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Electroacupuncture to alleviate postoperative pain after a laparoscopic appendectomy: study protocol for a three-arm, randomised, controlled trial

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Abstract

Introduction: The purpose of this study is to evaluate the efficacy and safety of electroacupuncture (EA) for postoperative pain after laparoscopic appendectomy compared with sham electroacupuncture (SEA) and no acupuncture treatment.

Methods and analysis: This study is a protocol for a three-arm, randomised, patient-assessor-blinded (to the type of acupuncture treatment), controlled, parallel trial. One-hundred thirty-eight participants diagnosed with appendicitis and scheduled for laparoscopic appendectomy will be randomly assigned to the EA group (n = 46), SEA group (n = 46) or control group (n = 46). The EA group will receive acupuncture treatment at both regional and distal acupuncture points with electrostimulation. The SEA group will receive sham acupuncture treatment with mock electrostimulation. Both EA and SEA groups will receive a total of 4 treatments 1 hour pre-operative, 1 hour post-operative and during the morning and afternoon the day after surgery with the same routine post-operative pain control. The control group will receive only routine post-operative pain control. The primary outcome is the 11-point Pain Intensity Numerical Rating Scale (PI-NRS) at 24 hours after surgery. The secondary outcomes are the PI-NRS, analgesic consumption, opioid-related side effects, time to first passing flatus, quality of life and adverse events evaluated 6, 12, 24 and 36 hours and 7 days after surgery.

Ethics and dissemination: The study was planned in accordance with the Helsinki Declaration and the Korean Good Clinical Practice Guidelines to protect the participants and was approved by the institutional review board of Kyung Hee University Medical Center (KMC IRB-1427-02). The results will be disseminated in peer-reviewed journals and presented at international conferences.

Trial registration number: Clinical Research Information Service (KCT0001328)

Keywords: Postoperative pain, Electroacupuncture, Laparoscopy, Appendectomy, Appendicitis, Randomised controlled trial.

Strengths and limitations of this study

- This study is comparing real electroacupuncture with sham electroacupuncute using non-penetrating placebo needles to reduce performance bias.
- The electroacupuncture regimen was already used and validated in the clinic.
- Electroacupuncture treatment is difficult to blind practitioners.

Introduction

Laparoscopic surgery is a general surgical technique with advantages over traditional open surgery such as reduced postoperative pain, shorter hospital stay, faster recovery time, decreased postoperative ileus, reduced scarring and preserved immune function.[1 2] Among various factors, pain is the most important independent predictor of recovery time after laparoscopic surgery.[3] Despite small incision size, laparoscopic surgery still results in substantial postoperative pain in the incision region (somatic pain). Moreover, inflation with carbon dioxide during the laparoscopic procedure induces shoulder pain due to irritation of the phrenic nerve, which is referred to as visceral pain.[4]

Multimodal approaches are beneficial for treating postoperative pain because there are multiple mechanisms of pain after laparoscopic surgery.[3] Opioid analgesics are generally used to control pain with rapid onset of action.[5] However, side effects associated with opioids such as nausea/vomiting, pruritus, and reduction in bowel motility (leading to ileus and constipation) may lead to a delayed hospital discharge.[6] Although other modalities, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors and local anesthetics are also used for postoperative pain, patients who have undergone laparoscopic surgery are generally unsatisfied with pain control and approximately 30–40% patients suffer from moderate pain after hospital discharge.[7]

Electroacupuncture (EA) shows the potential to reduce postoperative pain as an adjuvant therapy to conventional anesthetics. Several clinical trials have shown that preoperative or postoperative EA reduced postoperative pain and analgesic consumption with no significant adverse effects.[8 9 10 11] However, based on a recent systematic review, there is still insufficient evidence to conclude that EA is an effective method for controlling postoperative pain in surgery due to methodological flaws in the studies that have been performed. Moreover, previous acupuncture trials have mostly focused on postoperative pain after open surgery [12] or orthopedic surgery such as total knee arthroplasty [13 14 15] or back surgery.[16] For this reason, despite the potential benefits of EA for postoperative pain, the efficacy and safety of EA for laparoscopic surgery remains to be examined. We aim to evaluate the effects of EA on postoperative pain after laparoscopic appendectomy as a basic, common and representative laparoscopic surgery.

Methods/design

Objective

The aim of this study is to assess the efficacy and safety of EA for postoperative pain through pain intensity, analgesic consumption, opioid-related side effects, time to first passing flatus, quality of life and adverse events after laparoscopic appendectomy compared with sham electroacupuncture (SEA) and no acupuncture treatment.

Design and setting

This study is a single-center, three-arm, equal randomised, patient- and assessor-blinded (to the type of acupuncture treatment), parallel-group, clinical trial conducted in Korea.

Recruitment period

The participants will be recruited from the Kyung Hee University Medical Center in Seoul, Korea. Recruitment is expected to span from April 2015 to March 2017.

Methods of recruitment

A total of 138 participants diagnosed with appendicitis and scheduled for laparoscopic appendectomy through the outpatient department or emergency room will be recruited at the Department of Surgery of Kyung Hee University Medical Center.

Study setting

Oral and written consent will be obtained from patients who are potentially eligible for the study before surgery. A researcher will explain the two types of EA treatments as "classical EA, typically used in Korean medicine clinics" and "non-classical EA, rarely used in Korean medicine clinics."[17] After a patient voluntarily consents to the study, a researcher will screen whether the patient can participate in the study. If the patient satisfies the inclusion/exclusion criteria, a clinical research coordinator (CRC) will contact an independent researcher who has the random number table, and the patient will be randomly allocated into one of three groups (the EA, SEA or control group) at a 1:1:1 allocation ratio. Only the patients assigned to the EA or SEA group will receive the acupuncture treatment 1 hour before the scheduled laparoscopic surgery. The postoperative pain management of all patients will be performed according to the manual of the Department of Surgery of the Kyung Hee University Medical Center. The patients assigned to the EA or SEA groups will receive acupuncture treatments again 1 hour after surgery and the morning and afternoon of the following day. Patients will be discharged on 2 day after sugery, and follow-up visits will be scheduled on 7 (± 3) days after surgery (Figure 1).

Participants

Inclusion criteria

Participants who meet the following conditions will be included: (1) males or females aged 19 to 65 years, (2) diagnosed with appendicitis and scheduled for laparoscopic appendectomy and (3) agreement via written informed consent after being provided with an explanation regarding the purpose and characteristics of this study.

Exclusion criteria

Participants who have experienced or have one or more of the following conditions will be excluded: (1) accompanying complications such as perforated appendicitis or diffuse peritonitis, (2) development of a surgical site infection during the hospital stay, (3) regular use of painkillers or use of other pain relieving medicine on the day of the surgery, (4) cardiovascular disorders such as arrhythmia or use of a pacemaker, (5) received acupuncture treatment within 6 weeks prior to surgery, (6) known hypersensitive reaction to acupuncture treatment or the inability to cooperate with the acupuncture procedure, (7) pregnant, breast-feeding or expecting a pregnancy during the study period and (8) others that have been deemed inadequate for participation by research investigators.

Randomisation and allocation concealment

Enrolled participants will be randomly assigned to EA, SEA or control group (1:1:1). An independent, blinded statistician will generate the block randomisation scheme with block size of 6 using SAS PROC PLAN

The table will be managed by another independent researcher, who is not involved in the recruitment, acupuncture treatment or assessment. The CRC will send the assignment information to the researcher who will conduct random allocation, then the researcher will only provide assignment information to the doctors of Korean medicine (DKMs) that perform the acupuncture treatment. To ensure allocation concealment, the allocated group information will be recorded in an allocation log by the researcher and will not be opened until the data are locked.

Blinding

The participants will be blinded to the type of acupuncture treatment and the assessor, data managers, statisticians and study monitors will be blinded to the allocation. All participants who receive acupuncture will be treated using the Park sham device (PSD; Acuprime, Exeter, UK) regardless of what group they are included in. Moreover, mock EA will be provided with the same pulse sound and lamp light as real EA, so the participants will not be able to predict the allocated group based on the appearance of the acupuncture treatment. The blinding will be maintained until the data are locked. For blinding evaluation, allocation guessing will be assessed immediately after the final treatment. Practitioners and assessors will be instructed to treat the participants according to pre-defined standard operating procedures (SOPs) during the trial to maintain blinding.

Intervention

EA treatment will be conducted by DKMs with more than 6 years of Korean medicine college education and at least 2 years of clinical experience. A total of 4 acupuncture treatments will be performed in the EA and SEA groups. One hour pre-operative and 1 hour post-operative treatments will be performed on the day of the surgery (Day 0). On the day after surgery (Day 1), one treatment will be carried out in the morning (08:00-12:00) and another in the afternoon (13:00-17:00) with at least 4 hours between treatments. Each acupuncture treatment will be performed after the acupuncture points are sterilized with a disposable ethyl alcohol swab and the acupuncture needles will be retained for 30 minutes. Both EA and SEA are performed under the same conditions, except for the needling components,[18] and both groups will be given the same post-operative analgesics in accordance with the predefined protocol and SOPs. This information will be given to the practitioners during workshops before the study begins to ensure standardization of the treatments.

A Park sham needle guide-tube[19 20] (explained below) will be used for both EA and SEA groups to ensure that the patients remain unaware of the differences between the two acupuncture treatments. This will ensure that the patients do not discern any differences between the individualized, real acupuncture and sham acupuncture treatments, although the penetration of the needles will vary between the two groups.

Surgical procedure

The surgical department is part of a tertiary teaching hospital, in which 12 surgeons and 7 residents participate. Laparoscopic appendectomies are performed by surgeons or residents under the supervision of a surgeon. The operation is performed under general anesthesia with the patient in a supine position. A 12-mm trocar for the camera is inserted just below the umbilicus. Two additional 5-mm trocars are inserted in the suprapubic area and right or left lower abdomen. The surgical procedure is performed using standard laparoscopic instruments and in a usual manner including dividing the mesoappendix, ligating the appendix and removing the specimen using a pouch. The 12-mm port site is closed using 2–0 Vicryl sutures and the skin incision is closed with subcuticular sutures.

Electroacupuncture treatment

A total of 4 acupuncture sessions will be performed using 0.25×40-mm disposable sterile acupuncture needles (Dongbang Acupuncture Inc., Chungnam, Republic of Korea). After penetration, *deqi* sensation will be induced using reinforcing-reducing techniques such as rotating and lifting-thrusting methods. An EA device (Partner-1, ITC Co., Ltd. Daejeon, Korea) will be used to apply 2/120 Hz (acupuncture points: bilateral ST36, GB34, LI4, PC6, SP6, LR3) and 120 Hz (acupuncture points: 4 *ashi* points located within a diameter of 5 cm from the incision site) at 80% of the maximum intensity that the patient can endure. Acupuncture point selection (including local abdomen and distal points) and frequency of electrical stimulation were based on traditional acupuncture theory and clinical experience by clinicians. The practitioner will regulate the intensity based on the degree of the twitching of muscles, or by request from the subject, and only one adjustment will be allowed during treatment. In both acupuncture groups, an infrared lamp will be applied to keep the abdominal area of the patients warm during treatment (Figure 2).

Sham electroacupuncture treatment

PSD will be used for SEA treatment. It is a validated sham acupuncture device that consists of two tubes and a sham acupuncture needle.[20] The 'Guide tube' supports the needle as it penetrates the skin vertically. A larger tube called the 'Park tube' is attached to the ring base and allows the 'Guide tube' to move along the 'Park tube.' A silicon base is attached to the skin using double-sided tape.[19] A sham acupuncture needle of PSD is indistinguishable from a real acupuncture needle, but it does not penetrate the skin.

For local abdomen points, SEA treatment will be performed on the abdomen region (2 sites; 3 cm above and 2 cm lateral to the umbilicus). For distal points, both arms (2 sites per arm; 5 cm and 7 cm below the midpoint of the cubital crease) and both legs (2 sites; 7 cm above the medial malleolus and 0.3 cm lateral to the tibia, and 9 cm above the medial malleolus and 0.3 cm lateral to the tibia) will be treated using the PSD and sham acupuncture needles creating a false movement that is similar to the twisting maneuver of acupuncture. No *deqi* sensation will be induced. To simulate electrical stimulation, an electrical stimulating device (Partner-1, ITC Co., Ltd. Daejeon, Korea) will be connected to the needles, but no electrical current will be delivered. The patient will see the light and hear the sound of the pulse generator equal to those of the EA group. The rest of the procedure is equal to that of EA group.

Postoperative pain control

All participants will receive standard postoperative pain control in accordance with the manual of the Department of Surgery at Kyung Hee University Medical Center. The standard postoperative pain control procedure is as follows.

Nefopam hydrochloride (ACUPAN INJ 20 mg/2 ml, Pharmbio Korea, Chungju, Korea)

and Ketorolac tromethamine (KETOCIN INJ 30 mg/ml, Myungmoon Pharm., Seoul, Korea) will be routinely used to control postoperative pain. Nefopam hydrochloride 100 mg and Ketorolac tromethamine 60 mg will be mixed and diluted in 500 ml dextrose and given intravenously twice during the hospitalization period.

If additional pain control is needed, tramadol hydrochloride (TRAMADOL HCL INJ 50 mg/l, Shin Poong Pharm, Seoul, Korea) 50 mg (intramuscular or intravenous injection) will be administered no more than once every 4–5 hours, and the maximum dose of tramadol HCl will not exceed 400 mg per day. The total amount of tramadol use will be recorded by a blinded researcher.

Outcome measures

The details of the outcome measures and time points are shown in Table 1.

Table 1. **Schedule** for tre**atment and outcome measurements**

Period	S	T			F
Day	0	0	1	2	7
Informed consent	●				
Demographic characteristics	●				
Inclusion/exclusion criteria	●				
Conformity assessment	●				
Random allocation		●			
Acupuncture treatment		○	○		
Laparoscopic surgery		●			
Efficacy assessments					
PI-NRS		●	●	●	●
Consumption of analgesics		●	●	●	
Opioid-related side effects		●	●	●	
Time to first passing flatus		●	●	●	
EQ-5D		●	●	●	●
Blinding test				○	
Safety assessment		●	●	●	●

Day 0: surgery day; Day 1: 1 day after surgery; Day 2: 2 days after surgery; Day 7: 7 days after surgery (± 3 days); EQ-5D: EuroQol five dimensions questionnaire; F: follow-up visit; PI-NRS: 11-point Pain Intensity Numerical Rating Scale; S: screening visit; T: treatment period; Acupuncture treatment will be conducted 2 times at Day 1; Efficacy assessments will be conducted 6, 12, 24, 36 and 72 hours after surgery during the treatment period; ● All groups; ○ Both the electroacupuncture and sham acupuncture group.

Primary outcome

The primary outcome is pain intensity in the abdomen region using the 11-point Pain Intensity Numerical Rating Scale (PI-NRS; 0 = no pain and 10 = worst possible pain, 11-point Likert scale) 24 hours after surgery. The PI-NRS has been widely used to assess all kinds of pain and recently it has been validated for measuring postoperative pain intensity.[21] The patients are asked to choose a value that best represents the intensity of pain that they are experiencing at the moment. A written form with numeric values from 0 to 10 is frequently

used as well.

In a previous study, a threshold of NRS ≥ 4 was the cut-off value for distinguishing mild and moderate-to-severe postoperative pain intensity during the first 24 hours after surgery. This value was confirmed using four different methodological approaches.[22]

In cases where additional pain medicine is administered, the assessors will be instructed to evaluate pain intensity 2 hours after drug administration.

Secondary outcomes

The pain intensity of the abdomen region at rest, coughing and overall average will be measured by the PI-NRS at 6, 12, and 36 hours and 7 days after surgery. Moreover, laparoscopy-induced shoulder pain will also be measured 6, 12, 24, 36 hours and 7 days after surgery. We pre-defined the type of improvement for clinical relevance as follows: a 30% reduction in PI-NRS is "minimal improvement"; a 70% reduction in PI-NRS is "much improvement" and a 90% reduction in PI-NRS is "complete improvement."[23 24] Therefore, in this trial, both the absolute and relative score changes will be used to analyse the clinical relevance.

The total amount of analgesic consumption used will be evaluated by an independent researcher blinded to the allocation at 6, 12, 24, and 36 hours and 7 days after surgery.

The opioid-related side effects such as nausea, vomiting, itching and ileus will be measured by PI-NRS at 6, 12, 24, 36 hours and 7 days after surgery.

Time to fisrt passing flutus first after surgery will be checked.

The EuroQol five dimensions questionnaire **(**EQ-5D) will be used to evaluate the quality of life of a patient with postoperative pain at 24 hours and 7 days after surgery. EQ-5D is a standardized tool used to measure health outcomes that includes generic questions about quality of life as it relates to personal health status. EQ-5D is regarded as one of the most appropriate instruments to evaluate patient quality of life after surgery.[25] We will use the Korean version of the EQ-5D.[26]

Safety and adverse events

The practitioners will be instructed to record all unexpected and unintended responses that are not necessarily related to the EA treatment on an adverse event report form. Pain, bruising, bleeding, dizziness, anxiety and infection are some of the adverse events known to be related to EA treatments.[27] A causal relationship between the EA treatment and adverse events will be assessed using a 6-point scale (1 = definitely related, 2 = probably related, 3 = possibly related, 4 = probably not related, 5 = definitely not related and 6 = unknown), and the severity of the adverse events will be scored using a 4-point scale (1 = mild, 2 = moderate, 3 = severe and 4 = extremely severe).

Blinding assessment

At the end of treatment, the patients will guess to which group they were allocated: real or sham EA treatment. The patients will choose one of the following three options based on their personal feelings about the treatment they received: "classical acupuncture typically used in Korean medicine clinics", "non-classical acupuncture, rarely used in Korean medicine clinics" or "do not know".

Sample size calculation

The sample size was calculated based on the mean and standard deviation (SD) of NRS from the previous study.[9] The mean and SD of the EA group (2.1 and 1.2) and those of the

control group (3.2 and 1.8) were used as the expected values in our study. With a 2-sided significance level of 5% (α=0.05) and 80% power (1-β=0.8), 32 patients are required per treatment group. Considering a 30% drop-out rate, a total of 138 patients are needed for the study. The software PASS 12 (NCSS, LLC, Kaysville, Utah, USA) was used for the calculation.

Statistical analysis

Analysis populations

The analysis set will include a full analysis set (FAS), per protocol (PP) set and safety set. The safety set will consist of all randomised participants who received laparoscopic surgery or at least one EA, SEA or NA treatment during the course of the study. The FAS population will consist of all participants in the safety population who are evaluable for the primary outcome. The FAS population will be used as the primary population for all efficacy analyses. The PP population will consist of the all participants included in the FAS population, but will exclude the following: (1) Participants violating any inclusion/exclusion criterion and (2) participants with major protocol violations (e.g., poor compliance (<75% treatment compliance), incorrect completion of study); only sufficiently serious violations will warrant exclusion.

General statistical methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary outcomes. In general, summaries will be presented by the participant population and by treatment groups and/or overall. In general, continuous variable summaries will include the number of participant, mean, SD, median, minimum and maximum and first and third quartiles, as appropriate. Categorical variable summaries will include the frequency and percentage of participants who are in the particular category.

The last observation carried forward (LOCF) method will be used to process the missing data for the primary outcome. All hypothesis testing will be carried out at the 5% (2-sided) significance level. All secondary outcomes are exploratory and therefore no adjustment for multiple testing will be applied.

Statistical software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) by an independent biostatistician. Some analysis may be carried out in R version 3.2.0 or higher (https://www.r-project.org/).

Analysis of demographics and other baseline characteristics

Comparisons of demographic and other baseline characteristics among the three groups will be made using the Chi-square test, Fisher's exact test, Analysis of variance, or Kruskal Wallis test, according to the type of variable.

Primary efficacy outcome analysis

For a confirmatory analysis, an *a priori*-ordered 2-sided null hypothesis will be tested using the Student's *t* test or Wilcoxon rank sum test in a stepwise fashion with a significance level of 5%.[9 28] First, whether EA was more efficacious than no acupuncture treatment in reducing postoperative pain 24 hours after laparoscopic surgery will be investigated and, second (only if the first null hypothesis was rejected), whether EA was more efficacious than

SA will be investigated. All efficacy analyses will use the FAS and the PP population.

Secondary outcome analysis

The secondary outcomes will be evaluated using a Student's *t*-test or Wilcoxon rank sum test for continuous data or chi-squared test or Fisher's exact test for categorical data. These results will be compared with an adjusted result using an Analysis of covariance with the baseline measurements (e.g., PI-NRS before surgery, type of appendicitis (suppurative, exudative, gangrenous or perforated) and age) as a covariate, the treatment group as a fixed effect. Multivariate analysis using a mixed model for repeated measures (MMRM) will be performed for repeated measure outcomes.

Data and safety monitoring

To ensure the quality of the data is in accordance with the pre-determined protocol and SOPs, regular monitoring will be carried out. Monitors will be blinded to the allocation and will examine whether the recruitment procedures and data recording followed the protocol in the case report forms. In case modifications in the study methods are necessary, such as changes to the eligibility criteria, treatment regimens or duration of follow-up, the principal investigator may discuss the issue with independent researchers and statisticians. In case of severe adverse events or crucial issues, the principal investigator will determine whether the events are acceptable or whether it is necessary to change or terminate the trial.

Participant protections and ethics

The study was planned in accordance with the Helsinki Declaration and the Korean Good Clinical Practice Guidelines to protect the participants and was approved by the institutional review board (IRB) of Kyung Hee University Medical Center (KMC IRB-1427-02). The participants will be informed on the potential benefits, risks, alternatives and responsibilities of the study by the researchers during the consent process. To avoid potential adverse events, if there is a patient whom the practitioner considers unsuitable for EA treatment due to an abnormal health condition such as severe pain or vomiting, the treatment will be rescheduled within 2 hours at the practitioner's discretion.

Discussion

The purpose of this study is to evaluate the efficacy and safety of EA for postoperative pain after laparoscopic appendectomy compared with SEA and no acupuncture treatment. When planning an EA study, timing of treatment, treatment points and frequency of electric stimulation should all be carefully considered as these can affect the outcomes of EA. In several EA trials for postoperative pain, it is likely that the results varied because of heterogeneity in the protocol. For this reason, we established a regimented EA protocol based on previous research and our clinical experience. This protocol has been tested and optimized at the Kyung Hee University Medical Center.

While acupuncture is usually applied after the onset of pain in most pain-related conditions such as low back pain, knee pain or headache, acupuncture can be performed before, during or after surgery to alleviate postoperative pain. Most preoperative and postoperative acupuncture trials have shown to be effective for reducing postoperative pain and analgesic consumption. However, intraoperative EA has shown little to no effect on analgesic consumption, though only a few studies have been conducted. Adding the fact that it is realistically difficult to conduct EA during surgery, we planned to perform EA treatments only before and after surgery.

Previous studies have used various acupuncture points that include distal points such as ST36 and LI4,[8 9 11 29] local points around the incision region[29] or a combination of points.[10 30] There have not yet been any studies that directly compare the effects of distal and local points, but one study[29] reported that electrical nerve stimulation significantly reduced postoperative pain in both local and distal point treatment groups. Some studies used only distal points due to fear of potential adverse events by direct electrical stimulation around the incision site, but there has not been any reports of adverse events such as increased pain or infection of the surgical site in studies that have applied electrical stimulation directly near the surgical region.[10 29 30] Therefore, we utilized both local incision points as well as distal acupuncture points to maximize the effect of acupuncture treatment.

There is still a lot of debate on the optimal frequency of EA for pain control. Individual studies have used low, high or mixed frequencies and the effectiveness varies from study to study. In the case of EA at distal acupuncture points, the low frequency of 2 Hz generally releases β-endorphins, and high frequency (over 100 Hz) is known to release dynorphins. Therefore, a mixed combination of both low and high frequencies releases various opioid peptides and creates a synergetic effect that inhibits pain.[27 31] On the other hand, in case of EA around the incision site, high-frequency electrical stimulation (over 100 Hz) stimulates specific afferent nerve fibers instead of releasing endogenous opioid peptide and has been shown to be effective for superficial parietal pain caused by skin incision.[31] For this reason, one study suggested that mixed stimulation of local high frequency and remote low frequency by silver spike point offered the most relief for postoperative pain.[32] As a result, we are using different frequencies from two separate EA devices for local and distal points to maximize the effect of EA.

We expect that if the results show that EA treatment is a safe and effective option for reducing postoperative pain and analgesic consumption, the study may act as evidence to support the inclusion of EA treatment in a future 'enhanced recovery after surgery' program in conjunction with laparoscopic appendectomy.

Abbreviations

COX-2	Cyclooxygenase-2
CRC	Clinical research coordinator
DKMs	Doctors of Korean medicine
EA	Electroacupuncture
EQ-5D	EuroQol five dimensions questionnaire
FAS	Full analysis set
IRB	Institutional review board
LOCF	Last observation carried forward
MMRM	Mixed model for repeated measures
NSAIDs	Nonsteroidal anti-inflammatory drugs
PI-NRS	The 11-point pain intensity numerical rating scale
PP	Per protocol
PSD	Park sham device
SD	Standard deviation
SEA	Sham electroacupuncture
SOPs	Standard operating procedures

Trial status

Recruitment began in April 2015 and will be completed in March 2017. We expect the results will be reported by the end of 2017.

Competing interests
The authors have no competing interests to declare.

Authors' contributions

SL and SJP planned the overall study protocol. SL drafted the manuscript. SL, DN, MK, WSP and SJP participated in critical revision of the manuscript. SJP had the final responsibility for the decision to submit for publication. All of the authors have read and approved the final manuscript.

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Data sharing statement

We will share the data after the trial is finished. The full data set will be available by an author contact when this trial is completed and published.

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Legend

Figure 1. Flow chart of study process.

Figure 2. Acupuncture points of treatment.
(A) The hands will be treated at 2 standard acupuncture points (LI4 and PC6). (B) The legs will be treated at 4 standard acupuncture points (ST36, GB34, SP6 and LR3). (C) The abdomen will be treated 4 *ashi* points located within a diameter of 5 cm from the incision site. A Written consent for the picture was obtained from the pictured subject. Photograph by Seunghoon Lee.

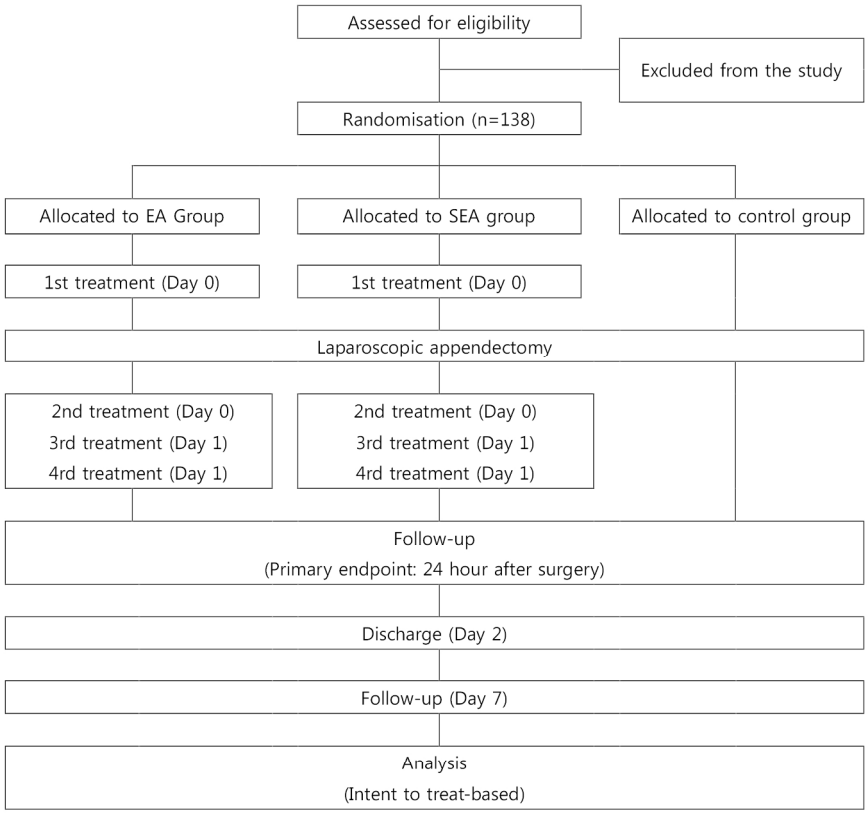

Figure 1. Flow chart of study process.

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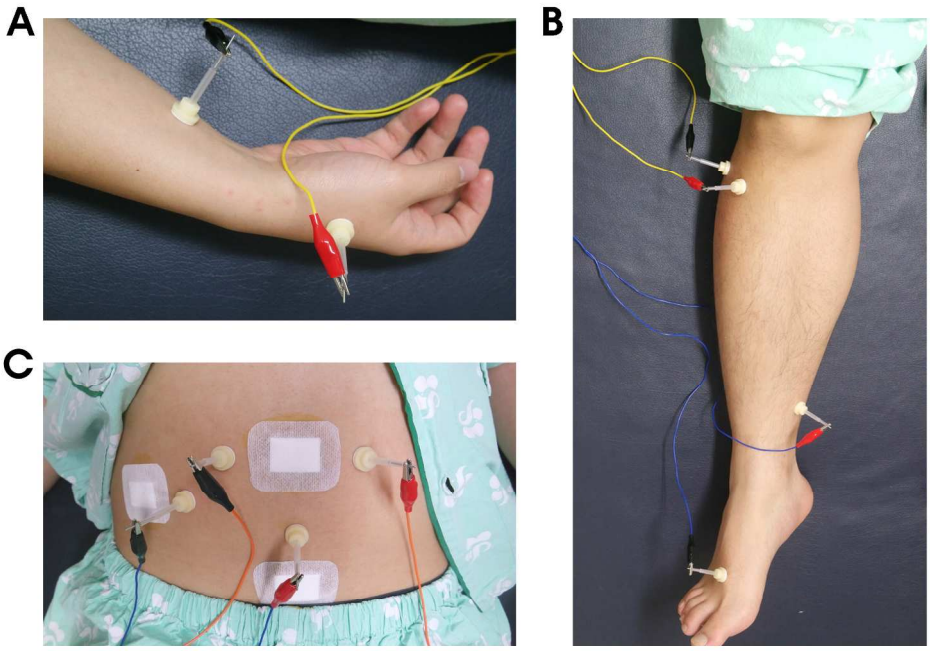

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211x158mm (300 x 300 DPI)

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Electroacupuncture to alleviate postoperative pain after a laparoscopic appendectomy: study protocol for a three-arm, randomised, controlled trial

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Electroacupuncture to alleviate postoperative pain after a laparoscopic appendectomy: study protocol for a three-arm, randomised, controlled trial

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Abstract

Introduction: The purpose of this study is to evaluate the efficacy and safety of electroacupuncture (EA) for postoperative pain after laparoscopic appendectomy compared with sham electroacupuncture (SEA) and no acupuncture treatment.

Methods and analysis: This study is a protocol for a three-arm, randomised, patient-assessor-blinded (to the type of acupuncture treatment), controlled, parallel trial. One-hundred thirty-eight participants diagnosed with appendicitis and scheduled for laparoscopic appendectomy will be randomly assigned to the EA group (n = 46), SEA group (n = 46) or control group (n = 46). The EA group will receive acupuncture treatment at both regional and distal acupuncture points with electrostimulation. The SEA group will receive sham acupuncture treatment with mock electrostimulation. Both EA and SEA groups will receive a total of 4 treatments 1 hour pre-operative, 1 hour post-operative and during the morning and afternoon the day after surgery with the same routine post-operative pain control. The control group will receive only routine post-operative pain control. The primary outcome is the 11-point Pain Intensity Numerical Rating Scale (PI-NRS) at 24 hours after surgery. The secondary outcomes are the PI-NRS, analgesic consumption, opioid-related side effects, time to first passing flatus, quality of life and adverse events evaluated 6, 12, 24 and 36 hours and 7 days after surgery.

Ethics and dissemination: The study was planned in accordance with the Helsinki Declaration and the Korean Good Clinical Practice Guidelines to protect the participants and was approved by the institutional review board of Kyung Hee University Medical Center (KMC IRB-1427-02). The results will be disseminated in peer-reviewed journals and presented at international conferences.

Trial registration number: Clinical Research Information Service (KCT0001328)

Keywords: Postoperative pain, Electroacupuncture, Laparoscopy, Appendectomy, Appendicitis, Randomised controlled trial.

Strengths and limitations of this study

- This study is comparing real electroacupuncture with sham electroacupuncute using non-penetrating placebo needles to reduce performance bias.
- The electroacupuncture regimen was already used and validated in the clinic.
- Electroacupuncture treatment is difficult to blind practitioners.

Introduction

Laparoscopic surgery is a general surgical technique with advantages over traditional open surgery such as reduced postoperative pain, shorter hospital stay, faster recovery time, decreased postoperative ileus, reduced scarring and preserved immune function.[1 2] Among various factors, pain is the most important independent predictor of recovery time after laparoscopic surgery.[3] Despite small incision size, laparoscopic surgery still results in substantial postoperative pain in the incision region (somatic pain). Moreover, inflation with carbon dioxide during the laparoscopic procedure induces shoulder pain due to irritation of the phrenic nerve, which is referred to as visceral pain.[4]

Multimodal approaches are beneficial for treating postoperative pain because there are multiple mechanisms of pain after laparoscopic surgery.[3] Opioid analgesics are generally used to control pain with rapid onset of action.[5] However, side effects associated with opioids such as nausea/vomiting, pruritus, and reduction in bowel motility (leading to ileus and constipation) may lead to a delayed hospital discharge.[6] Although other modalities, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors and local anesthetics are also used for postoperative pain, patients who have undergone laparoscopic surgery are generally unsatisfied with pain control and approximately 30–40% patients suffer from moderate pain after hospital discharge.[7]

Electroacupuncture (EA) shows the potential to reduce postoperative pain as an adjuvant therapy to conventional anesthetics. Several clinical trials have shown that preoperative or postoperative EA reduced postoperative pain and analgesic consumption with no significant adverse effects.[8 9 10 11] However, based on a recent systematic review, there is still insufficient evidence to conclude that EA is an effective method for controlling postoperative pain in surgery due to methodological flaws in the studies that have been performed. Moreover, previous acupuncture trials have mostly focused on postoperative pain after open surgery [12] or orthopedic surgery such as total knee arthroplasty [13 14 15] or back surgery.[16] For this reason, despite the potential benefits of EA for postoperative pain, the efficacy and safety of EA for laparoscopic surgery remains to be examined. We aim to evaluate the effects of EA on postoperative pain after laparoscopic appendectomy as a basic, common and representative laparoscopic surgery.

Methods/design

Objective

The aim of this study is to assess the efficacy and safety of EA for postoperative pain through pain intensity, analgesic consumption, opioid-related side effects, time to first passing flatus, quality of life and adverse events after laparoscopic appendectomy compared with sham electroacupuncture (SEA) and no acupuncture treatment.

Design and setting

This study is a single-center, three-arm, equal randomised, patient- and assessor-blinded (to the type of acupuncture treatment), parallel-group, clinical trial conducted in Korea.

Recruitment period

The participants will be recruited from the Kyung Hee University Medical Center in Seoul, Korea. Recruitment is expected to span from April 2015 to March 2017.

Methods of recruitment

A total of 138 participants diagnosed with appendicitis and scheduled for laparoscopic appendectomy through the outpatient department or emergency room will be recruited at the Department of Surgery of Kyung Hee University Medical Center.

Study setting

Oral and written consent will be obtained from patients who are potentially eligible for the study before surgery. A researcher will explain the two types of EA treatments as "classical EA, typically used in Korean medicine clinics" and "non-classical EA, rarely used in Korean medicine clinics."[17] After a patient voluntarily consents to the study, a researcher will screen whether the patient can participate in the study. If the patient satisfies the inclusion/exclusion criteria, a clinical research coordinator (CRC) will contact an independent researcher who has the random number table, and the patient will be randomly allocated into one of three groups (the EA, SEA or control group) at a 1:1:1 allocation ratio. Only the patients assigned to the EA or SEA group will receive the acupuncture treatment 1 hour before the scheduled laparoscopic surgery. The postoperative pain management of all patients will be performed according to the manual of the Department of Surgery of the Kyung Hee University Medical Center. The patients assigned to the EA or SEA groups will receive acupuncture treatments again 1 hour after surgery and the morning and afternoon of the following day. Patients will be discharged on 2 day after sugery, and follow-up visits will be scheduled on 7 (± 3) days after surgery (Figure 1).

Participants

Inclusion criteria

Participants who meet the following conditions will be included: (1) males or females aged 19 to 65 years, (2) diagnosed with appendicitis and scheduled for laparoscopic appendectomy and (3) agreement via written informed consent after being provided with an explanation regarding the purpose and characteristics of this study.

Exclusion criteria

Participants who have experienced or have one or more of the following conditions will be excluded: (1) accompanying complications such as perforated appendicitis or diffuse peritonitis, (2) development of a surgical site infection during the hospital stay, (3) regular use of painkillers or use of other pain relieving medicine on the day of the surgery, (4) cardiovascular disorders such as arrhythmia or use of a pacemaker, (5) received acupuncture treatment within 6 weeks prior to surgery, (6) known hypersensitive reaction to acupuncture treatment or the inability to cooperate with the acupuncture procedure, (7) pregnant, breast-feeding or expecting a pregnancy during the study period and (8) others that have been deemed inadequate for participation by research investigators.

Randomisation and allocation concealment

Enrolled participants will be randomly assigned to EA, SEA or control group (1:1:1). An independent, blinded statistician will generate the block randomisation scheme with block size of 6 using SAS PROC PLAN

The table will be managed by another independent researcher, who is not involved in the recruitment, acupuncture treatment or assessment. The CRC will send the assignment information to the researcher who will conduct random allocation, then the researcher will only provide assignment information to the doctors of Korean medicine (DKMs) that perform the acupuncture treatment. To ensure allocation concealment, the allocated group information will be recorded in an allocation log by the researcher and will not be opened until the data are locked.

Blinding

The participants will be blinded to the type of acupuncture treatment and the assessor, data managers, statisticians and study monitors will be blinded to the allocation. All participants who receive acupuncture will be treated using the Park sham device (PSD; Acuprime, Exeter, UK) regardless of what group they are included in. Moreover, mock EA will be provided with the same pulse sound and lamp light as real EA, so the participants will not be able to predict the allocated group based on the appearance of the acupuncture treatment. The blinding will be maintained until the data are locked. For blinding evaluation, allocation guessing will be assessed immediately after the final treatment. Practitioners and assessors will be instructed to treat the participants according to pre-defined standard operating procedures (SOPs) during the trial to maintain blinding.

Intervention

EA treatment will be conducted by DKMs with more than 6 years of Korean medicine college education and at least 2 years of clinical experience. A total of 4 acupuncture treatments will be performed in the EA and SEA groups. One hour pre-operative and 1 hour post-operative treatments will be performed on the day of the surgery (Day 0). On the day after surgery (Day 1), one treatment will be carried out in the morning (08:00-12:00) and another in the afternoon (13:00-17:00) with at least 4 hours between treatments. Each acupuncture treatment will be performed after the acupuncture points are sterilized with a disposable ethyl alcohol swab and the acupuncture needles will be retained for 30 minutes. Both EA and SEA are performed under the same conditions, except for the needling components,[18] and both groups will be given the same post-operative analgesics in accordance with the predefined protocol and SOPs. This information will be given to the practitioners during workshops before the study begins to ensure standardization of the treatments.

A Park sham needle guide-tube[19 20] (explained below) will be used for both EA and SEA groups to ensure that the patients remain unaware of the differences between the two acupuncture treatments. This will ensure that the patients do not discern any differences between the individualized, real acupuncture and sham acupuncture treatments, although the penetration of the needles will vary between the two groups.

Surgical procedure

The surgical department is part of a tertiary teaching hospital, in which 12 surgeons and 7 residents participate. Laparoscopic appendectomies are performed by surgeons or residents under the supervision of a surgeon. The operation is performed under general anesthesia with the patient in a supine position. A 12-mm trocar for the camera is inserted just below the umbilicus. Two additional 5-mm trocars are inserted in the suprapubic area and right or left lower abdomen. The surgical procedure is performed using standard laparoscopic instruments and in a usual manner including dividing the mesoappendix, ligating the appendix and removing the specimen using a pouch. The 12-mm port site is closed using 2–0 Vicryl sutures and the skin incision is closed with subcuticular sutures.

Electroacupuncture treatment

A total of 4 acupuncture sessions will be performed using 0.25×40-mm disposable sterile acupuncture needles (Dongbang Acupuncture Inc., Chungnam, Republic of Korea). After penetration, *deqi* sensation will be induced using reinforcing-reducing techniques such as rotating and lifting-thrusting methods. An EA device (Partner-1, ITC Co., Ltd. Daejeon, Korea) will be used to apply 2/120 Hz (acupuncture points: bilateral ST36, GB34, LI4, PC6, SP6, LR3) and 120 Hz (acupuncture points: 4 *ashi* points located within a diameter of 5 cm from the incision site) at 80% of the maximum intensity that the patient can endure. Acupuncture point selection (including local abdomen and distal points) and frequency of electrical stimulation were based on traditional acupuncture theory and clinical experience by clinicians. The practitioner will regulate the intensity based on the degree of the twitching of muscles, or by request from the subject, and only one adjustment will be allowed during treatment. In both acupuncture groups, an infrared lamp will be applied to keep the abdominal area of the patients warm during treatment (Figure 2).

Sham electroacupuncture treatment

PSD will be used for SEA treatment. It is a validated sham acupuncture device that consists of two tubes and a sham acupuncture needle.[20] The 'Guide tube' supports the needle as it penetrates the skin vertically. A larger tube called the 'Park tube' is attached to the ring base and allows the 'Guide tube' to move along the 'Park tube.' A silicon base is attached to the skin using double-sided tape.[19] A sham acupuncture needle of PSD is indistinguishable from a real acupuncture needle, but it does not penetrate the skin.

For local abdomen points, SEA treatment will be performed on the abdomen region (2 sites; 3 cm above and 2 cm lateral to the umbilicus). For distal points, both arms (2 sites per arm; 5 cm and 7 cm below the midpoint of the cubital crease) and both legs (2 sites; 7 cm above the medial malleolus and 0.3 cm lateral to the tibia, and 9 cm above the medial malleolus and 0.3 cm lateral to the tibia) will be treated using the PSD and sham acupuncture needles creating a false movement that is similar to the twisting maneuver of acupuncture. No *deqi* sensation will be induced. To simulate electrical stimulation, an electrical stimulating device (Partner-1, ITC Co., Ltd. Daejeon, Korea) will be connected to the needles, but no electrical current will be delivered. The patient will see the light and hear the sound of the pulse generator equal to those of the EA group. The rest of the procedure is equal to that of EA group.

Postoperative pain control

All participants will receive standard postoperative pain control in accordance with the manual of the Department of Surgery at Kyung Hee University Medical Center. The standard postoperative pain control procedure is as follows.

Nefopam hydrochloride (ACUPAN INJ 20 mg/2 ml, Pharmbio Korea, Chungju, Korea)

and Ketorolac tromethamine (KETOCIN INJ 30 mg/ml, Myungmoon Pharm., Seoul, Korea) will be routinely used to control postoperative pain. Nefopam hydrochloride 100 mg and Ketorolac tromethamine 60 mg will be mixed and diluted in 500 ml dextrose and given intravenously twice during the hospitalization period.

If additional pain control is needed, tramadol hydrochloride (TRAMADOL HCL INJ 50 mg/l, Shin Poong Pharm, Seoul, Korea) 50 mg (intramuscular or intravenous injection) will be administered no more than once every 4–5 hours, and the maximum dose of tramadol HCl will not exceed 400 mg per day. The total amount of tramadol use will be recorded by a blinded researcher.

Outcome measures

The details of the outcome measures and time points are shown in Table 1.

Table 1. **Schedule** for tre**atment and outcome measurements**

Period	S	T			F
Day	0	0	1	2	7
Informed consent	●				
Demographic characteristics	●				
Inclusion/exclusion criteria	●				
Conformity assessment	●				
Random allocation		●			
Acupuncture treatment		○	○		
Laparoscopic surgery		●			
Efficacy assessments					
PI-NRS		●	●	●	●
Consumption of analgesics		●	●	●	
Opioid-related side effects		●	●	●	
Time to first passing flatus		●	●	●	
EQ-5D		●	●	●	●
Blinding test				○	
Safety assessment		●	●	●	●

Day 0: surgery day; Day 1: 1 day after surgery; Day 2: 2 days after surgery; Day 7: 7 days after surgery (± 3 days); EQ-5D: EuroQol five dimensions questionnaire; F: follow-up visit; PI-NRS: 11-point Pain Intensity Numerical Rating Scale; S: screening visit; T: treatment period; Acupuncture treatment will be conducted 2 times at Day 1; Efficacy assessments will be conducted 6, 12, 24, 36 and 72 hours after surgery during the treatment period; ● All groups; ○ Both the electroacupuncture and sham acupuncture group.

Primary outcome

The primary outcome is pain intensity in the abdomen region using the 11-point Pain Intensity Numerical Rating Scale (PI-NRS; 0 = no pain and 10 = worst possible pain, 11-point Likert scale) 24 hours after surgery. The PI-NRS has been widely used to assess all kinds of pain and recently it has been validated for measuring postoperative pain intensity.[21] The patients are asked to choose a value that best represents the intensity of pain that they are experiencing at the moment. A written form with numeric values from 0 to 10 is frequently

used as well.

In a previous study, a threshold of NRS ≥ 4 was the cut-off value for distinguishing mild and moderate-to-severe postoperative pain intensity during the first 24 hours after surgery. This value was confirmed using four different methodological approaches.[22]

In cases where additional pain medicine is administered, the assessors will be instructed to evaluate pain intensity 2 hours after drug administration.

Secondary outcomes

The pain intensity of the abdomen region at rest, coughing and overall average will be measured by the PI-NRS at 6, 12, and 36 hours and 7 days after surgery. Moreover, laparoscopy-induced shoulder pain will also be measured 6, 12, 24, 36 hours and 7 days after surgery. We pre-defined the type of improvement for clinical relevance as follows: a 30% reduction in PI-NRS is "minimal improvement"; a 70% reduction in PI-NRS is "much improvement" and a 90% reduction in PI-NRS is "complete improvement."[23 24] Therefore, in this trial, both the absolute and relative score changes will be used to analyse the clinical relevance.

The total amount of analgesic consumption used will be evaluated by an independent researcher blinded to the allocation at 6, 12, 24, and 36 hours and 7 days after surgery.

The opioid-related side effects such as nausea, vomiting, itching and ileus will be measured by PI-NRS at 6, 12, 24, 36 hours and 7 days after surgery.

Time to fisrt passing flutus first after surgery will be checked.

The EuroQol five dimensions questionnaire **(**EQ-5D) will be used to evaluate the quality of life of a patient with postoperative pain at 24 hours and 7 days after surgery. EQ-5D is a standardized tool used to measure health outcomes that includes generic questions about quality of life as it relates to personal health status. EQ-5D is regarded as one of the most appropriate instruments to evaluate patient quality of life after surgery.[25] We will use the Korean version of the EQ-5D.[26]

Safety and adverse events

The practitioners will be instructed to record all unexpected and unintended responses that are not necessarily related to the EA treatment on an adverse event report form. Pain, bruising, bleeding, dizziness, anxiety and infection are some of the adverse events known to be related to EA treatments.[27] A causal relationship between the EA treatment and adverse events will be assessed using a 6-point scale (1 = definitely related, 2 = probably related, 3 = possibly related, 4 = probably not related, 5 = definitely not related and 6 = unknown), and the severity of the adverse events will be scored using a 4-point scale (1 = mild, 2 = moderate, 3 = severe and 4 = extremely severe).

Blinding assessment

At the end of treatment, the patients will guess to which group they were allocated: real or sham EA treatment. The patients will choose one of the following three options based on their personal feelings about the treatment they received: "classical acupuncture typically used in Korean medicine clinics", "non-classical acupuncture, rarely used in Korean medicine clinics" or "do not know".

Sample size calculation

The sample size was calculated based on the mean and standard deviation (SD) of NRS from the previous study.[9] The mean and SD of the EA group (2.1 and 1.2) and those of the

control group (3.2 and 1.8) were used as the expected values in our study. With a 2-sided significance level of 5% (α=0.05) and 80% power (1-β=0.8), 32 patients are required per treatment group. Considering a 30% drop-out rate, a total of 138 patients are needed for the study. The software PASS 12 (NCSS, LLC, Kaysville, Utah, USA) was used for the calculation.

Statistical analysis

Analysis populations

The analysis set will include a full analysis set (FAS), per protocol (PP) set and safety set. The safety set will consist of all randomised participants who received laparoscopic surgery or at least one EA, SEA or NA treatment during the course of the study. The FAS population will consist of all participants in the safety population who are evaluable for the primary outcome. The FAS population will be used as the primary population for all efficacy analyses. The PP population will consist of the all participants included in the FAS population, but will exclude the following: (1) Participants violating any inclusion/exclusion criterion and (2) participants with major protocol violations (e.g., poor compliance (<75% treatment compliance), incorrect completion of study); only sufficiently serious violations will warrant exclusion.

General statistical methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary outcomes. In general, summaries will be presented by the participant population and by treatment groups and/or overall. In general, continuous variable summaries will include the number of participant, mean, SD, median, minimum and maximum and first and third quartiles, as appropriate. Categorical variable summaries will include the frequency and percentage of participants who are in the particular category.

The last observation carried forward (LOCF) method will be used to process the missing data for the primary outcome. All hypothesis testing will be carried out at the 5% (2-sided) significance level. All secondary outcomes are exploratory and therefore no adjustment for multiple testing will be applied.

Statistical software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) by an independent biostatistician. Some analysis may be carried out in R version 3.2.0 or higher (https://www.r-project.org/).

Analysis of demographics and other baseline characteristics

Comparisons of demographic and other baseline characteristics among the three groups will be made using the Chi-square test, Fisher's exact test, Analysis of variance, or Kruskal Wallis test, according to the type of variable.

Primary efficacy outcome analysis

For a confirmatory analysis, an *a priori*-ordered 2-sided null hypothesis will be tested using the Student's *t* test or Wilcoxon rank sum test in a stepwise fashion with a significance level of 5%.[9 28] First, whether EA was more efficacious than no acupuncture treatment in reducing postoperative pain 24 hours after laparoscopic surgery will be investigated and, second (only if the first null hypothesis was rejected), whether EA was more efficacious than

SA will be investigated. All efficacy analyses will use the FAS and the PP population.

Secondary outcome analysis

The secondary outcomes will be evaluated using a Student's *t*-test or Wilcoxon rank sum test for continuous data or chi-squared test or Fisher's exact test for categorical data. These results will be compared with an adjusted result using an Analysis of covariance with the baseline measurements (e.g., PI-NRS before surgery, type of appendicitis (suppurative, exudative, gangrenous or perforated) and age) as a covariate, the treatment group as a fixed effect. Multivariate analysis using a mixed model for repeated measures (MMRM) will be performed for repeated measure outcomes.

Data and safety monitoring

To ensure the quality of the data is in accordance with the pre-determined protocol and SOPs, regular monitoring will be carried out. Monitors will be blinded to the allocation and will examine whether the recruitment procedures and data recording followed the protocol in the case report forms. In case modifications in the study methods are necessary, such as changes to the eligibility criteria, treatment regimens or duration of follow-up, the principal investigator may discuss the issue with independent researchers and statisticians. In case of severe adverse events or crucial issues, the principal investigator will determine whether the events are acceptable or whether it is necessary to change or terminate the trial.

Participant protections and ethics

The study was planned in accordance with the Helsinki Declaration and the Korean Good Clinical Practice Guidelines to protect the participants and was approved by the institutional review board (IRB) of Kyung Hee University Medical Center (KMC IRB-1427-02). The participants will be informed on the potential benefits, risks, alternatives and responsibilities of the study by the researchers during the consent process. To avoid potential adverse events, if there is a patient whom the practitioner considers unsuitable for EA treatment due to an abnormal health condition such as severe pain or vomiting, the treatment will be rescheduled within 2 hours at the practitioner's discretion.

Discussion

The purpose of this study is to evaluate the efficacy and safety of EA for postoperative pain after laparoscopic appendectomy compared with SEA and no acupuncture treatment. When planning an EA study, timing of treatment, treatment points and frequency of electric stimulation should all be carefully considered as these can affect the outcomes of EA. In several EA trials for postoperative pain, it is likely that the results varied because of heterogeneity in the protocol. For this reason, we established a regimented EA protocol based on previous research and our clinical experience. This protocol has been tested and optimized at the Kyung Hee University Medical Center.

While acupuncture is usually applied after the onset of pain in most pain-related conditions such as low back pain, knee pain or headache, acupuncture can be performed before, during or after surgery to alleviate postoperative pain. Most preoperative and postoperative acupuncture trials have shown to be effective for reducing postoperative pain and analgesic consumption. However, intraoperative EA has shown little to no effect on analgesic consumption, though only a few studies have been conducted. Adding the fact that it is realistically difficult to conduct EA during surgery, we planned to perform EA treatments only before and after surgery.

Previous studies have used various acupuncture points that include distal points such as ST36 and LI4,[8 9 11 29] local points around the incision region[29] or a combination of points.[10 30] There have not yet been any studies that directly compare the effects of distal and local points, but one study[29] reported that electrical nerve stimulation significantly reduced postoperative pain in both local and distal point treatment groups. Some studies used only distal points due to fear of potential adverse events by direct electrical stimulation around the incision site, but there has not been any reports of adverse events such as increased pain or infection of the surgical site in studies that have applied electrical stimulation directly near the surgical region.[10 29 30] Therefore, we utilized both local incision points as well as distal acupuncture points to maximize the effect of acupuncture treatment.

There is still a lot of debate on the optimal frequency of EA for pain control. Individual studies have used low, high or mixed frequencies and the effectiveness varies from study to study. In the case of EA at distal acupuncture points, the low frequency of 2 Hz generally releases β-endorphins, and high frequency (over 100 Hz) is known to release dynorphins. Therefore, a mixed combination of both low and high frequencies releases various opioid peptides and creates a synergetic effect that inhibits pain.[27 31] On the other hand, in case of EA around the incision site, high-frequency electrical stimulation (over 100 Hz) stimulates specific afferent nerve fibers instead of releasing endogenous opioid peptide and has been shown to be effective for superficial parietal pain caused by skin incision.[31] For this reason, one study suggested that mixed stimulation of local high frequency and remote low frequency by silver spike point offered the most relief for postoperative pain.[32] As a result, we are using different frequencies from two separate EA devices for local and distal points to maximize the effect of EA.

We expect that if the results show that EA treatment is a safe and effective option for reducing postoperative pain and analgesic consumption, the study may act as evidence to support the inclusion of EA treatment in a future 'enhanced recovery after surgery' program in conjunction with laparoscopic appendectomy.

Abbreviations

COX-2	Cyclooxygenase-2
CRC	Clinical research coordinator
DKMs	Doctors of Korean medicine
EA	Electroacupuncture
EQ-5D	EuroQol five dimensions questionnaire
FAS	Full analysis set
IRB	Institutional review board
LOCF	Last observation carried forward
MMRM	Mixed model for repeated measures
NSAIDs	Nonsteroidal anti-inflammatory drugs
PI-NRS	The 11-point pain intensity numerical rating scale
PP	Per protocol
PSD	Park sham device
SD	Standard deviation
SEA	Sham electroacupuncture
SOPs	Standard operating procedures

Trial status

Recruitment began in April 2015 and will be completed in March 2017. We expect the results will be reported by the end of 2017.

Competing interests
The authors have no competing interests to declare.

Authors' contributions

SL and SJP planned the overall study protocol. SL drafted the manuscript. SL, DN, MK, WSP and SJP participated in critical revision of the manuscript. SJP had the final responsibility for the decision to submit for publication. All of the authors have read and approved the final manuscript.

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Data sharing statement

We will share the data after the trial is finished. The full data set will be available by an author contact when this trial is completed and published.

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Legend

Figure 1. Flow chart of study process.

Figure 2. Acupuncture points of treatment.
(A) The hands will be treated at 2 standard acupuncture points (LI4 and PC6). (B) The legs will be treated at 4 standard acupuncture points (ST36, GB34, SP6 and LR3). (C) The abdomen will be treated 4 *ashi* points located within a diameter of 5 cm from the incision site. A Written consent for the picture was obtained from the pictured subject. Photograph by Seunghoon Lee.

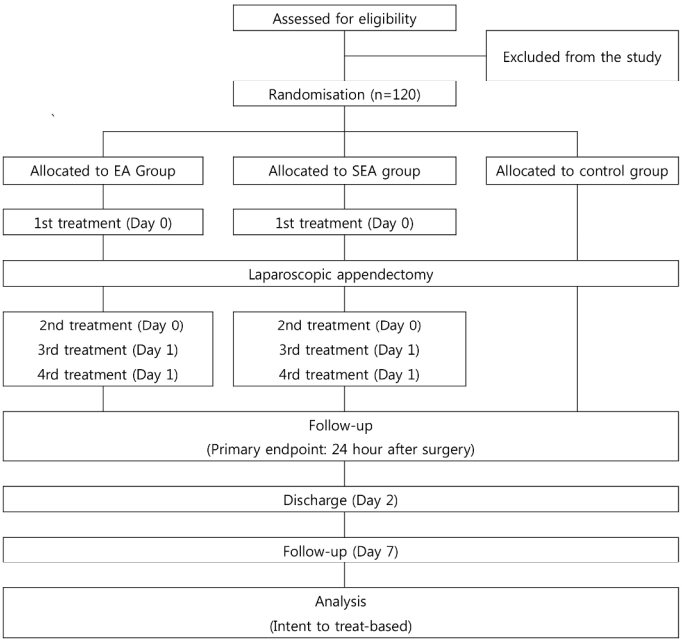

Figure 1. Flow chart of study process.

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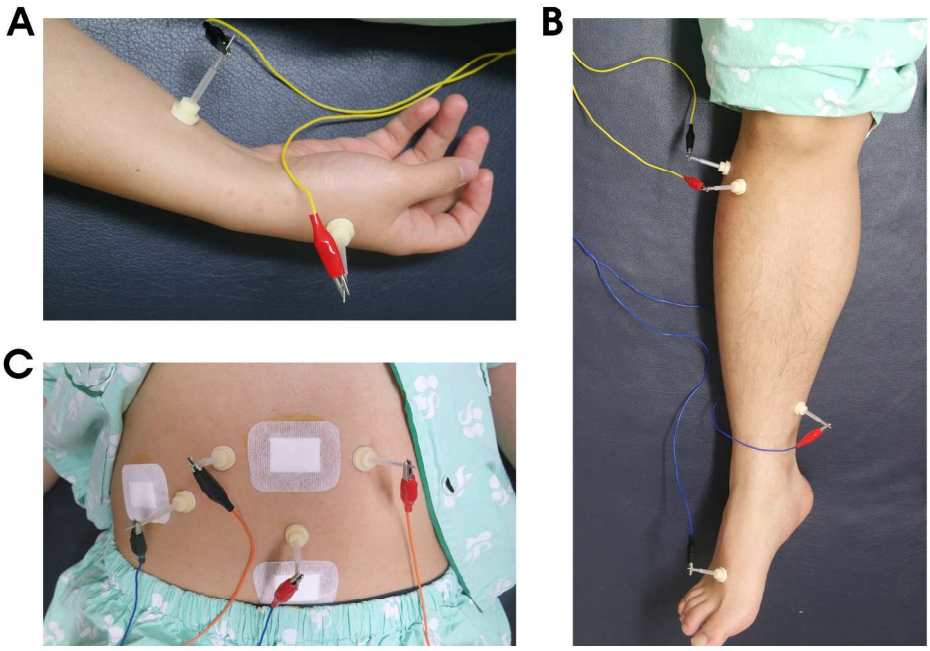

Figure 2. Acupuncture points of treatment.
(A) The hands will be treated at 2 standard acupuncture points (LI4 and PC6). (B) The legs will be treated at 4 standard acupuncture points (ST36, GB34, SP6 and LR3). (C) The abdomen will be treated 4 ashi points located within a diameter of 5 cm from the incision site. A Written consent for the picture was obtained from the pictured subject. Photograph by Seunghoon Lee.

211x158mm (300 x 300 DPI)

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

Section/item	Item No	Description	Reported on page No.
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	Not applicable
Protocol version	3	Date and version identifier	Not applicable
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	Not applicable
	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	Not applicable
	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)	11
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

	6b	Explanation for choice of comparators	Not done
Objectives	7	Specific objectives or hypotheses	4
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	5
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)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	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)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not done
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-9 , Table 1, Figure 1

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	10 (sample size)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Not done
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	Not done

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
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	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
	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)	10-11
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	11
	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	Not done
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	Not done
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11

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)	Not done
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	Not done
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	Not reported
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	Not reported
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	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported
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	Not applicable

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

BMJ Open

Electroacupuncture to alleviate postoperative pain after a laparoscopic appendectomy: study protocol for a three-arm, randomised, controlled trial

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Electroacupuncture to alleviate postoperative pain after a laparoscopic appendectomy: study protocol for a three-arm, randomised, controlled trial

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Abstract

Introduction: The purpose of this study is to evaluate the efficacy and safety of electroacupuncture (EA) for postoperative pain after laparoscopic appendectomy compared with sham electroacupuncture (SEA) and no acupuncture treatment.

Methods and analysis: This study is a protocol for a three-arm, randomised, patient-assessor-blinded (to the type of acupuncture treatment), controlled, parallel trial. One-hundred thirty-eight participants diagnosed with appendicitis and scheduled for laparoscopic appendectomy will be randomly assigned to the EA group (n = 46), SEA group (n = 46) or control group (n = 46). The EA group will receive acupuncture treatment at both regional and distal acupuncture points with electrostimulation. The SEA group will receive sham acupuncture treatment with mock electrostimulation. Both EA and SEA groups will receive a total of 4 treatments 1 hour pre-operative, 1 hour post-operative and during the morning and afternoon the day after surgery with the same routine post-operative pain control. The control group will receive only routine post-operative pain control. The primary outcome is the 11-point Pain Intensity Numerical Rating Scale (PI-NRS) at 24 hours after surgery. The secondary outcomes are the PI-NRS, analgesic consumption, opioid-related side effects, time to first passing flatus, quality of life and adverse events evaluated 6, 12, 24 and 36 hours and 7 days after surgery.

Ethics and dissemination: The study was planned in accordance with the Helsinki Declaration and the Korean Good Clinical Practice Guidelines to protect the participants and was approved by the institutional review board of Kyung Hee University Medical Center (KMC IRB-1427-02). The results will be disseminated in peer-reviewed journals and presented at international conferences.

Trial registration number: Clinical Research Information Service (KCT0001328)

Keywords: Postoperative pain, Electroacupuncture, Laparoscopy, Appendectomy, Appendicitis, Randomised controlled trial.

Strengths and limitations of this study

- This study is comparing real electroacupuncture with sham electroacupuncute using non-penetrating placebo needles to reduce performance bias.
- The electroacupuncture regimen was already used and validated in the clinic.
- Electroacupuncture treatment is difficult to blind practitioners.

Introduction

Laparoscopic surgery is a general surgical technique with advantages over traditional open surgery such as reduced postoperative pain, shorter hospital stay, faster recovery time, decreased postoperative ileus, reduced scarring and preserved immune function.[1 2] Among various factors, pain is the most important independent predictor of recovery time after laparoscopic surgery.[3] Despite small incision size, laparoscopic surgery still results in substantial postoperative pain in the incision region (somatic pain). Moreover, inflation with carbon dioxide during the laparoscopic procedure induces shoulder pain due to irritation of the phrenic nerve, which is referred to as visceral pain.[4]

Multimodal approaches are beneficial for treating postoperative pain because there are multiple mechanisms of pain after laparoscopic surgery.[3] Opioid analgesics are generally used to control pain with rapid onset of action.[5] However, side effects associated with opioids such as nausea/vomiting, pruritus, and reduction in bowel motility (leading to ileus and constipation) may lead to a delayed hospital discharge.[6] Although other modalities, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors and local anesthetics are also used for postoperative pain, patients who have undergone laparoscopic surgery are generally unsatisfied with pain control and approximately 30–40% patients suffer from moderate pain after hospital discharge.[7]

Electroacupuncture (EA) shows the potential to reduce postoperative pain as an adjuvant therapy to conventional anesthetics. Several clinical trials have shown that preoperative or postoperative EA reduced postoperative pain and analgesic consumption with no significant adverse effects.[8 9 10 11] However, based on a recent systematic review, there is still insufficient evidence to conclude that EA is an effective method for controlling postoperative pain in surgery due to methodological flaws in the studies that have been performed. Moreover, previous acupuncture trials have mostly focused on postoperative pain after open surgery [12] or orthopedic surgery such as total knee arthroplasty [13 14 15] or back surgery.[16] For this reason, despite the potential benefits of EA for postoperative pain, the efficacy and safety of EA for laparoscopic surgery remains to be examined. We aim to evaluate the effects of EA on postoperative pain after laparoscopic appendectomy as a basic, common and representative laparoscopic surgery.

Methods/design

Objective

The aim of this study is to assess the efficacy and safety of EA for postoperative pain through pain intensity, analgesic consumption, opioid-related side effects, time to first passing flatus, quality of life and adverse events after laparoscopic appendectomy compared with sham electroacupuncture (SEA) and no acupuncture treatment.

Design and setting

This study is a single-center, three-arm, equal randomised, patient- and assessor-blinded (to the type of acupuncture treatment), parallel-group, clinical trial conducted in Korea.

Recruitment period

The participants will be recruited from the Kyung Hee University Medical Center in Seoul, Korea. Recruitment is expected to span from April 2015 to March 2017.

Methods of recruitment

A total of 138 participants diagnosed with appendicitis and scheduled for laparoscopic appendectomy through the outpatient department or emergency room will be recruited at the Department of Surgery of Kyung Hee University Medical Center.

Study setting

Oral and written consent will be obtained from patients who are potentially eligible for the study before surgery. A researcher will explain the two types of EA treatments as "classical EA, typically used in Korean medicine clinics" and "non-classical EA, rarely used in Korean medicine clinics."[17] After a patient voluntarily consents to the study, a researcher will screen whether the patient can participate in the study. If the patient satisfies the inclusion/exclusion criteria, a clinical research coordinator (CRC) will contact an independent researcher who has the random number table, and the patient will be randomly allocated into one of three groups (the EA, SEA or control group) at a 1:1:1 allocation ratio. Only the patients assigned to the EA or SEA group will receive the acupuncture treatment 1 hour before the scheduled laparoscopic surgery. The postoperative pain management of all patients will be performed according to the manual of the Department of Surgery of the Kyung Hee University Medical Center. The patients assigned to the EA or SEA groups will receive acupuncture treatments again 1 hour after surgery and the morning and afternoon of the following day. Patients will be discharged on 2 day after sugery, and follow-up visits will be scheduled on 7 (± 3) days after surgery (Figure 1).

Participants

Inclusion criteria

Participants who meet the following conditions will be included: (1) males or females aged 19 to 65 years, (2) diagnosed with appendicitis and scheduled for laparoscopic appendectomy and (3) agreement via written informed consent after being provided with an explanation regarding the purpose and characteristics of this study.

Exclusion criteria

Participants who have experienced or have one or more of the following conditions will be excluded: (1) accompanying complications such as perforated appendicitis or diffuse peritonitis, (2) development of a surgical site infection during the hospital stay, (3) regular use of painkillers or use of other pain relieving medicine on the day of the surgery, (4) cardiovascular disorders such as arrhythmia or use of a pacemaker, (5) received acupuncture treatment within 6 weeks prior to surgery, (6) known hypersensitive reaction to acupuncture treatment or the inability to cooperate with the acupuncture procedure, (7) pregnant, breast-feeding or expecting a pregnancy during the study period and (8) others that have been deemed inadequate for participation by research investigators.

Randomisation and allocation concealment

Enrolled participants will be randomly assigned to EA, SEA or control group (1:1:1). An independent, blinded statistician will generate the block randomisation scheme with block size of 6 using SAS PROC PLAN

The table will be managed by another independent researcher, who is not involved in the recruitment, acupuncture treatment or assessment. The CRC will send the assignment information to the researcher who will conduct random allocation, then the researcher will only provide assignment information to the doctors of Korean medicine (DKMs) that perform the acupuncture treatment. To ensure allocation concealment, the allocated group information will be recorded in an allocation log by the researcher and will not be opened until the data are locked.

Blinding

The participants will be blinded to the type of acupuncture treatment and the assessor, data managers, statisticians and study monitors will be blinded to the allocation. All participants who receive acupuncture will be treated using the Park sham device (PSD; Acuprime, Exeter, UK) regardless of what group they are included in. Moreover, mock EA will be provided with the same pulse sound and lamp light as real EA, so the participants will not be able to predict the allocated group based on the appearance of the acupuncture treatment. The blinding will be maintained until the data are locked. For blinding evaluation, allocation guessing will be assessed immediately after the final treatment. Practitioners and assessors will be instructed to treat the participants according to pre-defined standard operating procedures (SOPs) during the trial to maintain blinding.

Intervention

EA treatment will be conducted by DKMs with more than 6 years of Korean medicine college education and at least 2 years of clinical experience. A total of 4 acupuncture treatments will be performed in the EA and SEA groups. One hour pre-operative and 1 hour post-operative treatments will be performed on the day of the surgery (Day 0). On the day after surgery (Day 1), one treatment will be carried out in the morning (08:00-12:00) and another in the afternoon (13:00-17:00) with at least 4 hours between treatments. Each acupuncture treatment will be performed after the acupuncture points are sterilized with a disposable ethyl alcohol swab and the acupuncture needles will be retained for 30 minutes. Both EA and SEA are performed under the same conditions, except for the needling components,[18] and both groups will be given the same post-operative analgesics in accordance with the predefined protocol and SOPs. This information will be given to the practitioners during workshops before the study begins to ensure standardization of the treatments.

A Park sham needle guide-tube[19 20] (explained below) will be used for both EA and SEA groups to ensure that the patients remain unaware of the differences between the two acupuncture treatments. This will ensure that the patients do not discern any differences between the individualized, real acupuncture and sham acupuncture treatments, although the penetration of the needles will vary between the two groups.

Surgical procedure

The surgical department is part of a tertiary teaching hospital, in which 12 surgeons and 7 residents participate. Laparoscopic appendectomies are performed by surgeons or residents under the supervision of a surgeon. The operation is performed under general anesthesia with the patient in a supine position. A 12-mm trocar for the camera is inserted just below the umbilicus. Two additional 5-mm trocars are inserted in the suprapubic area and right or left lower abdomen. The surgical procedure is performed using standard laparoscopic instruments and in a usual manner including dividing the mesoappendix, ligating the appendix and removing the specimen using a pouch. The 12-mm port site is closed using 2–0 Vicryl sutures and the skin incision is closed with subcuticular sutures.

Electroacupuncture treatment

A total of 4 acupuncture sessions will be performed using 0.25×40-mm disposable sterile acupuncture needles (Dongbang Acupuncture Inc., Chungnam, Republic of Korea). After penetration, *deqi* sensation will be induced using reinforcing-reducing techniques such as rotating and lifting-thrusting methods. An EA device (Partner-1, ITC Co., Ltd. Daejeon, Korea) will be used to apply 2/120 Hz (acupuncture points: bilateral ST36, GB34, LI4, PC6, SP6, LR3) and 120 Hz (acupuncture points: 4 *ashi* points located within a diameter of 5 cm from the incision site) at 80% of the maximum intensity that the patient can endure. Acupuncture point selection (including local abdomen and distal points) and frequency of electrical stimulation were based on traditional acupuncture theory and clinical experience by clinicians. The practitioner will regulate the intensity based on the degree of the twitching of muscles, or by request from the subject, and only one adjustment will be allowed during treatment. In both acupuncture groups, an infrared lamp will be applied to keep the abdominal area of the patients warm during treatment (Figure 2).

Sham electroacupuncture treatment

PSD will be used for SEA treatment. It is a validated sham acupuncture device that consists of two tubes and a sham acupuncture needle.[20] The 'Guide tube' supports the needle as it penetrates the skin vertically. A larger tube called the 'Park tube' is attached to the ring base and allows the 'Guide tube' to move along the 'Park tube.' A silicon base is attached to the skin using double-sided tape.[19] A sham acupuncture needle of PSD is indistinguishable from a real acupuncture needle, but it does not penetrate the skin.

For local abdomen points, SEA treatment will be performed on the abdomen region (2 sites; 3 cm above and 2 cm lateral to the umbilicus). For distal points, both arms (2 sites per arm; 5 cm and 7 cm below the midpoint of the cubital crease) and both legs (2 sites; 7 cm above the medial malleolus and 0.3 cm lateral to the tibia, and 9 cm above the medial malleolus and 0.3 cm lateral to the tibia) will be treated using the PSD and sham acupuncture needles creating a false movement that is similar to the twisting maneuver of acupuncture. No *deqi* sensation will be induced. To simulate electrical stimulation, an electrical stimulating device (Partner-1, ITC Co., Ltd. Daejeon, Korea) will be connected to the needles, but no electrical current will be delivered. The patient will see the light and hear the sound of the pulse generator equal to those of the EA group. The rest of the procedure is equal to that of EA group.

Postoperative pain control

All participants will receive standard postoperative pain control in accordance with the manual of the Department of Surgery at Kyung Hee University Medical Center. The standard postoperative pain control procedure is as follows.

Nefopam hydrochloride (ACUPAN INJ 20 mg/2 ml, Pharmbio Korea, Chungju, Korea)

and Ketorolac tromethamine (KETOCIN INJ 30 mg/ml, Myungmoon Pharm., Seoul, Korea) will be routinely used to control postoperative pain. Nefopam hydrochloride 100 mg and Ketorolac tromethamine 60 mg will be mixed and diluted in 500 ml dextrose and given intravenously twice during the hospitalization period.

If additional pain control is needed, tramadol hydrochloride (TRAMADOL HCL INJ 50 mg/l, Shin Poong Pharm, Seoul, Korea) 50 mg (intramuscular or intravenous injection) will be administered no more than once every 4–5 hours, and the maximum dose of tramadol HCl will not exceed 400 mg per day. The total amount of tramadol use will be recorded by a blinded researcher.

Outcome measures

The details of the outcome measures and time points are shown in Table 1.

Table 1. **Schedule** for tre**atment and outcome measurements**

Period	S	T			F
Day	0	0	1	2	7
Informed consent	●				
Demographic characteristics	●				
Inclusion/exclusion criteria	●				
Conformity assessment	●				
Random allocation		●			
Acupuncture treatment		○	○		
Laparoscopic surgery		●			
Efficacy assessments					
PI-NRS		●	●	●	●
Consumption of analgesics		●	●	●	
Opioid-related side effects		●	●	●	
Time to first passing flatus		●	●	●	
EQ-5D		●	●	●	●
Blinding test				○	
Safety assessment		●	●	●	●

Day 0: surgery day; Day 1: 1 day after surgery; Day 2: 2 days after surgery; Day 7: 7 days after surgery (± 3 days); EQ-5D: EuroQol five dimensions questionnaire; F: follow-up visit; PI-NRS: 11-point Pain Intensity Numerical Rating Scale; S: screening visit; T: treatment period; Acupuncture treatment will be conducted 2 times at Day 1; Efficacy assessments will be conducted 6, 12, 24, 36 and 72 hours after surgery during the treatment period; ● All groups; ○ Both the electroacupuncture and sham acupuncture group.

Primary outcome

The primary outcome is pain intensity in the abdomen region using the 11-point Pain Intensity Numerical Rating Scale (PI-NRS; 0 = no pain and 10 = worst possible pain, 11-point Likert scale) 24 hours after surgery. The PI-NRS has been widely used to assess all kinds of pain and recently it has been validated for measuring postoperative pain intensity.[21] The patients are asked to choose a value that best represents the intensity of pain that they are experiencing at the moment. A written form with numeric values from 0 to 10 is frequently

used as well.

In a previous study, a threshold of NRS ≥ 4 was the cut-off value for distinguishing mild and moderate-to-severe postoperative pain intensity during the first 24 hours after surgery. This value was confirmed using four different methodological approaches.[22]

In cases where additional pain medicine is administered, the assessors will be instructed to evaluate pain intensity 2 hours after drug administration.

Secondary outcomes

The pain intensity of the abdomen region at rest, coughing and overall average will be measured by the PI-NRS at 6, 12, and 36 hours and 7 days after surgery. Moreover, laparoscopy-induced shoulder pain will also be measured 6, 12, 24, 36 hours and 7 days after surgery. We pre-defined the type of improvement for clinical relevance as follows: a 30% reduction in PI-NRS is "minimal improvement"; a 70% reduction in PI-NRS is "much improvement" and a 90% reduction in PI-NRS is "complete improvement."[23 24] Therefore, in this trial, both the absolute and relative score changes will be used to analyse the clinical relevance.

The total amount of analgesic consumption used will be evaluated by an independent researcher blinded to the allocation at 6, 12, 24, and 36 hours and 7 days after surgery.

The opioid-related side effects such as nausea, vomiting, itching and ileus will be measured by PI-NRS at 6, 12, 24, 36 hours and 7 days after surgery.

Time to fisrt passing flutus first after surgery will be checked.

The EuroQol five dimensions questionnaire **(**EQ-5D) will be used to evaluate the quality of life of a patient with postoperative pain at 24 hours and 7 days after surgery. EQ-5D is a standardized tool used to measure health outcomes that includes generic questions about quality of life as it relates to personal health status. EQ-5D is regarded as one of the most appropriate instruments to evaluate patient quality of life after surgery.[25] We will use the Korean version of the EQ-5D.[26]

Safety and adverse events

The practitioners will be instructed to record all unexpected and unintended responses that are not necessarily related to the EA treatment on an adverse event report form. Pain, bruising, bleeding, dizziness, anxiety and infection are some of the adverse events known to be related to EA treatments.[27] A causal relationship between the EA treatment and adverse events will be assessed using a 6-point scale (1 = definitely related, 2 = probably related, 3 = possibly related, 4 = probably not related, 5 = definitely not related and 6 = unknown), and the severity of the adverse events will be scored using a 4-point scale (1 = mild, 2 = moderate, 3 = severe and 4 = extremely severe).

Blinding assessment

At the end of treatment, the patients will guess to which group they were allocated: real or sham EA treatment. The patients will choose one of the following three options based on their personal feelings about the treatment they received: "classical acupuncture typically used in Korean medicine clinics", "non-classical acupuncture, rarely used in Korean medicine clinics" or "do not know".

Sample size calculation

The sample size was calculated based on the mean and standard deviation (SD) of NRS from the previous study.[9] The mean and SD of the EA group (2.1 and 1.2) and those of the

control group (3.2 and 1.8) were used as the expected values in our study. With a 2-sided significance level of 5% (α=0.05) and 80% power (1-β=0.8), 32 patients are required per treatment group. Considering a 30% drop-out rate, a total of 138 patients are needed for the study. The software PASS 12 (NCSS, LLC, Kaysville, Utah, USA) was used for the calculation.

Statistical analysis

Analysis populations

The analysis set will include a full analysis set (FAS), per protocol (PP) set and safety set. The safety set will consist of all randomised participants who received laparoscopic surgery or at least one EA, SEA or NA treatment during the course of the study. The FAS population will consist of all participants in the safety population who are evaluable for the primary outcome. The FAS population will be used as the primary population for all efficacy analyses. The PP population will consist of the all participants included in the FAS population, but will exclude the following: (1) Participants violating any inclusion/exclusion criterion and (2) participants with major protocol violations (e.g., poor compliance (<75% treatment compliance), incorrect completion of study); only sufficiently serious violations will warrant exclusion.

General statistical methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary outcomes. In general, summaries will be presented by the participant population and by treatment groups and/or overall. In general, continuous variable summaries will include the number of participant, mean, SD, median, minimum and maximum and first and third quartiles, as appropriate. Categorical variable summaries will include the frequency and percentage of participants who are in the particular category.

The last observation carried forward (LOCF) method will be used to process the missing data for the primary outcome. All hypothesis testing will be carried out at the 5% (2-sided) significance level. All secondary outcomes are exploratory and therefore no adjustment for multiple testing will be applied.

Statistical software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) by an independent biostatistician. Some analysis may be carried out in R version 3.2.0 or higher (https://www.r-project.org/).

Analysis of demographics and other baseline characteristics

Comparisons of demographic and other baseline characteristics among the three groups will be made using the Chi-square test, Fisher's exact test, Analysis of variance, or Kruskal Wallis test, according to the type of variable.

Primary efficacy outcome analysis

For a confirmatory analysis, an *a priori*-ordered 2-sided null hypothesis will be tested using the Student's *t* test or Wilcoxon rank sum test in a stepwise fashion with a significance level of 5%.[9 28] First, whether EA was more efficacious than no acupuncture treatment in reducing postoperative pain 24 hours after laparoscopic surgery will be investigated and, second (only if the first null hypothesis was rejected), whether EA was more efficacious than

SA will be investigated. All efficacy analyses will use the FAS and the PP population.

Secondary outcome analysis

The secondary outcomes will be evaluated using a Student's *t*-test or Wilcoxon rank sum test for continuous data or chi-squared test or Fisher's exact test for categorical data. These results will be compared with an adjusted result using an Analysis of covariance with the baseline measurements (e.g., PI-NRS before surgery, type of appendicitis (suppurative, exudative, gangrenous or perforated) and age) as a covariate, the treatment group as a fixed effect. Multivariate analysis using a mixed model for repeated measures (MMRM) will be performed for repeated measure outcomes.

Data and safety monitoring

To ensure the quality of the data is in accordance with the pre-determined protocol and SOPs, regular monitoring will be carried out. Monitors will be blinded to the allocation and will examine whether the recruitment procedures and data recording followed the protocol in the case report forms. In case modifications in the study methods are necessary, such as changes to the eligibility criteria, treatment regimens or duration of follow-up, the principal investigator may discuss the issue with independent researchers and statisticians. In case of severe adverse events or crucial issues, the principal investigator will determine whether the events are acceptable or whether it is necessary to change or terminate the trial.

Ethics and dissemination

The study was planned in accordance with the Helsinki Declaration and the Korean Good Clinical Practice Guidelines to protect the participants and was approved by the institutional review board (IRB) of Kyung Hee University Medical Center (KMC IRB-1427-02). The participants will be informed on the potential benefits, risks, alternatives and responsibilities of the study by the researchers during the consent process. To avoid potential adverse events, if there is a patient whom the practitioner considers unsuitable for EA treatment due to an abnormal health condition such as severe pain or vomiting, the treatment will be rescheduled within 2 hours at the practitioner's discretion. The findings will be disseminated in peer-reviewed journals and conference presentations.

Discussion

The purpose of this study is to evaluate the efficacy and safety of EA for postoperative pain after laparoscopic appendectomy compared with SEA and no acupuncture treatment. When planning an EA study, timing of treatment, treatment points and frequency of electric stimulation should all be carefully considered as these can affect the outcomes of EA. In several EA trials for postoperative pain, it is likely that the results varied because of heterogeneity in the protocol. For this reason, we established a regimented EA protocol based on previous research and our clinical experience. This protocol has been tested and optimized at the Kyung Hee University Medical Center.

While acupuncture is usually applied after the onset of pain in most pain-related conditions such as low back pain, knee pain or headache, acupuncture can be performed before, during or after surgery to alleviate postoperative pain. Most preoperative and postoperative acupuncture trials have shown to be effective for reducing postoperative pain and analgesic consumption. However, intraoperative EA has shown little to no effect on analgesic consumption, though only a few studies have been conducted. Adding the fact that it is realistically difficult to conduct EA during surgery, we planned to perform EA treatments only before and after surgery.

Previous studies have used various acupuncture points that include distal points such as ST36 and LI4,[8 9 11 29] local points around the incision region[29] or a combination of points.[10 30] There have not yet been any studies that directly compare the effects of distal and local points, but one study[29] reported that electrical nerve stimulation significantly reduced postoperative pain in both local and distal point treatment groups. Some studies used only distal points due to fear of potential adverse events by direct electrical stimulation around the incision site, but there has not been any reports of adverse events such as increased pain or infection of the surgical site in studies that have applied electrical stimulation directly near the surgical region.[10 29 30] Therefore, we utilized both local incision points as well as distal acupuncture points to maximize the effect of acupuncture treatment.

There is still a lot of debate on the optimal frequency of EA for pain control. Individual studies have used low, high or mixed frequencies and the effectiveness varies from study to study. In the case of EA at distal acupuncture points, the low frequency of 2 Hz generally releases β-endorphins, and high frequency (over 100 Hz) is known to release dynorphins. Therefore, a mixed combination of both low and high frequencies releases various opioid peptides and creates a synergetic effect that inhibits pain.[27 31] On the other hand, in case of EA around the incision site, high-frequency electrical stimulation (over 100 Hz) stimulates specific afferent nerve fibers instead of releasing endogenous opioid peptide and has been shown to be effective for superficial parietal pain caused by skin incision.[31] For this reason, one study suggested that mixed stimulation of local high frequency and remote low frequency by silver spike point offered the most relief for postoperative pain.[32] As a result, we are using different frequencies from two separate EA devices for local and distal points to maximize the effect of EA.

We expect that if the results show that EA treatment is a safe and effective option for reducing postoperative pain and analgesic consumption, the study may act as evidence to support the inclusion of EA treatment in a future 'enhanced recovery after surgery' program in conjunction with laparoscopic appendectomy.

Abbreviations

COX-2	Cyclooxygenase-2
CRC	Clinical research coordinator
DKMs	Doctors of Korean medicine
EA	Electroacupuncture
EQ-5D	EuroQol five dimensions questionnaire
FAS	Full analysis set
IRB	Institutional review board
LOCF	Last observation carried forward
MMRM	Mixed model for repeated measures
NSAIDs	Nonsteroidal anti-inflammatory drugs
PI-NRS	The 11-point pain intensity numerical rating scale
PP	Per protocol
PSD	Park sham device
SD	Standard deviation
SEA	Sham electroacupuncture
SOPs	Standard operating procedures

Trial status

Recruitment began in April 2015 and will be completed in March 2017. We expect the results will be reported by the end of 2017.

Competing interests
The authors have no competing interests to declare.

Authors' contributions

SL and SJP planned the overall study protocol. SL drafted the manuscript. SL, DN, MK, WSP and SJP participated in critical revision of the manuscript. SJP had the final responsibility for the decision to submit for publication. All of the authors have read and approved the final manuscript.

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Data sharing statement

We will share the data after the trial is finished. The full data set will be available by an author contact when this trial is completed and published.

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Legend

Figure 1. Flow chart of study process.

Figure 2. Acupuncture points of treatment.
(A) The hands will be treated at 2 standard acupuncture points (LI4 and PC6). (B) The legs will be treated at 4 standard acupuncture points (ST36, GB34, SP6 and LR3). (C) The abdomen will be treated 4 *ashi* points located within a diameter of 5 cm from the incision site. A Written consent for the picture was obtained from the pictured subject. Photograph by Seunghoon Lee.

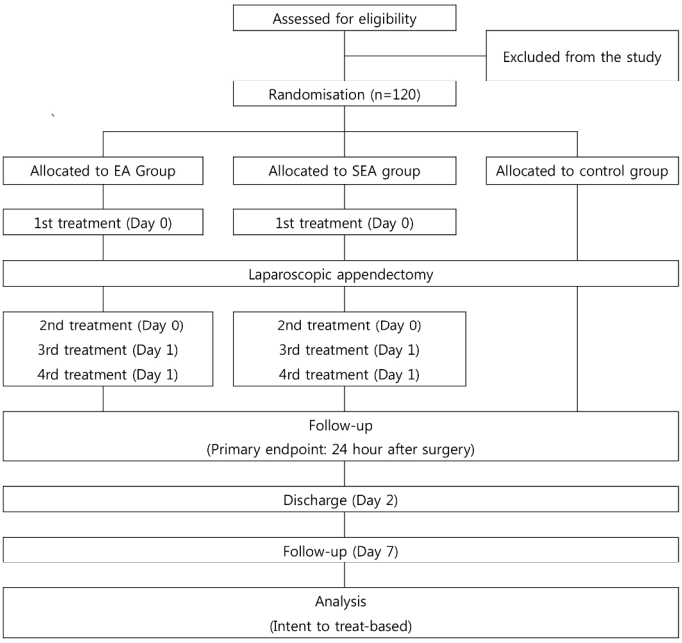

Figure 1. Flow chart of study process.

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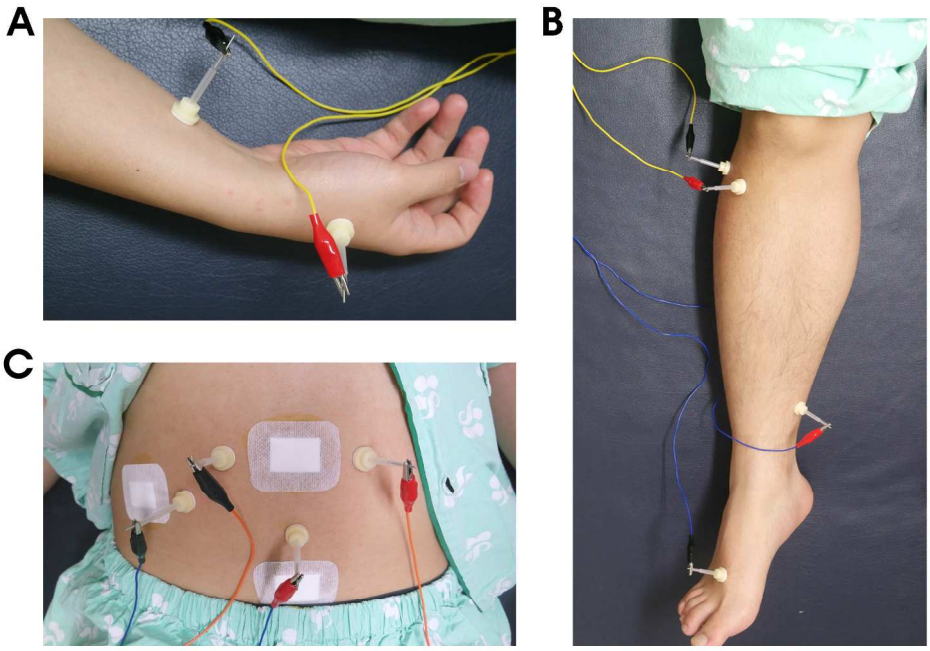

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(A) The hands will be treated at 2 standard acupuncture points (LI4 and PC6). (B) The legs will be treated at 4 standard acupuncture points (ST36, GB34, SP6 and LR3). (C) The abdomen will be treated 4 ashi points located within a diameter of 5 cm from the incision site. A Written consent for the picture was obtained from the pictured subject. Photograph by Seunghoon Lee.

211x158mm (300 x 300 DPI)

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

Section/item	Item No	Description	Reported on page No.
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	Not applicable
Protocol version	3	Date and version identifier	Not applicable
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	Not applicable
	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	Not applicable
	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)	11
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

	6b	Explanation for choice of comparators	Not done
Objectives	7	Specific objectives or hypotheses	4
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	5
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)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	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)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not done
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-9 , Table 1, Figure 1

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	10 (sample size)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Not done
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	Not done

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
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	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
	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)	10-11
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	11
	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	Not done
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	Not done
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11

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)	Not done
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	Not done
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	Not reported
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	Not reported
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	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported
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	Not applicable

*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.