



Identifying the optimal timing of preoperative electroacupuncture for postoperative nausea and vomiting and pain in patients undergoing laparoscopic gynecologic surgery: Study protocol for a randomized controlled trial

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ABSTRACT

Introduction: Electroacupuncture (EA) has been shown to have antiemetic and analgesic effects; however, optimal timing for the therapy is unclear. Our study aims firstly to investigate the effectiveness and safety of preoperative EA, delivered 24 h before surgery, on postoperative nausea and vomiting (PONV) and postoperative pain in patients undergoing gynecologic laparoscopic surgery; and secondly to identify the optimal timing and dose of stimulation of preoperative EA for preventing PONV and postoperative pain.

Methods: This is a single-center, randomized, controlled, four-arm clinical trial. Participants who meet the selection criteria will be randomly assigned to one of the following four groups: Group 1 (EA delivered 24 h before surgery, n = 103), Group 2 (EA delivered 30 min before surgery, n = 103), Group 3 (EA delivered both 24 h before, and 30 min before surgery, n = 103), Group 4 (usual care, n = 103). All groups will receive routine treatment for PONV and pain. EA will be delivered at bilateral Neiguan (PC6) and Zusanli (ST36). The primary outcomes are the incidence of postoperative nausea (PON) and postoperative vomiting (POV), and pain scores at 24 h after the operation. Secondary outcomes include the incidence of PON and POV, and pain scores at 6 h, 48 h and 72 h after the operation, also the severity of PON and POV, consumption of opioid medications, Quality of Recovery-15 (QoR-15), days in hospital and time to passage of first flatus. The assessor and the treating anesthetists will be blinded from group allocation. Participants in the three EA groups are unaware of the purpose of the study.

Discussion: An understanding of optimal timing and dosage of preoperative acupuncture will facilitate the implementation of this non-drug therapy and contribute to the overall improvement of post-surgical care.

1. Introduction

Postoperative nausea and vomiting (PONV) is a common complication of anesthesia and surgery. The incidence of PONV after general anesthesia is up to 30% when inhalational anesthetics are used with no prophylaxis [1]. In a subset of high risk patients, the incidence is as great as 70–80% [2,3]. Unresolved PONV may cause electrolyte imbalance and tearing of sutures [4,5]. Furthermore, severe PONV often

results in delayed recovery, and increased costs to individuals and to the health care system [6,7]. Currently, the standard treatments for PONV are pharmaceutical interventions. Although modern antiemetic drugs are effective, their adverse effects such as the QT prolongation, visual disturbances, dry mouth, and dizziness are potentially serious and cannot be ignored [8,9]. At present, no therapy is absolutely effective in preventing PONV, especially in high risk patients [4].

As a non-pharmacological technique, acupuncture plays an

Abbreviations: PONV, postoperative nausea and vomiting; TCM, traditional Chinese medicine; EA, electroacupuncture; PC6, Neiguan; ST36, Zusanli; BIS, bispectral index; PACU, post-anesthesia care unit; QoR-15, quality of recovery-15; TENS, transcutaneous electrical nerve stimulation

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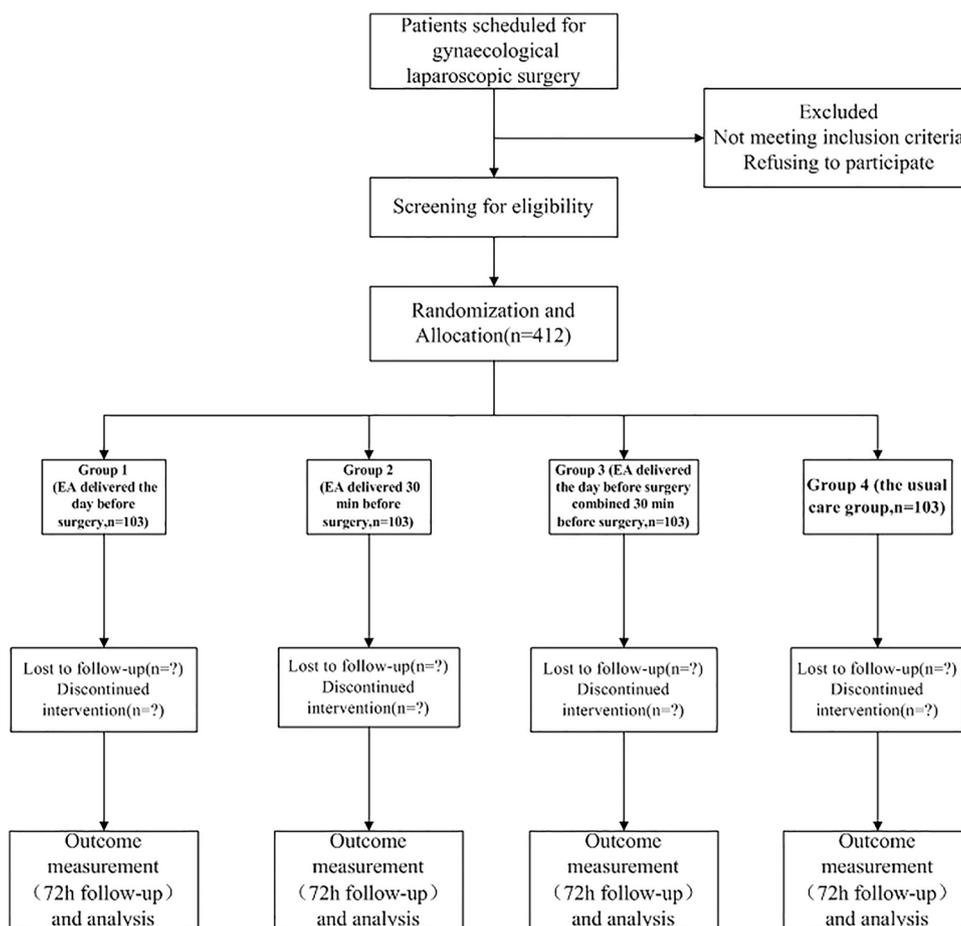


Fig. 1. Flow chart of participants in the study.

EA: Electroacupuncture. Timeline of measurements includes: Baseline, 24 h pre-operative, 30 min pre-operative, 6 h, 24 h, 48 h and 72 h postoperative.

important role in postoperative care [10]. Lee et al. [11] found moderate-quality evidence showing an equivalent effect between Neiguan (PC6) acupoint stimulation and antiemetic drugs for preventing PONV. Acupuncture for PONV is effective, safe and low cost, and is the only non-pharmacological intervention recommended in the international management guidelines for PONV [8,12,13]. Recent systemic reviews concluded acupuncture improved postoperative pain and reduced postoperative opioid medication use [14,15]. Postoperative opioids use enhances the incidence of PONV. Acupuncture may have multi-facet effects on PONV and postoperative pain, and presents itself an ideal non-pharmacological intervention for postoperative care [16]. To implement acupuncture for PONV and postoperative pain, it is essential to identify the optimal protocol of acupuncture as a prophylactic and as a treatment. One of the key unresolved clinical questions is the most effective timing of acupuncture.

Among trials of acupuncture for postoperative nausea and vomiting, PC6 is the most commonly used point [12]; whereas Hegu (LI4), PC6 and Zusanli(ST36) are commonest points used to pre-empt or reduce post-operative pain [17]. A study found that stimulation of these three points before anaesthesia significantly reduced intra-operative remifentanyl consumption and alleviated postoperative complication in patients undergoing sinusotomy [18]. According to traditional Chinese medicine theory (TCM), surgery impacts on the balanced state of the human body, disturbs the movement of both qi and blood, reverses the direction of stomach qi, and causes nausea and vomiting [19]. Neiguan (PC6) on the wrist could regulate the function of the stomach, correct the adverse flow of qi, and is an effective acupoint in preventing nausea and vomiting [19]. Zusanli (ST36) on the anterior tibia helps adjust qi and blood, food transport and gastrointestinal activity [12]. Stimulation

of PC6 and ST36 together could produce a stronger antiemetic effect than stimulating either acupoint alone [20].

The optimal timing of acupuncture for PONV is unknown. A previous meta-analysis reported that it is ineffective when acupuncture was delivered intraoperatively to anesthetized patients [21]. The majority of acupuncture studies delivered electrical stimulation to acupoint PC6 approximately 30 min prior to induction of anesthesia [22–24] and PONV was effectively prevented [10,25,26]. This mode of delivery has its disadvantages due to limited time before surgery, and patient anxiety about the coming operation. Based on the theory of TCM, delivering acupuncture the day before the surgery has advantages since the patients are more relaxed, and are likely to benefit from acupuncture. Coura and colleagues [27] reported that acupuncture one day prior to surgery produced better pain reduction than acupuncture given 30 min prior to the surgery. Our pilot study of 40 patients undergoing gynecologic laparoscopic surgery showed that it was feasible and safe to deliver a single session of electroacupuncture (EA) treatment within 24 h preoperatively. When compared with the standard care group, preoperative EA reduced postoperative pain by 20%, and PONV by 15% [16].

Another unresolved question about the optimal acupuncture protocol for PONV and postoperative pain is the number of treatment sessions required. Few studies have examined the dosage effect, i.e. the number of treatment sessions of acupuncture. Ruan and colleagues found that acupuncture had a cumulative effect for chronic insomnia, and a sufficient number of treatments, in that case two sessions were needed before the effect could be demonstrated [28]. The number of perioperative EA sessions for PONV prevention and postoperative pain has not been examined in the previous literature.

In this RCT, we aim to: 1) investigate the effects of preoperative EA on PONV and postoperative pain in patients undergoing gynecologic laparoscopic surgery when compared with usual care; 2) identify the optimal timing and dose of stimulation of EA for the prophylaxis of PONV and postoperative pain after gynecologic laparoscopic surgery.

2. Methods

2.1. Design

This is a single-center, randomized, four-arm clinical trial. The trial protocol adheres to CONSORT and STRICTA guidelines, and has been approved by the Human Research Ethics Committee of the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine (2016NL-019-02). It has been registered with the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/showproj.aspx?proj=16248>, ChiCTR-INR-16010035). The trial is being conducted at the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine between December 2016 and December 2019, Nanjing, Jiangsu Province, China, and in accordance with the Declaration of Helsinki (version Fortaleza, 2010). Written informed consent is obtained from each patient prior to their participation in the study. The procedure of the trial is presented in Fig. 1.

2.2. Power and sample size calculation

Using the data from our pilot study [16], we calculated that the sample size needed is 75 per group to detect a 15% reduction in vomiting with 80% power using the following formula:

$$n = \frac{(1.96\sqrt{2pq} + 0.8416\sqrt{p_0q_0 + p_1q_1})^2}{(p_1 - p_0)^2}$$

$$(q_0 = 1 - p_0, q_1 = 1 - p_1, p = \frac{p_0 + p_1}{2}, q = 1 - p)$$

n represents the sample size of the groups with EA being delivered the day before surgery and the usual care, and p_0 and p_1 represent the incidence of vomiting in the two groups, respectively. Considering a 35% potential loss due to change of surgery and attrition, we will need 103 patients per group, or a total of 412 patients.

2.3. Selection criteria inclusion criteria

Participants who fulfill the following criteria will be included:

- 1) female patients aged between 18–50 years old, ASA physical status class I or II;
- 2) undergoing elective gynecological laparoscopic surgery under general anesthesia with an operating time shorter than 3 h;
- 3) volunteering to participate in this study and signing a consent form;
- 4) willing to receive acupuncture.

Exclusion criteria

Participants that meet any of the following criteria will be excluded:

- 1) cognitive impairment, psychiatric, or neurological disease;
- 2) difficulty in communicating or expressing themselves ;
- 3) known allergy to the drugs used in the study;
- 4) implantation of a cardiac pacemaker, cardioverter, or defibrillator;
- 5) rash or local infection over the acupoint stimulation skin area.

2.4. Randomization and blinding

Written informed consent will be obtained from each participant. Participants who meet all selection criteria will be recruited and randomly assigned to one of the following four groups: group 1 (EA

delivered the day before surgery, $n = 103$), group 2 (EA delivered 30 min before surgery, $n = 103$), group 3 (EA delivered the day before surgery combined 30 min before surgery, $n = 103$), group 4 (the usual care group, $n = 103$). The randomization sequence will be generated by an independent researcher using a random number table. Each number will be printed on a piece of paper, and then will be put in an opaque sealed envelope. All envelopes will be stored in a locked cabinet that can only be accessed by the researcher. Each eligible participant will pick an envelope after baseline data has been collected. Participants will be instructed not to disclose their acupuncture treatment to anyone else and will be unaware of the purpose of the study. The surgeons, anesthetists, nurses in the theater, postanesthesia care unit (PACU) and on the ward, and investigators who collect the data are all blinded to the group allocation.

2.5. Electroacupuncture interventions

Participants in Groups 1–3 will receive EA at bilateral Neiguan (PC6) and Zusanli (ST36). Stainless steel needles (Suzhou Medical Supplies Factory Co. Ltd, 0.30 x 40 mm, China) will be used for the acupuncture used in this study. After needle insertion and de qi sensation, electrical stimulation will be applied with the dense-disperse stimulation mode (20–100 HZ) using a stimulator (XS-998B, Nanjing Xiaosong Medical Instrument Research Institute, Nanjing, China) for 30 min. The intensity of stimulation will be strong but comfortable, adjusted by the acupuncturist according to the sensation reported by the patients. The EA will be delivered by the same registered acupuncture doctor in the hospital. The treatment will be terminated if participants report discomfort or dizziness.

For Group 1, EA is delivered 24 h prior to the surgery on the ward. For Group 2, EA is delivered in an isolated, curtained off area in PACU 30 min prior to surgery. After EA, patients will be transported to the operating theatre. For Group 3, EA is delivered twice: once 24 h prior to the surgery on the ward, and once 30 min before surgery in the PACU as per group 2. For Group 4, only usual care will be given without EA.

2.6. Usual care

All participants will receive a standard preoperative preparation protocol. All participants will fast for 8 h before general anesthesia. After participants enter the operating theatre, standard monitoring procedures will be used, including ECG, non-invasive blood pressure, pulse oximetry, and end-tidal CO₂. The depth of anesthesia will be monitored using bispectrality index (BIS). A standardized anesthetic protocol will be applied by four trained anesthetists, who are blinded to the group allocation. Induction of anesthesia will be achieved with midazolam 0.05 mg/kg i.v., propofol 2–3 mg/kg i.v., sufentanil 0.2–0.4 µg/kg i.v., vecuronium 0.1 mg/kg i.v., and lidocaine 1 mg/kg i.v. After induction, dexamethasone 5 mg i.v. will be administered to all groups. Anesthesia will be maintained with intravenous infusion of propofol, remifentanyl and vecuronium. Lactated Ringer's solution will be given intravenously on the basis of calculated preoperative deficits, surgical procedure, and estimated intraoperative blood loss. All participants will be placed in the Trendelenburg position after laparoscopies performed with CO₂ insufflation. Patients' lungs will be mechanically ventilated, the respiratory rate and the volume will be adjusted to maintain normocapnia (end-tidal CO₂ between 4.3 and 5.1 kPa). Parecoxib 40 mg i.v. and incision infiltration of ropivacaine 0.25% (10 ml) will be administered as a routine postoperative analgesia treatment at the end of surgery. Tropisetron 5 mg will be used i.v. at the end of skin closure for prophylaxis of PONV. Participants will be continually monitored in PACU after surgery. Once participants regain consciousness from anesthesia, tracheal extubation will be undertaken. Neostigmine 0–5 mg and atropine 0–2.5 mg will be used to reverse residual muscle relaxant effects. Furbiprofen 100 mg will be administered when postoperative pain is more than 3 out of 10 as rated with a

numerical pain rating scale, and metoclopramide 10 mg will be infused as a rescue therapy to any patient who experiences nausea, an episode of vomiting, or both and requests rescue medication.

As part of the usual care, approximately 30 min after extubation, four vaccaria seeds will be taped to the auricular points for all the participants by a registered acupuncture doctor. The points are Stomach, Large Intestine point, Shen Men and Uterus. The seeds will be pressed 4 times daily for 2 min per point, with patients assisted by nurses in the ward. The vaccaria seeds will be retained for 3 days.

2.7. Withdrawal

Participants who unexpectedly develop intraoperative drug allergy, are converted to open procedures, or have surgery-related post-operative complications will be excluded from the study.

2.8. Missing data

Missing data will be dealt with Expectation-Maximisation procedure, which is a more robust imputation method of dealing with missing data than the method of the last value carry forward or regression. It is a method to “best guess the missing value based on the specific model and the existing data points” [29].

2.9. Primary outcome measures

The primary outcomes are the incidence of PON and POV, and pain scores at 24 h after the operation. All participants will be followed up at 6, 24, 48, and 72 h after surgery for the incidence of nausea, vomiting or both. Participants will be asked if they experience any nausea or vomiting during the specific period. A numerical rating scale (0–10) will be used to rate pain on movement, with 0 indicating no pain and 10 the worst possible pain.

2.10. Secondary outcome measures

Secondary outcome measures include the incidence of PON and POV, and pain scores at 6 h, 48 h and 72 h after the operation, also the severity of PON and POV, quality of recovery as measured with the validated Quality of Recovery-15 (QoR-15) questionnaire [30], consumption of opioid medications during the surgery, number of days in hospital, and time to passage of first flatus. A validated four-point rating scale for nausea and vomiting (from 0=no nausea to 3=the worst imaginable nausea, from 0=no vomiting to 3=the worst imaginable vomiting) [31] will be used to rate the severity of PON and POV.

Demographic and baseline data including age, weight, height, Apfel score, and perioperative indexes, including anesthesia time, surgery time, surgical type, bleeding volume, transfusion volume, vital signs such as non-invasive blood pressure, pulse oximetry and heart rates will be recorded. All outcome measures will be recorded by an independent research nurse, who is not involved in the management of patients and is blinded to the group allocation. Table 1 lists the outcome measures and the time schedule of enrolment, interventions and assessment of participants.

2.11. Assessment of safety and report of serious adverse events

Adverse events of EA will be recorded by the acupuncturist using a side effects record form. Common EA related adverse events are pain, bleeding, fainting during acupuncture and infection. These will be scored using six-point scales (0=none and 5=extremely severe) [32]. Perioperative index will also be used to monitor the safety aspects of EA.

2.12. Data storage and access

Secure locked cabinets will be used to keep all participants' files. Data in electronic files will be de-identified and files password protected on the hospital intranet and managed by an independent research nurse. Only aggregated data will be presented in publications.

2.13. Statistical analysis

Statistical Package for Social Sciences for Windows (SPSS) V.19.0 will be used to analyze the data. Descriptive statistics will be presented as mean (\pm standard deviation). Chi-square test or Fisher's exact test are used to compare the categorical outcomes, including incidence of PON, POV or PONV, among groups. Analysis of variance (ANOVA) will be used to compare continuous outcomes, including severity of PONV, among groups. The p value < 0.05 is considered statistically significant. If a significant difference is found among groups, post-hoc analysis will be conducted using Bonferroni corrected t-tests to identify between which groups there are differences.

3. Discussion

The incidence of PONV in gynecological patients undergoing laparoscopic surgery is as high as 40–77% without prophylactic antiemetics [33,34]. Growing evidence supports the antiemetic effect of EA. However, the best time to deliver EA for PONV and postoperative pain is unclear. The effect of acupuncture delivered during general anesthesia is uncertain for PONV and postoperative pain. Delivering acupuncture during recovery might not be practical as patients are often too weak. Delivering acupuncture during and immediately after surgery is against Chinese medicine theory as acupuncture relies on a certain level of Qi or strength of patients to be effective. Acupuncture on extremely weak patients is often prohibited in primary practice, and this principle may be applicable to patients undergoing surgery. From the point of view of TCM and ethics, EA delivered before surgery is beneficial to the patients, and may be more practical or feasible.

There are two key limitations to this study. Firstly, this is not a sham-acupuncture controlled RCT, therefore placebo effects cannot be ruled out. The latest Cochrane review by Lee and colleagues [11] however states there is evidence supporting acupuncture being superior to sham interventions for PONV and further sham acupuncture trials will not change this conclusion. The next stage of research must focus on identifying the ideal protocols of treatment. This trial is designed to address this issue. Secondly this study is limited to one hospital and includes only short duration surgery patients. It is unclear whether our findings will be representative of other populations or other surgeries.

This study has a few strengths. Firstly, only participants with moderate to high PONV risk (score 2–4 out of 4) will be recruited and guideline-recommended PONV prevention is adopted. Participants' risk will be assessed using the valid and reliable Apfel score. According to the PONV management guidelines [8], 1–2 prophylactic antiemetics should be given intraoperatively for this population. The administration of dexamethasone and tropisetron to all participants in this study is consistent with this recommendation. This practice may reduce the overall incidence of PONV in all four groups, and may make it harder to detect adjunctive effects of EA. This however reflects the modern practice of PONV prevention and management. It is based on this standard practice that we examine the effects of different EA protocols. Consequently, our results will be applicable to daily practice rather than reflecting a controlled research environment.

Secondly, while those participants in the non-EA group are not blinded, those in the three EA groups will be blinded from the purpose of the study, i.e. the ideal timing of acupuncture treatment. Also importantly the study acupuncturists will be blinded from the outcome measures and the anesthetists will be blinded from group allocation. This is a therapist-assessor blinded study.

Table 1
SPIRIT-Figure of measurements of patient characteristics and outcomes.

	STUDY PERIOD									
	Enrolment	Allocation	Pre-OP	Intra-OP	PACU	Postoperative Treatment period				Close-up
Timepoint						6 h	24 h	48 h	72 h	
Enrolment										
Informed consent	√									
Assessment of eligibility	√									
Randomisation		√								
Demographics	√									
Apfel score	√									
Interventions										
EA			√							
Standard antiemetic				√						
Standard analgesic				√						
Auricular Assessments					√					
PON						√	√	√	√	
POV						√	√	√	√	
Pain on movement						√	√	√	√	
QoR-15			√			√	√			
Consumption of opioid medications				√						
Number of days in hospital										√
Time to first flatus passage						√	√	√	√	

PON: postoperative nausea, POV: postoperative vomiting, EA: Electroacupuncture, QoR-15: Quality of Recovery-15.

Thirdly, this trial is based on our pilot study, which shows that EA, delivered the day before surgery, is well-accepted by patients, and easily administered by acupuncturists. It is also safe and has multi-dimensional effects on postoperative recovery. This proposed study expands from the pilot study.

The results of this study may show that EA delivered the day before surgery could prevent PONV, pre-empt postoperative pain, and improve the quality of recovery of patients undergoing gynecologic laparoscopic surgery. The outcome of the study will help identify a practical and effective EA protocol, according to intervention time, acupoints and number of sessions, for prophylaxis of PONV and post-operative pain.

Trial status

The trial is open to recruitment and will be completed by the end of December 2019. We expect the results will be published in 2020.

Authors' contributions

MZ, SL and ZZ initiated the concept and developed the study protocol. JG and WZW contributed to the development of the detailed protocol. GY will recruit and randomize patients. JG will collect data from all participants. XQW will deliver acupuncture. SL drafted the manuscript and all other authors commented on the drafts and approved the final version.

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Ethics approval and consent to participate

The trial protocol has been approved by the Human Research Ethics Committee of the Affiliated Hospital of Nanjing University of

Traditional Chinese Medicine (2016NL-019-02). It has been registered with the Chinese Clinical Trial Registry (ChiCTR-INR-16010035). All participants will give written informed consent to take part in the trial.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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