of the innate immune system and inhibit the inflammatory response. This effect may be achieved by activation of the vagal nervous system[20,21]. Other studies have shown that transcutaneous electrical acupoint stimulation (TEAS) and EA have similar effects in the treatment of pain and alleviating the inflammatory response[22,23].

Traditional Chinese medicine holds that the best treatment for disease is prevention . Based on all of the above studies, we hypothesize that the use of TEAS as a preoperative treatment may reduce the incidence of POI. There have, so far, not been any studies that address this question. We have, therefore, designed a randomized, controlled trial to investigate whether pretreatment with TEAS can reduce the incidence of POI in patients undergoing laparoscopic colon resection. The study is also designed to verify that the anti-inflammatory effect is associated with the immunomodulatory function of TEAS.

Methods and analysis

Study objective

The primary objective is to assess the effect of TEAS on clinical recovery of bowel function after laparoscopic colon surgery. The secondary objective is to verify that suppression of overactivation of the innate immune system and reduction of the inflammatory response are the mechanisms underlying the ability of pretreatment of percutaneous acupuncture to prevent POI.

Study location

A prospective, single-center, single-blinded, randomized, controlled trial will be conducted at Shuguang Hospital, which is affiliated to the Shanghai University of Traditional Chinese Medicine, China.

Study population

Participants will be recruited according to the inclusion and exclusion criteria.

Inclusion criteria

1. Male and female patients aged 18–75 years
2. Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such as left colectomy, right colectomy, and anterior resection of the upper part of the rectum and lower part of the sigmoid)
3. Body mass index (BMI) 18–31 kg/m^2
4. ASA classification I–III
5. Patients provide signed informed consent

Exclusion criteria

1. Middle and lower rectal resection, total/proctocolectomy or the need for complex endoscopic surgery
2. Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation
3. History of abdominal/pelvic operations or complications
4. Patients receiving epidural anesthesia or epidural analgesia
5. Patients with skin infections, surgical incision or scar at the point of application of acupuncture
6. Patients with limbs, spinal surgery or nerve injury

7. Patients who participated in other clinical trials, or received other acupuncture therapy, in the previous four weeks
8. Patients with cardiac pacemakers
9. Patients with preoperative combined pain, patients using centrally active analgesic drugs, opioid addiction or dependency, patients with a history of alcoholism
10. Patients with preoperative combination of severe central nervous system disease and severe mental illness

Endpoints

Primary endpoint

First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.

Secondary endpoints

Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to walk independently (h), length of hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital discharge include stability of vital signs with no fever, achievement of flatus or defecation, ability to tolerate solid food without vomiting, control of postoperative pain, absence of other postoperative complications and ability to function at home independently or with home care provided. Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1, 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the worst pain intensity). Postoperative requirements for analgesia will also be assessed. Inflammatory mediators (IFN-β, IFN-γ, IL-6 and IL-1β) in blood will be measured before TEAS/STEAS intervention and on days 1, 3 and 5 after the operation. Postoperative complications will be recorded using the Clavien - Dindo classification for complication assessment[24]. The follow-up period will be at least 6 months.

Randomization and blinding

Patients will be randomized to receive either TEAS or STEAS by stratified randomization according to sex, in a 1:1 ratio (Figure 1). Using a computer-generated random sequence, a sealed envelope will be opened to determine to which group the patient has been assigned. The

acupuncturist will be aware of the treatment group, but the nurse anesthetist, as outcome investigator, will be blinded to the treatment allocation.

Current sample size justification

According to Wang Jian and Song Jiangang's preliminary study of transcutaneous electrical acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing laparoscopic colon surgery in Shuguang Hospital, the mean time to first defecation following laparoscopic colon surgery was 62 ± 19 h (M ± SD). Working on the assumption that a clinically meaningful difference in mean time to first defecation between the TEAS and STEAS groups is 1 day or 24 h, 66 patients would be needed in each group to reach a power of 80% and a 5% Type I error rate. If the drop-out rate is 10%, a total sample size of 146 patients for the two groups is needed for this study.

Statistical analysis

Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance of oral diet, time to walking independently, length of hospital stay) will be reported using the mean and standard deviation (M± SD) for normally distributed data or median (range) for skewed data. Data for categorical variables will be expressed as a number (percentage). Intergroup differences will be assessed using the Student's t-test or Mann-Whitney U test. Outcomes such as time to first flatus, time to tolerance of oral diet, GI-2 and time to walking independently will be included in multiple linear regression to identify independent predictors that affect length of hospital stay. The significance level will be set at 5%. All data will be analyzed using SPSS 17.0 software or other appropriate statistical software packages.

Pretreatment

Patients randomized to the TEAS and STEAS groups will undergo two treatment sessions daily for three consecutive days before surgery. The patients will then be treated for a final time 30 minutes before anesthesia.

For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists

carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China), at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness, distention and heaviness. The STEAS group will receive a strong, but comfortable current for 30 s, and the current will then gradually vanish over the next 15 s. The participants will be told that they are receiving TEAS, but that sensation thresholds differ and that there may be no precise perception of current stimulation. Each session of acupoints treatment will last for 30 min. During the application of TEAS, patients will be required not to change the current settings themselves. A prompt beep at the end of TEAS will indicate the end of treatment.

All surgery will be carried out under general anesthesia, using standardized anesthetic procedures. Patients will be fasted for 12 h before surgery. Right upper extremity venous access will be established before the patients entering the operating theater. Ringer's lactate solution (8 mL/kg) will be administered by intravenous infusion for compensatory expansion before induction of anesthesia. Patients will then receive midazolam (0.04 mg/kg), fentanyl (3 μg/kg), vecuronium bromide (0.1 mg/kg) and propofol (1.5–2.0 mg/kg) intravenously for induction of anesthesia. Anesthesia will be maintained using a CP-600 anesthesia delivery system (Slgo Medical Technology Co., Ltd., Beijing, China). The dose of propofol will be adjusted to maintain the bispectral index (BIS) in the range 40–60. After surgery, all patients will remain in the post anesthesia care unit and then return to the ward for recovery until discharge.

The perioperative management of all patients will be standardized. Early ambulation will be encouraged and oral feeding will be resumed as early as possible. All patients will be followed-up for at least 6 months after discharge from the hospital.

Adverse events

All adverse reactions will be closely monitored through spontaneous reports by patients or direct observation by clinicians, or by asking the patients about adverse events using open questions. All adverse reactions will be recorded and appropriate treatment will be provided if necessary. Serious adverse events will be reported to the ethics committee.

Data collection and management

Demographic variables and clinical data will be collected from all patients. During the study, blood pressure, heart rate and oxygen saturation will also be monitored. Any adverse events will be recorded. Data will be collected throughout the study and will be securely managed under conditions of confidentiality. Data collection will be performed by a nurse anesthetist. The participants will be referred to by their participant number rather than by their name throughout the study, unless otherwise specified. All relevant documents and files will be archived for 5 years. The data will be accessible only by investigators who sign the confidential disclosure agreement and by institutional or governmental auditors during the study. Data without patient identifiers will be publicly accessible after the study. Data collection and management will be monitored by the Institutional Ethics Committee for Clinical Research of Shuguang Hospital.

Patient and public involvement

This study is currently in the recruitment phase. The participants will be able to access the study results through social media.

Discussion

POI continues to represent an important cause of morbidity following colon surgery. The prevention of postoperative bowel paralysis is thus of great importance in reducing perioperative complications and reducing hospitalization costs. Although it has been shown that EA can shorten the duration of POI[18], the effectiveness of TEAS, which is a similar technique, in preventing POI has not been investigated. It is, therefore, important to assess the effectiveness of TEAS in preventing POI through a clinical study.

This study has several strengths. Firstly, the intervention strategy of the protocol will be pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic effect. For example, pretreatment with TEAS has been shown to improve pain treatment[25,26] and to improve resuscitation after anesthesia, with reduction of postoperative nausea and vomiting[27].. It is, however, unclear whether preoperative TEAS can prevent POI. Studies suggest that early preoperative intervention may be more beneficial in regulating physiological

functions and preventing gastrointestinal paralysis[28]. In an extension to these findings, the present study will help to determine whether TEAS pretreatment could improvement postoperative bowel paralysis.

Secondly, the effectiveness of TEAS will be evaluated by assessing clinical function and by serological examination. In this randomized controlled trial of patients undergoing laparoscopic colorectal surgery, our aim is to assess the effects of preoperative TEAS on POI using relevant clinical parameters associated with bowel function. These include time to first defecation, time to first flatus, time to tolerance of oral diet and GI-2. Importantly, we will also measure serum concentrations of inflammatory mediators associated with POI, such as IFN-β, IFN-γ, IL-6 and IL-1β. Our findings may, thus, provide deeper insights into the mechanisms by which TEAS improves POI.

There are also limitations to this protocol. Various clinical indicators have been used in studies for the diagnosis of POI, but there is no consensus on which clinical parameter is the best for assessment of gastrointestinal (GI) transit[9,29,30]. Two indicators that are widely used to assess bowel movement will be used in this study. Time to first defecation will be the primary outcome and time to first flatus will be one of the secondary outcomes. There is a possibility that we may observe conflicting results (i.e., significant improvement in time to flatus, but not defecation). Because flatus can vary considerably between patients, clinical trials support the time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to first tolerance of solid food and time to first bowel movement) as supplementary secondary outcomes to measure the recovery time of GI function and these will be used in this study[31,32]. Other limitations of these indicators are that they require objective measurement of motility and are time consuming to measure[33,34]. Recently, this situation has been improved by the use of in vivo monitoring techniques to assess the function of gastrointestinal movements. Innovative devices, such as Sitz markers, have been used to evaluate postoperative recovery of small bowel movement by counting the number of Sitz markers that did not pass through the ileocecal valve, but remained in the small intestine using radiography[35]. The SmartPill is a swallowable device that record parameters within the GI tract. Indicators, such as pH,

temperature and intracavitary pressure, can be collected to analyze gastrointestinal transit times in vivo[36]. These devices acquire objective parameters to evaluate bowel movement and could save time. Research into the satisfaction of both doctors and patients with these device needs to be carried out. Furthermore, this study is a single-center trial and, because the therapeutic effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-center and large sample studies in the future.

Notwithstanding its limitations, this study can clearly indicate the overall effects of TEAS on postoperative recovery. We hypothesize that pretreatment with TEAS could improve recovery of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides positive results, it will be possible to recommend this pretreatment strategy for patients undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of consideration.

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Availability of data and materials

The dataset to be generated during the study will be available from the corresponding author on reasonable request via email.

Author contributions

Jian Wang conceived the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated in its design and coordination. Wen-ting Chen, Yue Yong, Jia-qun He and Jun Guo collected references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistical analyses. Rui Feng will follow-up with patients and record data. Jian Wang, Li-hua Fan and Jian-gang Song drafted the manuscript. All authors have read and approved the final manuscript.

Competing interests

None declared.

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Figure Legend

Figure 1. Flow chart of the study protocol

Figure 2. Acupoints selected in this trial (a) Hegu (IL-4) and Neiguan (P-6); (b) Zusanli (ST-36) and Shangjuxu (ST-37); (c) Han's acupoint nerve stimulator

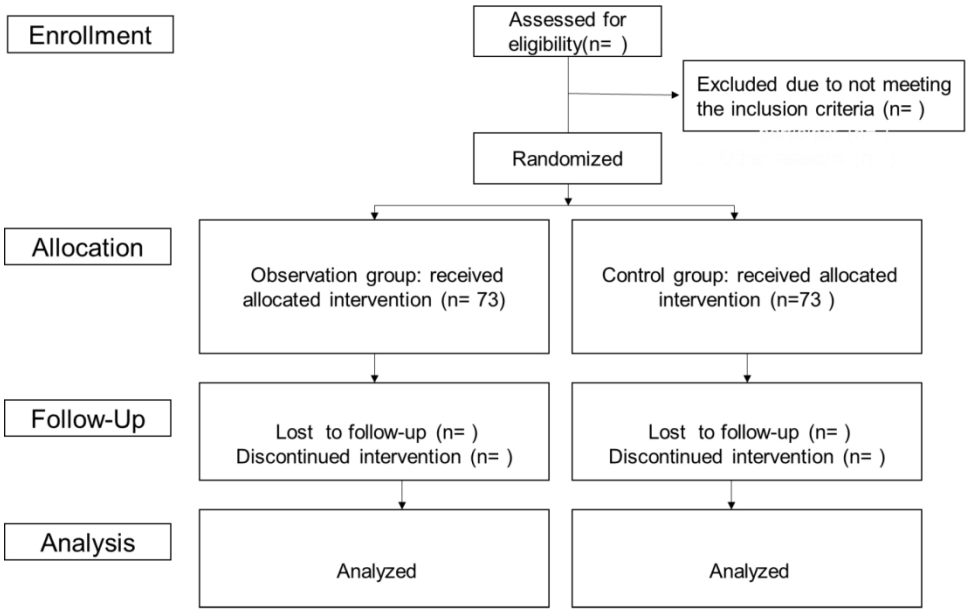

Figure 1. Flow chart of the study

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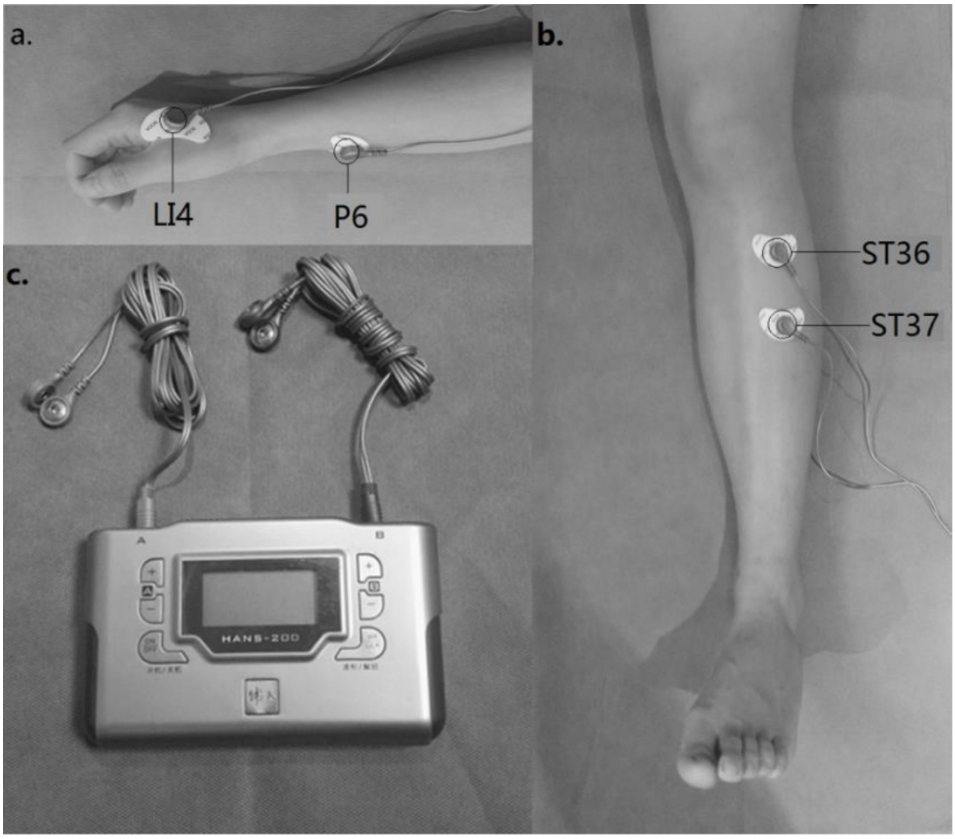

Figure 2. Acupoints selected in this trial. (a) shows Hegu (IL-4), Neiguan (P-6). (b) shows Zusanli (ST-36), Shangjuxu (ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&11
	5b	Name and contact information for the trial sponsor	11
	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	11
	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)	9

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&5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5
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)	5
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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8&9
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	7
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)	7

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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	9
	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	9

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	9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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)	8
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	9
	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	9
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
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)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	9
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	9
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	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.

BMJ Open

Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

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Secondary Subject Heading:	Anaesthesia, Gastroenterology and hepatology, Surgery
Keywords:	Transcutaneous electrical acupoint stimulation (TEAS), postoperative ileus (POI), Pretreatment

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Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

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Abstract

Introduction: Postoperative ileus (POI), a common complication after surgery, severely affects postoperative recovery. It is unclear whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can improve recovery from POI. This trial will evaluate the effects of pretreatment with TEAS on POI.

Methods and analysis: This will be a prospective, randomized, controlled trial. ASA I–III level patients, aged 18–75 years and scheduled for laparoscopic colon surgery, will be included in the study. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS (STEAS) groups. The groups will undergo two sessions of TEAS/STEAS daily for three days before surgery, with a final TEAS/STEAS treatment 30 minutes before anesthesia. The primary endpoint of the study will be time to first defecation. Secondary endpoints will include time to first flatus, time to tolerance of oral diet, GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to independent walking , length of hospital stay, postoperative pain VAS score on the first three days after surgery, analgesic requirements, complications, and plasma concentrations of IFN-β, IFN-γ, IL-6 and IL-1β. Multiple linear regression will be used to identify independent predictors of outcome measures.

Ethics and dissemination: This study has been approved by the Chinese Registered Clinical Trial Ethics Review Committee (NO.ChiECRCT-20170084). The results of the trial will be published in an international peer-reviewed journal.

Trial registration: This study has been registered with the Chinese Clinical Trial Registry (NO. ChiCTR-INR-17013184).

Trial status: The study was in the recruitment phase at the time of manuscript submission.

Abbreviations: POI = postoperative ileus, TCM = traditional Chinese medicine, EA = electro-acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index, PACU = post anesthesia care unit, ERAS= enhanced recovery after surgery.

Key words: transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI); pretreatment.

Strengths and limitations of the study

- This study aims to evaluate whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can prevent postoperative ileus (POI).
- TEAS is a safe, noninvasive and easily accepted adjunctive intervention.
- This study will provide deeper insights into the mechanism by which TEAS pretreatment reduces the inflammatory response.
- This is a single-center study, which is a potential limitation.

Introduction

Postoperative ileus (POI) is a transient dysfunction of gastrointestinal propulsion that often occurs after abdominal surgery and may also occur following surgery at other sites[1]. The main symptoms of POI include abdominal pain and distention, nausea, vomiting, difficult defecation and intolerance to solid food. POI is usually temporary, but if prolonged, may lead to surgical incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection, intestinal ischemia, aspiration pneumonia and other serious complications[2-4]. A retrospective cohort study involving nearly 500 hospitals in the United States showed that POI is a key reason for prolonged hospitalization and increased medical costs for patients undergoing abdominal surgery[1]. The United States spends more than $1.46 billion treating POI every year[5]. At present, the most common methods used to treat POI include: rational perioperative use of narcotic drugs and opioids, eating as soon as possible after surgery, avoidance of nasogastric tubes after the operation, early ambulation, postoperative epidural analgesia, restriction of fluid intake, the use of minimally invasive surgery (such as laparoscopic), drug therapy and the use of chewing gum. Despite the numerous treatment strategies, POI remains a difficult clinical challenge that compromises the rapid recovery of postoperative patients. It is, therefore, necessary to find more effective, convenient and economical treatment methods[6-10].

The main mechanism underlying POI may be activation of macrophages in the external muscular layer during the surgical procedure[11]. Intestinal manipulation during surgery can activate macrophages in the outer muscle layer of the small intestine, leading to release of inflammatory factors (IL-6, IL-1β) and the chemokine MIP-1α, together with increased expression of the adhesion molecule ICAM-1 on endothelial cells and induction of neutrophils and monocytes in the circulation into the small intestine muscle layer. These cells, and activated macrophages, can release a large amount of inducible nitric oxide synthase (iNOS) and prostaglandin, which inhibit the movement and contraction of the gastrointestinal tract[12,13]. Transport of these inflammatory mediators in the blood stream causes activation of macrophages in the distal gastrointestinal tract, leading to postoperative ileus over the entire

intestinal tract[14]. It has been confirmed by a large number of animal experiments that reducing the inflammatory response is an effective way to treat POI[15-17].

There is a long history in traditional Chinese medicine (TCM) of using acupuncture to treat functional gastrointestinal diseases and, in recent years, there has been significant global interest in the beneficial effects of acupuncture on POI. The positive effect of electroacupuncture (EA) on POI has been clearly demonstrated. Ng *et al.* used EA to treat POI in patients undergoing laparoscopic colon surgery[18]. Defecation time and length of hospital stay were significantly shortened in patients who received EA compared with those who did not receive the treatment. In patients undergoing hepatic resection, You *et al*. found a significant reduction in the incidence of POI in patients treated with a combination of acupuncture and Chinese herbal medicine. The length of hospitalization was also significantly shortened in the treated group (14.0 ± 4.9 d vs 16.5 ± 6.8 d, $P = 0.014$)[19].

In previous studies, we proved that pretreatment with acupuncture could reduce excessive activation of the innate immune system and inhibit the inflammatory response. This effect may be achieved by activation of the vagal nervous system[20,21]. Other studies have shown that transcutaneous electrical acupoint stimulation (TEAS) and EA have similar effects in the treatment of pain and alleviating the inflammatory response[22,23].

Traditional Chinese medicine holds that the best treatment for disease is prevention. Based on all of the above studies, we hypothesize that the use of TEAS as a preoperative treatment may reduce the incidence of POI. There have, so far, not been any studies that address this question. We have, therefore, designed a randomized, controlled trial to investigate whether pretreatment with TEAS can reduce the incidence of POI in patients undergoing laparoscopic colon resection. The study is also designed to verify that the anti-inflammatory effect is associated with the immunomodulatory function of TEAS.

Methods and analysis

Study objective

The primary objective is to assess the effect of TEAS on clinical recovery of bowel function after laparoscopic colon surgery. The secondary objective is to verify that suppression of overactivation of the innate immune system and reduction of the inflammatory response are the mechanisms underlying the ability of pretreatment of percutaneous acupuncture to prevent POI.

Study location

A prospective, single-center, double-blinded, randomized, controlled trial will be conducted at Shuguang Hospital, which is affiliated to the Shanghai University of Traditional Chinese Medicine, China.

Study population

Participants will be recruited according to the inclusion and exclusion criteria.

Inclusion criteria

1. Male and female patients aged 18–75 years
2. Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such as left colectomy, right colectomy, and anterior resection of the upper part of the rectum and lower part of the sigmoid)
3. Body mass index (BMI) 18–31 kg/m^2
4. ASA classification I–III
5. Patients provide signed informed consent

Exclusion criteria

1. Middle and lower rectal resection, total/proctocolectomy or the need for complex endoscopic surgery
2. Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation
3. History of abdominal/pelvic operations or complications
4. Patients receiving epidural anesthesia or epidural analgesia
5. Patients with skin infections, surgical incision or scar at the point of application of acupuncture
6. Patients have a history of limb surgery, spinal surgery or nerve injury

7. Patients who participated in other clinical trials, or received other acupuncture therapy, in the previous four weeks
8. Patients with cardiac pacemakers
9. Patients have one of the following conditions before surgery: chronic pain, drug addiction or alcohol dependence
10. Patients with preoperative combination of severe central nervous system disease and severe mental illness

Endpoints

Primary endpoint

First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.

Secondary endpoints

Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to walk independently (h), length of hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital discharge include stability of vital signs with no fever, achievement of flatus or defecation, ability to tolerate solid food without vomiting, control of postoperative pain, absence of other postoperative complications and ability to function at home independently or with home care provided. Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1, 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the worst pain intensity). Postoperative requirements for analgesia will also be assessed. Inflammatory mediators (IFN-β, IFN-γ, IL-6 and IL-1β) in blood will be measured before TEAS/STEAS intervention and on days 1, 3 and 5 after the operation. Postoperative complications will be recorded using the Clavien - Dindo classification for complication assessment[24]. The follow-up period will be at least 6 months.

Randomization and blinding

Patients will be randomized to receive either TEAS or STEAS by stratified randomization according to sex, in a 1:1 ratio (Figure 1). Using a computer-generated random sequence, a sealed envelope will be opened to determine to which group the patient has been assigned. The

acupuncturist will be aware of the treatment group. Patients as well as the outcome investigator (nurse anesthetist) , will be blinded to the treatment allocation.

Current sample size justification

According to Wang Jian and Song Jiangang's preliminary study of transcutaneous electrical acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing laparoscopic colon surgery in Shuguang Hospital, the mean time to first defecation following laparoscopic colon surgery was 62 ± 19 h (M ± SD). Working on the assumption that a clinically meaningful difference in mean time to first defecation between the TEAS and STEAS groups is 1 day or 24 h, 66 patients would be needed in each group to reach a power of 80% and a 5% Type I error rate. If the drop-out rate is 10%, a total sample size of 146 patients for the two groups is needed for this study.

Statistical analysis

Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance of oral diet, time to walking independently, length of hospital stay) will be reported using the mean and standard deviation (M± SD) for normally distributed data or median (range) for skewed data. Data for categorical variables will be expressed as a number (percentage). Intergroup differences will be assessed using the Student's t-test or Mann-Whitney U test. Intergroup differences in inflammatory mediators (at time points of pre-TEAS/STEAS treatment, and on post-operative days 1, 3, and 5) were assessed by two-way repeated measures analysis of variance with Bonferroni post hoc test. The significance level will be set at 5%. All data will be analyzed using SPSS 17.0 software or other appropriate statistical software packages.

Pretreatment

Patients randomized to the TEAS and STEAS groups will undergo two treatment sessions daily for three consecutive days before surgery. The patients will then be treated for a final time 30 minutes before anesthesia.

For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes

(Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China), at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness, distention and heaviness. The STEAS group will receive a strong, but comfortable current for 30 s, and the current will then gradually vanish over the next 15 s[25]. The participants of both groups will be told that they are receiving current stimulation. Each session of acupoints treatment will last for 30 min. During the application of TEAS, patients will be required not to change the current settings themselves. A prompt beep at the end of TEAS will indicate the end of treatment.

All surgery will be carried out under general anesthesia, using standardized anesthetic procedures. Patients will be fasted for 12 h before surgery. Right upper extremity venous access will be established before the patients entering the operating theater. Ringer's lactate solution (8 mL/kg) will be administered by intravenous infusion for compensatory expansion before induction of anesthesia. Patients will then receive midazolam (0.04 mg/kg), fentanyl (3 μg/kg), vecuronium bromide (0.1 mg/kg) and propofol (1.5–2.0 mg/kg) intravenously for induction of anesthesia. Anesthesia will be maintained using a CP-600 anesthesia delivery system (Slgo Medical Technology Co., Ltd., Beijing, China). The dose of propofol will be adjusted to maintain the bispectral index (BIS) in the range 40–60. After surgery, all patients will remain in the post anesthesia care unit and then return to the ward for recovery until discharge.

The perioperative management of all patients will be standardized. Early ambulation will be encouraged and oral feeding will be resumed as early as possible. All patients will be followed-up for at least 6 months after discharge from the hospital.

Adverse events

All adverse reactions will be closely monitored through spontaneous reports by patients or direct observation by clinicians, or by asking the patients about adverse events using open

questions. All adverse reactions will be recorded and appropriate treatment will be provided if necessary. Serious adverse events will be reported to the ethics committee.

Data collection and management

Demographic variables and clinical data will be collected from all patients. During the study, blood pressure, heart rate and oxygen saturation will also be monitored. Any adverse events will be recorded. Data will be collected throughout the study and will be securely managed under conditions of confidentiality. Data collection will be performed by a nurse anesthetist. The participants will be referred to by their participant number rather than by their name throughout the study, unless otherwise specified. All relevant documents and files will be archived for 5 years. The data will be accessible only by investigators who sign the confidential disclosure agreement and by institutional or governmental auditors during the study. Data without patient identifiers will be publicly accessible after the study. Data collection and management will be monitored by the Institutional Ethics Committee for Clinical Research of Shuguang Hospital.

Patient and public involvement

This study is currently in the recruitment phase. The participants will be able to access the study results through social media.

Discussion

POI continues to represent an important cause of morbidity following colon surgery. The prevention of POI is thus of great importance in reducing perioperative complications and reducing hospitalization costs. Although it has been shown that EA can shorten the duration of POI[18], the effectiveness of TEAS, which is a similar technique, in preventing POI has not been investigated. It is, therefore, important to assess the effectiveness of TEAS in preventing POI through a clinical study.

This study has several strengths. Firstly, the intervention strategy of the protocol will be pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic effect. For example, pretreatment with TEAS has been shown to improve pain treatment[26,27] and to improve resuscitation after anesthesia, with reduction of postoperative nausea and

vomiting[28]. It is, however, unclear whether preoperative TEAS can prevent POI. Studies suggest that early preoperative intervention may be more beneficial in regulating physiological functions and preventing POI[29]. In an extension to these findings, the present study will help to determine whether TEAS pretreatment could improvement POI.

Secondly, the effectiveness of TEAS will be evaluated by assessing clinical function and by serological examination. In this randomized controlled trial of patients undergoing laparoscopic colorectal surgery, our aim is to assess the effects of preoperative TEAS on POI using relevant clinical parameters associated with bowel function. These include time to first defecation, time to first flatus, time to tolerance of oral diet and GI-2. Importantly, we will also measure serum concentrations of inflammatory mediators associated with POI, such as IFN-β, IFN-γ, IL-6 and IL-1β. Our findings may, thus, provide deeper insights into the mechanisms by which TEAS improves POI.

There are also limitations to this protocol. Various clinical indicators have been used in studies for the diagnosis of POI, but there is no consensus on which clinical parameter is the best for assessment of gastrointestinal (GI) transit[9,30,31]. Two indicators that are widely used to assess bowel movement will be used in this study. Time to first defecation will be the primary outcome and time to first flatus will be one of the secondary outcomes. There is a possibility that we may observe conflicting results (i.e., significant improvement in time to flatus, but not defecation). Because flatus can vary considerably between patients, clinical trials support the time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to first tolerance of solid food and time to first bowel movement) as supplementary secondary outcomes to measure the recovery time of GI function and these will be used in this study[32,33]. Other limitations of these indicators are that they require objective measurement of motility and are time consuming to measure[34,35]. Recently, this situation has been improved by the use of in vivo monitoring techniques to assess the function of gastrointestinal movements. Innovative devices, such as Sitz markers, have been used to evaluate postoperative recovery of small bowel movement by counting the number of Sitz markers that did not pass through the ileocecal valve, but remained in the small intestine using radiography[36]. The SmartPill is a

swallowable device that record parameters within the GI tract. Indicators, such as pH, temperature and intracavitary pressure, can be collected to analyze gastrointestinal transit times in vivo[37]. These devices acquire objective parameters to evaluate bowel movement and could save time. Research into the satisfaction of both doctors and patients with these device needs to be carried out. Furthermore, this study is a single-center trial and, because the therapeutic effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-center and large sample studies in the future.

Notwithstanding its limitations, this study can clearly indicate the overall effects of TEAS on postoperative recovery. We hypothesize that pretreatment with TEAS could improve recovery of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides positive results, it will be possible to recommend this pretreatment strategy for patients undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of consideration.

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Availability of data and materials

The dataset to be generated during the study will be available from the corresponding author on reasonable request via email.

Author contributions

Jian Wang conceived the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated in its design and coordination. Wen-ting Chen, Yue Yong, Wei Song and Jun Guo collected references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistical analyses. Rui Feng will follow-up with patients and record data. Jian Wang, Li-hua Fan and

Jian-gang Song drafted the manuscript. All authors have read and approved the final manuscript.

Competing interests

None declared.

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Figure Legend

Figure 1. Flow chart of the study protocol

Figure 2. Acupoints selected in this trial (a) Hegu (IL-4) and Neiguan (P-6); (b) Zusanli (ST-36) and Shangjuxu (ST-37); (c) Han's acupoint nerve stimulator

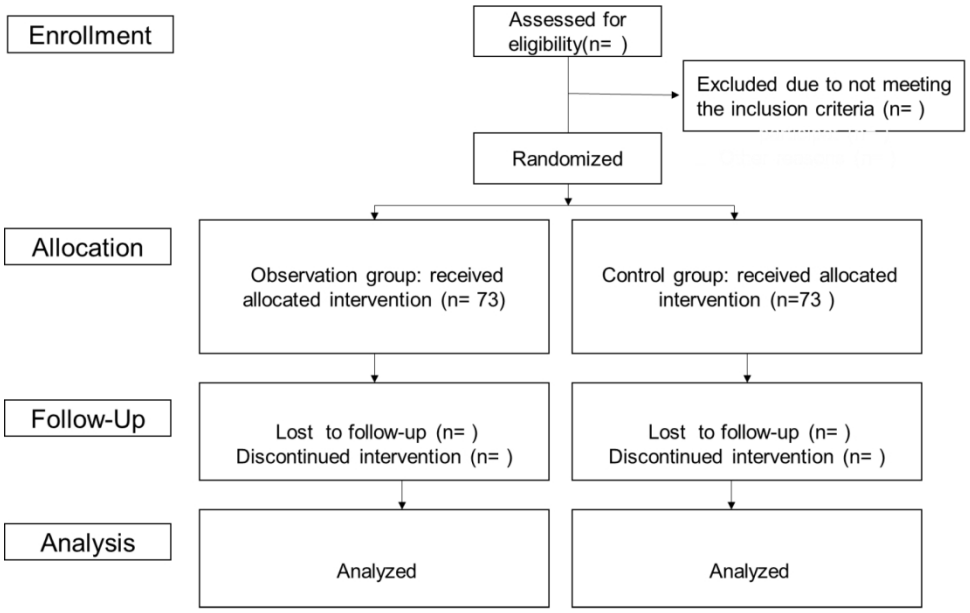

Figure 1. Flow chart of the study

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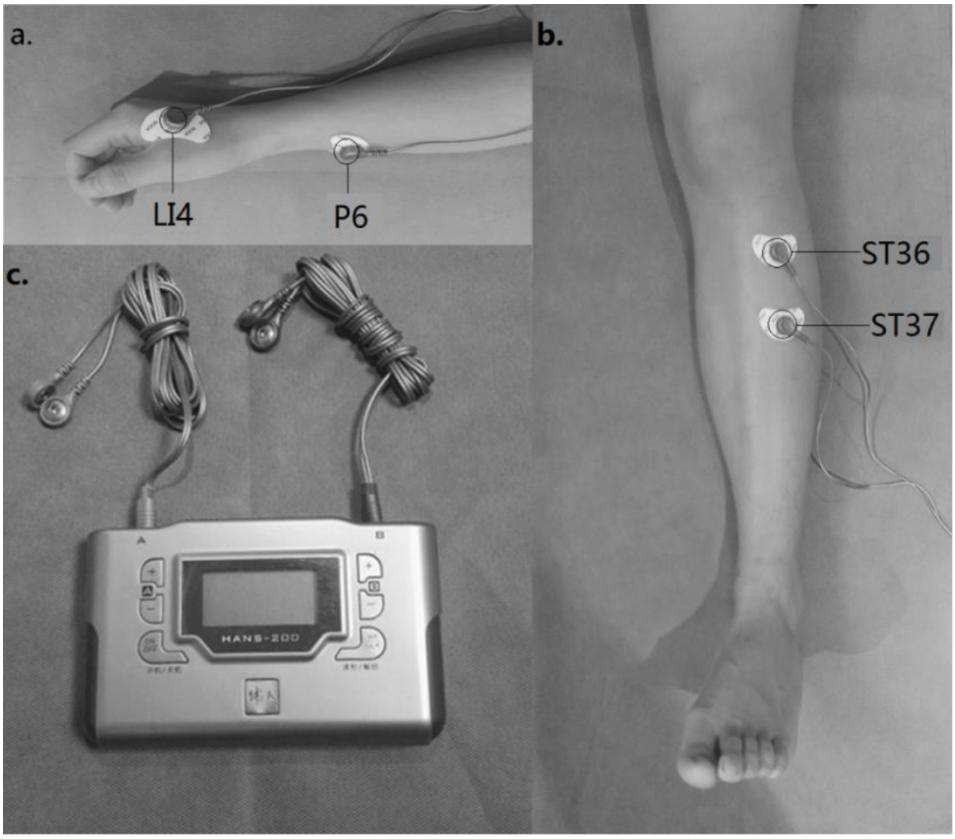

Figure 2. Acupoints selected in this trial. (a) shows Hegu (IL-4), Neiguan (P-6). (b) shows Zusanli (ST-36), Shangjuxu (ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&11
	5b	Name and contact information for the trial sponsor	11
	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	11
	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)	9

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&5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5
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)	5
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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8&9
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	7
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)	7

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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	9
	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	9

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	9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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)	8
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	9
	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	9
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
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)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	9
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	9
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	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.

BMJ Open

Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Anaesthesia, Gastroenterology and hepatology, Surgery
Keywords:	Transcutaneous electrical acupoint stimulation (TEAS), postoperative ileus (POI), Pretreatment

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Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

Wang, Jian MD[1,#]; Li, Dongli MD[2,#]; Tang, Wei MD[1]; Guo, Jun MD[1]; Chen, Wenting MD[1]; Yong, Yue MD[1]; Song, Wei[1]; Yu, Guijie MD[1]; Feng, Rui MD[1]; Yuan, Lan MD[1]; Fu, Guoqiang MD[1]; Song, Jiangang MD[1,*]; Fan, Lihua MD[2,*]

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Abstract

Introduction: Postoperative ileus (POI), a common complication after surgery, severely affects postoperative recovery. It is unclear whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can improve recovery from POI. This trial will evaluate the effects of pretreatment with TEAS on POI.

Methods and analysis: This will be a prospective, randomized, controlled trial. ASA I–III level patients, aged 18–75 years and scheduled for laparoscopic colon surgery, will be included in the study. It is planned that 146 subjects will be randomized to the TEAS and sham TEAS (STEAS) groups. The groups will undergo two sessions of TEAS/STEAS daily for three days before surgery, with a final TEAS/STEAS treatment 30 minutes before anesthesia. The primary endpoint of the study will be time to first defecation. Secondary endpoints will include time to first flatus, time to tolerance of oral diet, GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to independent walking , length of hospital stay, postoperative pain VAS score on the first three days after surgery, analgesic requirements, complications, and plasma concentrations of IFN-β, IFN-γ, IL-6 and IL-1β. Multiple linear regression will be used to identify independent predictors of outcome measures.

Ethics and dissemination: This study has been approved by the Chinese Registered Clinical Trial Ethics Review Committee (NO.ChiECRCT-20170084). The results of the trial will be published in an international peer-reviewed journal.

Trial registration: This study has been registered with the Chinese Clinical Trial Registry (NO. ChiCTR-INR-17013184).

Trial status: The study was in the recruitment phase at the time of manuscript submission.

Abbreviations: POI = postoperative ileus, TCM = traditional Chinese medicine, EA = electro-acupuncture, TEAS = transcutaneous electrical acupoint stimulation, BIS = bispectral index, PACU = post anesthesia care unit, ERAS= enhanced recovery after surgery.

Key words: transcutaneous electrical acupoint stimulation (TEAS); postoperative ileus (POI); pretreatment.

Strengths and limitations of the study

- This study aims to evaluate whether pretreatment with transcutaneous electrical acupoint stimulation (TEAS) can prevent postoperative ileus (POI).
- TEAS is a safe, noninvasive and easily accepted adjunctive intervention.
- This study will provide deeper insights into the mechanism by which TEAS pretreatment reduces the inflammatory response.
- This is a single-center study, which is a potential limitation.

Introduction

Postoperative ileus (POI) is a transient dysfunction of gastrointestinal propulsion that often occurs after abdominal surgery and may also occur following surgery at other sites[1]. The main symptoms of POI include abdominal pain and distention, nausea, vomiting, difficult defecation and intolerance to solid food. POI is usually temporary, but if prolonged, may lead to surgical incision dehiscence, intestinal anastomotic fistula, abdominal cavity infection, intestinal ischemia, aspiration pneumonia and other serious complications[2-4]. A retrospective cohort study involving nearly 500 hospitals in the United States showed that POI is a key reason for prolonged hospitalization and increased medical costs for patients undergoing abdominal surgery[1]. The United States spends more than $1.46 billion treating POI every year[5]. At present, the most common methods used to treat POI include: rational perioperative use of narcotic drugs and opioids, eating as soon as possible after surgery, avoidance of nasogastric tubes after the operation, early ambulation, postoperative epidural analgesia, restriction of fluid intake, the use of minimally invasive surgery (such as laparoscopic), drug therapy and the use of chewing gum. Despite the numerous treatment strategies, POI remains a difficult clinical challenge that compromises the rapid recovery of postoperative patients. It is, therefore, necessary to find more effective, convenient and economical treatment methods[6-10].

The main mechanism underlying POI may be activation of macrophages in the external muscular layer during the surgical procedure[11]. Intestinal manipulation during surgery can activate macrophages in the outer muscle layer of the small intestine, leading to release of inflammatory factors (IL-6, IL-1β) and the chemokine MIP-1α, together with increased expression of the adhesion molecule ICAM-1 on endothelial cells and induction of neutrophils and monocytes in the circulation into the small intestine muscle layer. These cells, and activated macrophages, can release a large amount of inducible nitric oxide synthase (iNOS) and prostaglandin, which inhibit the movement and contraction of the gastrointestinal tract[12,13]. Transport of these inflammatory mediators in the blood stream causes activation of macrophages in the distal gastrointestinal tract, leading to postoperative ileus over the entire

intestinal tract[14]. It has been confirmed by a large number of animal experiments that reducing the inflammatory response is an effective way to treat POI[15-17].

There is a long history in traditional Chinese medicine (TCM) of using acupuncture to treat functional gastrointestinal diseases and, in recent years, there has been significant global interest in the beneficial effects of acupuncture on POI. The positive effect of electroacupuncture (EA) on POI has been clearly demonstrated. Ng *et al.* used EA to treat POI in patients undergoing laparoscopic colon surgery[18]. Defecation time and length of hospital stay were significantly shortened in patients who received EA compared with those who did not receive the treatment. In patients undergoing hepatic resection, You *et al*. found a significant reduction in the incidence of POI in patients treated with a combination of acupuncture and Chinese herbal medicine. The length of hospitalization was also significantly shortened in the treated group (14.0 ± 4.9 d vs 16.5 ± 6.8 d, $P = 0.014$)[19].

In previous studies, we proved that pretreatment with acupuncture could reduce excessive activation of the innate immune system and inhibit the inflammatory response. This effect may be achieved by activation of the vagal nervous system[20,21]. Other studies have shown that transcutaneous electrical acupoint stimulation (TEAS) and EA have similar effects in the treatment of pain and alleviating the inflammatory response[22,23].

Traditional Chinese medicine holds that the best treatment for disease is prevention. Based on all of the above studies, we hypothesize that the use of TEAS as a preoperative treatment may reduce the incidence of POI. There have, so far, not been any studies that address this question. We have, therefore, designed a randomized, controlled trial to investigate whether pretreatment with TEAS can reduce the incidence of POI in patients undergoing laparoscopic colon resection. The study is also designed to verify that the anti-inflammatory effect is associated with the immunomodulatory function of TEAS.

Methods and analysis

Study objective

The primary objective is to assess the effect of TEAS on clinical recovery of bowel function after laparoscopic colon surgery. The secondary objective is to verify that suppression of overactivation of the innate immune system and reduction of the inflammatory response are the mechanisms underlying the ability of pretreatment of percutaneous acupuncture to prevent POI.

Study location

A prospective, single-center, double-blinded, randomized, controlled trial will be conducted at Shuguang Hospital, which is affiliated to the Shanghai University of Traditional Chinese Medicine, China.

Study population

Participants will be recruited according to the inclusion and exclusion criteria.

Inclusion criteria

1. Male and female patients aged 18–75 years
2. Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such as left colectomy, right colectomy, and anterior resection of the upper part of the rectum and lower part of the sigmoid)
3. Body mass index (BMI) 18–31 kg/m^2
4. ASA classification I–III
5. Patients provide signed informed consent (the consent form can be viewed in online supplementary appendix 1.)

Exclusion criteria

1. Middle and lower rectal resection, total/proctocolectomy or the need for complex endoscopic surgery
2. Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation
3. History of abdominal/pelvic operations or complications
4. Patients receiving epidural anesthesia or epidural analgesia
5. Patients with skin infections, surgical incision or scar at the point of application of acupuncture
6. Patients have a history of limb surgery, spinal surgery or nerve injury

7. Patients who participated in other clinical trials, or received other acupuncture therapy, in the previous four weeks
8. Patients with cardiac pacemakers
9. Patients have one of the following conditions before surgery: chronic pain, drug addiction or alcohol dependence
10. Patients with preoperative combination of severe central nervous system disease and severe mental illness

Endpoints

Primary endpoint

First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.

Secondary endpoints

Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to walk independently (h), length of hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital discharge include stability of vital signs with no fever, achievement of flatus or defecation, ability to tolerate solid food without vomiting, control of postoperative pain, absence of other postoperative complications and ability to function at home independently or with home care provided. Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1, 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the worst pain intensity). Postoperative requirements for analgesia will also be assessed. Inflammatory mediators (IFN-β, IFN-γ, IL-6 and IL-1β) in blood will be measured before TEAS/STEAS intervention and on days 1, 3 and 5 after the operation. Postoperative complications will be recorded using the Clavien-Dindo classification for complication assessment[24]. The follow-up period will be at least 6 months.

We add GI-2 as a secondary 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 defecation and time to tolerance of oral diet). There will be no harm to subjects, no additional cost and no more work.

Randomization and blinding

Patients will be randomized to receive either TEAS or STEAS by stratified randomization according to sex, in a 1:1 ratio (Figure 1). Using a computer-generated random sequence, a sealed envelope will be opened to determine to which group the patient has been assigned. The acupuncturist will be aware of the treatment group. Patients as well as the outcome investigator (nurse anesthetist) , will be blinded to the treatment allocation.

Current sample size justification

According to Wang Jian and Song Jiangang's preliminary study of transcutaneous electrical acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing laparoscopic colon surgery in Shuguang Hospital, the mean time to first defecation following laparoscopic colon surgery was 62 ± 19 h (M ± SD). Working on the assumption that a clinically meaningful difference in mean time to first defecation between the TEAS and STEAS groups is 1 day or 24 h, 66 patients would be needed in each group to reach a power of 80% and a 5% Type I error rate. If the drop-out rate is 10%, a total sample size of 146 patients for the two groups is needed for this study.

Statistical analysis

Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance of oral diet, time to walking independently, length of hospital stay) will be reported using the mean and standard deviation (M± SD) for normally distributed data or median (range) for skewed data. Data for categorical variables will be expressed as a number (percentage). Intergroup differences will be assessed using the Student's t-test or Mann-Whitney U test. Intergroup differences in inflammatory mediators (at time points of pre-TEAS/STEAS treatment, and on post-operative days 1, 3, and 5) were assessed by two-way repeated measures analysis of variance with Bonferroni post hoc test. The significance level will be set at 5%. All data will be analyzed using SPSS 17.0 software or other appropriate statistical software packages.

Pretreatment

Patients randomized to the TEAS and STEAS groups will undergo two treatment sessions daily for three consecutive days before surgery. The patients will then be treated for a final time 30 minutes before anesthesia.

For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China), at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness, distention and heaviness. The STEAS group will receive a strong, but comfortable current for 30 s, and the current will then gradually vanish over the next 15 s[25]. The participants of both groups will be told that they are receiving current stimulation. Each session of acupoints treatment will last for 30 min. During the application of TEAS, patients will be required not to change the current settings themselves. A prompt beep at the end of TEAS will indicate the end of treatment.

All surgery will be carried out under general anesthesia, using standardized anesthetic procedures. Patients will be fasted for 12 h before surgery. Right upper extremity venous access will be established before the patients entering the operating theater. Ringer’s lactate solution (8 mL/kg) will be administered by intravenous infusion for compensatory expansion before induction of anesthesia. Patients will then receive midazolam (0.04 mg/kg), fentanyl (3 μg/kg), vecuronium bromide (0.1 mg/kg) and propofol (1.5–2.0 mg/kg) intravenously for induction of anesthesia. Anesthesia will be maintained using a CP-600 anesthesia delivery system (Slgo Medical Technology Co., Ltd., Beijing, China). The dose of propofol will be adjusted to maintain the bispectral index (BIS) in the range 40–60. After surgery, all patients will remain in the post anesthesia care unit and then return to the ward for recovery until discharge.

The perioperative management of all patients will be standardized. Early ambulation will be encouraged and oral feeding will be resumed as early as possible. All patients will be followed-up for at least 6 months after discharge from the hospital.

Adverse events

All adverse reactions will be closely monitored through spontaneous reports by patients or direct observation by clinicians, or by asking the patients about adverse events using open questions. All adverse reactions will be recorded and appropriate treatment will be provided if necessary. Serious adverse events will be reported to the ethics committee.

Data collection and management

Demographic variables and clinical data will be collected from all patients. During the study, blood pressure, heart rate and oxygen saturation will also be monitored. Any adverse events will be recorded. Data will be collected throughout the study and will be securely managed under conditions of confidentiality. Data collection will be performed by a nurse anesthetist. The participants will be referred to by their participant number rather than by their name throughout the study, unless otherwise specified. All relevant documents and files will be archived for 5 years. The data will be accessible only by investigators who sign the confidential disclosure agreement and by institutional or governmental auditors during the study. Data without patient identifiers will be publicly accessible after the study. Data collection and management will be monitored by the Institutional Ethics Committee for Clinical Research of Shuguang Hospital.

Patient and public involvement

This study is currently in the recruitment phase. Patients and/or public were not involved in study design or conduct of the study. The participants will be able to access the study results through social media.

Discussion

POI continues to represent an important cause of morbidity following colon surgery. The prevention of POI is thus of great importance in reducing perioperative complications and reducing hospitalization costs. Although it has been shown that EA can shorten the duration of

POI[18], the effectiveness of TEAS, which is a similar technique, in preventing POI has not been investigated. It is, therefore, important to assess the effectiveness of TEAS in preventing POI through a clinical study.

This study has several strengths. Firstly, the intervention strategy of the protocol will be pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic effect. For example, pretreatment with TEAS has been shown to improve pain treatment[26,27] and to improve resuscitation after anesthesia, with reduction of postoperative nausea and vomiting[28]. It is, however, unclear whether preoperative TEAS can prevent POI. Studies suggest that early preoperative intervention may be more beneficial in regulating physiological functions and preventing POI[29]. In an extension to these findings, the present study will help to determine whether TEAS pretreatment could improvement POI.

Secondly, the effectiveness of TEAS will be evaluated by assessing clinical function and by serological examination. In this randomized controlled trial of patients undergoing laparoscopic colorectal surgery, our aim is to assess the effects of preoperative TEAS on POI using relevant clinical parameters associated with bowel function. These include time to first defecation, time to first flatus, time to tolerance of oral diet and GI-2. Importantly, we will also measure serum concentrations of inflammatory mediators associated with POI, such as IFN-β, IFN-γ, IL-6 and IL-1β. Our findings may, thus, provide deeper insights into the mechanisms by which TEAS improves POI.

There are also limitations to this protocol. Various clinical indicators have been used in studies for the diagnosis of POI, but there is no consensus on which clinical parameter is the best for assessment of gastrointestinal (GI) transit[9,30,31]. Two indicators that are widely used to assess bowel movement will be used in this study. Time to first defecation will be the primary outcome and time to first flatus will be one of the secondary outcomes. There is a possibility that we may observe conflicting results (i.e., significant improvement in time to flatus, but not defecation). Because flatus can vary considerably between patients, clinical trials support the time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to first tolerance of solid food and time to first bowel movement) as supplementary

secondary outcomes to measure the recovery time of GI function and these will be used in this study[32,33]. Other limitations of these indicators are that they require objective measurement of motility and are time consuming to measure[34,35]. Recently, this situation has been improved by the use of in vivo monitoring techniques to assess the function of gastrointestinal movements. Innovative devices, such as Sitz markers, have been used to evaluate postoperative recovery of small bowel movement by counting the number of Sitz markers that did not pass through the ileocecal valve, but remained in the small intestine using radiography[36]. The SmartPill is a swallowable device that record parameters within the GI tract. Indicators, such as pH, temperature and intracavitary pressure, can be collected to analyze gastrointestinal transit times in vivo[37]. These devices acquire objective parameters to evaluate bowel movement and could save time. Research into the satisfaction of both doctors and patients with these device needs to be carried out. Furthermore, this study is a single-center trial and, because the therapeutic effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-center and large sample studies in the future.

Notwithstanding its limitations, this study can clearly indicate the overall effects of TEAS on postoperative recovery. We hypothesize that pretreatment with TEAS could improve recovery of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides positive results, it will be possible to recommend this pretreatment strategy for patients undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of consideration.

Acknowledgements

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Availability of data and materials

The dataset to be generated during the study will be available from the corresponding author on reasonable request via email.

Author contributions

Jian Wang conceived the study. Dong-li Li, Wei Tang, Jun Guo and Guo-qiang Fu participated in its design and coordination. Wen-ting Chen, Yue Yong, Wei Song and Jun Guo collected references and developed the protocol. Gui-jie Yu and Lan Yuan will perform statistical analyses. Rui Feng will follow-up with patients and record data. Jian Wang, Li-hua Fan and Jian-gang Song drafted the manuscript. All authors have read and approved the final manuscript.

Competing interests

None declared.

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Figure Legend

Figure 1. Flow chart of the study protocol

Figure 2. Acupoints selected in this trial (a) Hegu (IL-4) and Neiguan (P-6); (b) Zusanli (ST-36) and Shangjuxu (ST-37); (c) Han's acupoint nerve stimulator

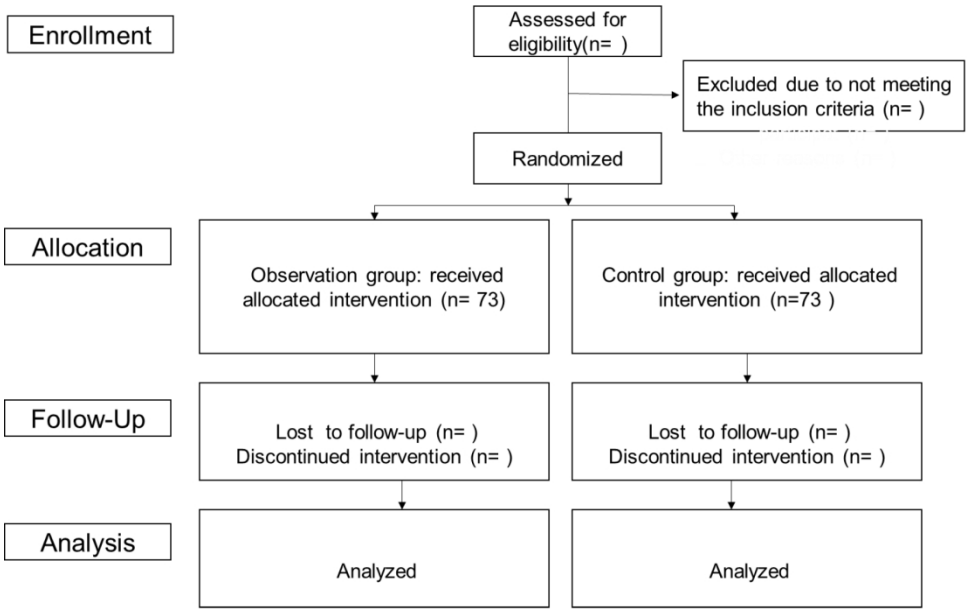

Figure 1. Flow chart of the study

177x109mm (300 x 300 DPI)

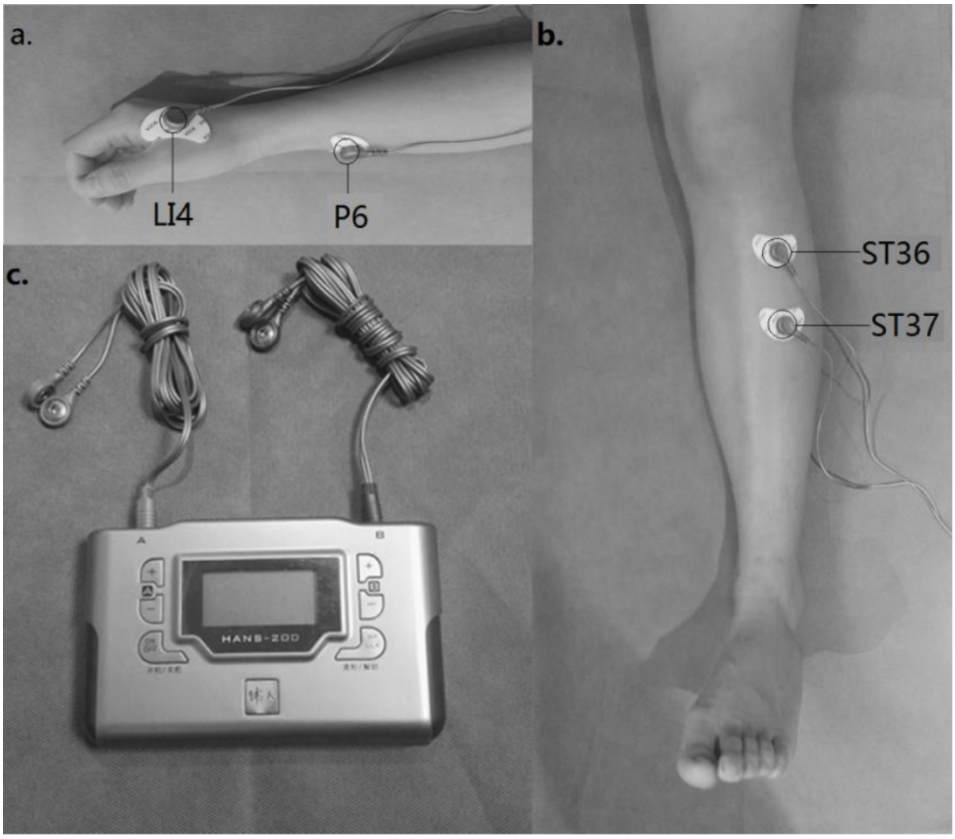

Figure 2. Acupoints selected in this trial. (a) shows Hegu (IL-4), Neiguan (P-6). (b) shows Zusanli (ST-36), Shangjuxu (ST-37). (c) Han's acupoint nerve stimulator.

103x87mm (300 x 300 DPI)

Informed consent · informed consent page

Dear Mr/Miss,

We will invite you to participate in a study, this study is supported by the project of the National Natural Science Foundation of China (No. 81703898, 81603702, 81603700 and 81774108) and the commercial sponsorship of SINCH Pharmaceuticals Tech. Co., Ltd. This study protocol has been reviewed by the Chinese Registered Clinical Trial Ethics Review Committee (NO.ChiECRCT-20170084) and approved for clinical study. Before you decide whether or not to participate in this study, please read the following as carefully as possible. It will help you understand the study and why it was conducted, the procedures and duration of the study, and the benefits, risks and discomfort that may result from your participation in the study. If you wish, you can also discuss it with your relatives or friends, or ask your doctor for an explanation to help you make a decision.

I. Research background and purpose

1.1 Disease burden and treatment status

Postoperative ileus (POI) refers to the stagnation of gastrointestinal propulsion caused by surgical operation after abdominal surgery, which is mainly manifested as abdominal pain, abdominal distension, nausea and vomiting, cessation of exhaust and defecation, and intolerance of solid food.

Postoperative intestinal paralysis is usually temporary, but if the duration of intestinal paralysis is prolonged, it may lead to serious complications such as surgical incision dehiscence, intestinal anastomotic fistula, abdominal infection, intestinal ischemia, and aspiration pneumonia.

A retrospective cohort study of nearly 500 U.S. hospitals showed that postoperative ileus was an important cause of longer hospital stays and higher medical costs for patients undergoing abdominal surgery. The United States spends more than $1.46 billion annually on treatment for POI. At present, measures used in treating POI mainly include: perioperative rational use of narcotic drugs and opioids, eat early after surgery, avoid to use nasogastric tube after operation, early ambulation, postoperative epidural analgesia, restrict fluid intake, the minimally invasive surgery (such as laparoscopic), drug therapy, chewing gum, etc. However, although there are many treatment measures, they are affected by many factors (such as complicated operation, whether the patient accepts, cost-benefit ratio, surgical conditions, etc.), and the mechanism of POI is complex and far from clear, so the clinical treatment effect is still not ideal.

POI is still a clinical problem that seriously affects patients' postoperative recovery.

Therefore, it is necessary to find more effective, convenient and economical treatment methods.

1.2 purpose of this study

The purpose of this study is to assess the effect of TEAS on clinical recovery of bowel function after laparoscopic colon surgery and explore the mechanism of TEAS treatment on POI.

II. What will be required to participate in the study?

1.Before you are enrolled in the study, the doctor will inquire and record your medical history, and perform physical examination, blood routine, urine routine, stool routine, liver function, kidney function and other physical and chemical examinations, as well as 12-lead electrocardiogram.

You are eligible for inclusion. You may participate in the study voluntarily and sign the informed consent.
If you do not wish to participate in the study, we will treat you as you wish.

2. If you are willing to participate in the study, you will follow the following steps:

- **Sign the informed consent**

- **TEAS treatment**

We will provide you with TEAS treatment in 3 consecutive days before surgery, twice a day, each time for 30 minutes, giving another acupoint electrical stimulation treatment for 30 minutes before anesthesia.

- **Clinical test indicators:**

You will need to cooperate to provide the following information, which will be recorded by the researcher

- First defecation time (h) i.e., time to first anal defecation after laparoscopic surgery.
- Time to first flatus (h), time to tolerance of solid oral diet (h), GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet), time to walk independently (h)
- Pain will be assessed using the visual analogue scale (VAS) on postoperative days 1, 2 and 3 (scale of 0 to 10, where 0 represents complete absence of pain and 10 represent the worst pain intensity).
- Inflammatory mediators (IFN-β, IFN-γ, IL-6 and IL-1β) in blood will be measured before TEAS/STEAS intervention and on days 1, 3 and 5 after the

operation.

- Postoperative complications will be recorded, and the follow-up period will be at least 6 months.

3. Clinical safety evaluation:

Patients were assessed for clinical safety by spontaneous reporting, direct observation by clinicians, or by non-inductive questioning about adverse events.

- **Quality control during operation and anesthesia:**

All surgery will be carried out under general anesthesia, using standardized anesthetic procedures. After surgery, all patients will remain in the post anesthesia care unit and then return to the ward for recovery until discharge. The perioperative management of all patients will be standardized.

- **Postoperative complications will be recorded, and the follow-up period will be at least 6 months.**

Other matters requiring your cooperation
You must come to the hospital according to the follow-up time agreed by the doctor and you (generally medical records, personal treatment diary card, etc.).
Your follow-up is important because your doctor will determine whether the treatment you receive is truly effective and will guide you in a timely manner.

III. Potential benefits of participating in the study

Although there is evidence that transcutaneous electrical acupoint stimulation has a satisfactory effect, it is not guaranteed to be effective for you.
The percutaneous electrical stimulation of acupoints used in this study is not the only method for the treatment of postoperative intestinal paralysis.
If it does not work for you, ask your doctor about alternative treatments that may be available.

IV. Possible adverse reactions, risks, discomfort and inconvenience

The transcutaneous electrical acupoint stimulation used in this study has the advantages of safety, noninvasiveness and small impact on cardiovascular system. No serious adverse reactions have occurred during the treatment.
If you experience any discomfort, illness aggravating or any unexpected circumstances during the study, whether related to the study or not, you should inform your doctor in time. He/she will make a judgment on this and give appropriate medical treatment.
During the study, you need to come to the hospital on time for follow-up visits and

some examinations, which may take up some of your time and may also cause trouble or inconvenience to you.

V. Related expenses

The drugs and related tests used in this study are free of charge. If you have any injury related to this study, the research group will pay your medical expenses. In case of serious adverse events, the research team will pay compensation according to relevant national regulations. For other diseases that you combine at the same time, the treatment and examination required will not be free of charge

VI. Confidentiality of personal information

Your medical records (study records /CRF, lab notes, etc.) will be kept intact in the hospital you visit.
Your doctor will record the results of tests and other tests on your medical record.
Researchers, ethics committees and drug regulators will be allowed to access your medical records.
Any public report on the results of this study will not disclose your personal identity.
We will make every effort to protect the privacy of your personal medical data to the extent permitted by law.
In accordance with medical research ethics, in addition to personal privacy information, test data will be available for public inquiry and sharing, which will be limited to web-based electronic databases, ensuring that no personal privacy information will be disclosed.

VII. How to get more information?

You may raise any questions about this study at any time and get the corresponding answers.
If there is any important new information during the study that may affect your willingness to continue to participate in the study, your doctor will inform you in time.

VIII. You may voluntarily participate in the study or withdraw from the study

Participation in the study is entirely up to you.
You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect the relationship between you and the doctor, nor will it affect your medical treatment or the loss of other benefits.
In your best interests, the doctor or researcher may discontinue your participation in this study at any time during the study.
If you withdraw from the study for any reason, you may be asked about the use of the test drug.
You may also be required to have a laboratory and physical examination if your

doctor deems it necessary.

IX. What should I do now?

Participation in this study is up to you (and your family).
Before you make a decision to participate in the study, please ask your doctor as many questions as possible. Thank you for reading the material. If you decide to participate in this study, please tell your doctor that he/she will arrange all matters related to the study for you. Please keep this information.

Informed consent

Clinical study title: Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial

Project unit: Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

Project partner: _ _ _ _ _ _ _ _ _ _ _ _ _

Project assignment no.: _ _ _ _ _ _ _ _ _ _ _ _ _

Agree with the statement

I have read the above introduction to this study and have the opportunity to discuss and raise questions with my doctor about this study.

All my questions were answered satisfactorily.

I know the possible risks and benefits of participating in this study.

I understand that participation in the study is voluntary and I confirm that I have had sufficient time to consider this and understand that:

- I can consult my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights and interests will not be affected.

I also know that if I drop out of the study, especially if I drop out of the study due to drugs, if I tell the doctor about my condition change and complete the corresponding physical examination and physical and chemical examination, it will be very beneficial to the whole study.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him the truth afterwards.

I agree with the ethics committee of the drug regulatory agency or the sponsor's representative to access my research materials.

I will receive a copy of the signed and dated informed consent form.

In the end, I decided to agree to participate in this study, and promised to follow the doctor's advice as much as possible.

Patient signature: _ _ _ _ _ _ _ _ _ _ _ _ _ _ DATE: _ _ _ _(YYYY-MM-DD)

Contact number: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

I confirm that I have explained to the patient the details of this trial, including its rights and possible benefits and risks, and have given it a copy of the signed informed consent.

Signature of doctor: _ _ _ _ _ _ _ _ _ _ _ _ _ DATE: _ _ _ _(YYYY-MM-DD)

Contact number: _ _ _ _ _ _ _ _ _ _ _ _ _ _

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist for the ReTrain pilot RCT: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&11
	5b	Name and contact information for the trial sponsor	11
	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	11
	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)	9

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&5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5
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)	5
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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8&9
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	7
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)	7

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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	9
	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	9

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	9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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)	8
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	9
	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	9
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
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)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	9
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	9
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	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.