STUDY PROTOCOL

EFFICACY OF PC6 ELECTROACUPUNCTURE IN THE PREVENTION OF NAUSEA VOMITING IN CAESAREAN PATIENT UNDER SPINAL ANAESTHESIA

NMRR ID: 19-3279-51524(IIR)

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Sponsor: Self-sponsored study

Institution:

Hospital Raja Permaisuri Bainun Ipoh

Sampling Method

Potential study subject is identified when booking for elective is made to the Maternal Operating Theatre. Upon identification of potential subject, the patient shall be seen by the anaesthetic doctor in the ward for recruitment purposes a day before the operation (patient scheduled for elective LSCS will be admitted a day before in maternal ward and will be seen by anaesthetist in the ward a day before). The patient is then further assessed by investigators for suitability for recruitment into the study, and if the patient fulfils the criterion, patient is then counselled for enrolment into the study. Patient will be informed on the study objectives, electroacupuncture and its potential side effects including minimal discomfort over the puncture site, redness after removal of needle. They will also be informed that randomization will take place and that they may receive granisetron and sham acupuncture or electroacupunture and granisetron.

Subsequently, assessment for data collection will also be explained to them i.e. nausea and vomiting assessment. The subject will be informed regarding circumstances where they will be excluded or withdrawn from the study. Upon agreement for enrolment, informed consent form will be provided to the patient and explained in detail the process of randomisation, study procedure including procedures for provision of spinal anesthesia, method of assessment postoperatively, as well as the potential side effects of electroacupuncture before they sign and date on the informed consent form. Once the patient agreed to get enrolled, she will be consented a day before the operation.

When the patient is successfully enrolled, by using simple randomization they will be assigned to one of two groups (EA or sham group) using sealed envelope method. Sham group

shall receive 1mg of IV granisetron and sham acupuncture while the EA group shall receive 1mg of IV granisetron and electroacupuncture throughout the surgery.

The identity of the envelop shall only be known by an independent assisting nurse and acupuncture performer (In this study, principal investigator will be the acupuncture performer).

Study protocol

All patients scheduled to have surgery will be approached and given time to read the information sheet and entered into the study after signing the consent form a day before the operation in maternal ward.

Subarachnoid puncture in the L3-L4 or L4-L5 interspace will be performed by an anesthesiologist with the patients in the sitting position, using a 27 gauge sprotte spinal needle. Patients will receive dosage of heavy Marcaine 0.5% range from 1.8-2.2ml according to patient height (figure3), fentanyl 15mcg, morphine 0.1mg, in order to achieve T4-T6 sensory blockade. Then the patients will be repositioned into supine position. The level of anesthesia will be evaluated. In order to prevent inferior vena cava syndrome (supine hypotension syndrome) the beds will be rotated 15^0 to the left. Patients will receive 3 l/min of oxygen by nasal canula. None-invasive blood pressure measurement will be performed every 2 minutes until the patient left the operating room. A decrease in systolic blood pressure (>25% decrease or BP<90 mmHg) will be treated with 100 mcg intravenous phenylephrine or 6mg ephedrine. A decline in pulse rates (<50 beats per min) will be treated with 0.5 mg intravenous atropine.

141cm-150cm	1.8ml-2.0ml

151cm-160cm	2.0ml-2.1ml
161cm-170cm	2.2ml-2.3ml
>170cm	2.3ml

Table 1. Dosage of 0.5% heavy bupivacaine according to patient's height

Patients in the EA group will have the acupuncture needles inserted at bilateral Pericardium Meridian point 6 (PC6) and large intestine meridian point 4 (LI4) (Figure 1) after given spinal anaesthesia and in supine position.

The pericardium meridian PC6 point (Neiguan) is defined as follows. The patient's four fingerbreadths will be placed on the medial aspect of their forearm with the edge of the 4th finger on the wrist crease. This is then subtracted from the width of the interphalangeal joint of her thumb. The point between the tendons of extensor carpi radialis and palmaris longus was the pericardium meridian PC6 point (Neiguan) (Figure 1). The large intestine LI4 point (Hegu) located on the dorsum of the hand, between the first and second metacarpal bones, at the midpoint of the second metacarpal bone and close to its radial border (Figure 1).

In this study, principal investigator is a trained acupuncture performer and given priviledge to perform acupuncture procedure in Hospital Raja Permaisuri Bainun ever since she was trained in Guangzhou (A programme organized by kementerian

Kesihatan in 2011). The principal investigator will be responsible for locating and demarcating the correct acupoint. The needles will be inserted by using a "flicking in" technique with a needling guide tube to ensure it is at an appropriate depth (0.5-1 cun). The EA needles will be stimulated before the start of surgery until the end of surgery at a frequency of 2 Hertz that will be produced by Electronic Acupuncture Treatment. It will be set at intensity level 1 with continuous wave emission. This device uses alternating current (AC) for a substantial step-down in voltage and amperage and ensured that there will be virtually no current transmitted through the patient's body for intraoperative safety. The proximal and distal electrodes will be clipped on to the sterile single use acupuncture needles. Stimulation was stopped and needles removed at end of surgery.

In sham/placebo group, patient will have the acupuncture needles inserted at non-acupoint 2cm radial to PC6 and between 2nd and 3rd metacarpal bone bilaterally as shown in the figure 6, superficial skin piercing (adequate depth to let patient feels needle is inserted). After the acupuncture needles are inserted, it will be attached to the electronic acupuncture electrode but without stimulation. To facilitate blinding, the machine is placed caudal to the patient, patient is unaware of the machine on/off but patient will be able to observe the procedure (needle insertion) being performed on both hands.

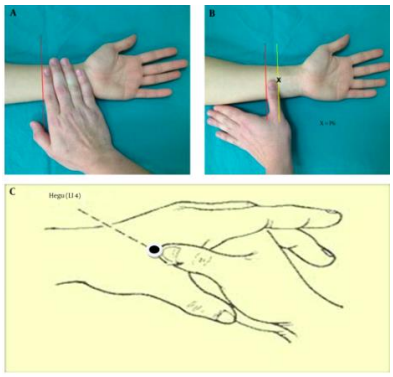

Figure 1

Position of electrodes: (figure 2)

The proximal and distal electrodes have to be on opposite sides for both arms. Eg:

Right hand: PC6…yellow, LI4: red, Left hand: PC6…red, LI4: yellow

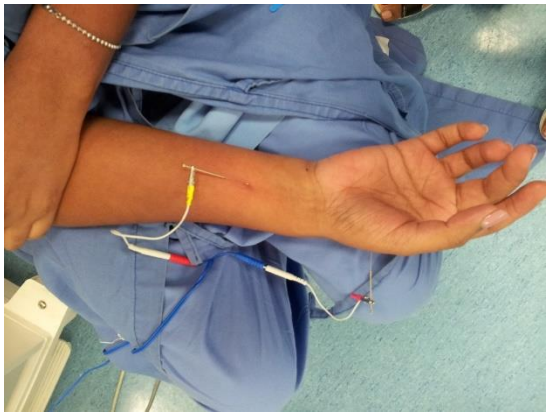

Figure 3: position of electrodes

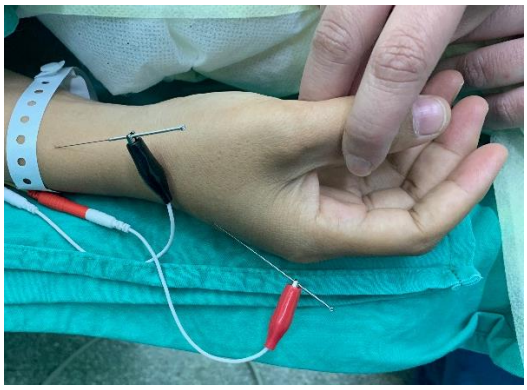

Figure 4: Sham acupoints

After the CS is implemented, the patient will be brought to the recovery room, and left there after regaining the sensory level of T10 (umbilical level) with a stable situation. Nausea and vomiting during the surgery or in the recovery room will be treated with 10 mg i.v. metoclopramide (usual treatment dose for nausea and vomiting) The data regarding the occurrence of nausea or vomiting within the theatre or recovery rooms were written in the checklists by the anesthesiology technician. PONV was observed at the ward by the nurses up to 24 hours post operation. Nausea and vomiting in ward will be prescribed with IV metoclopramide 10mg(0-6 hours post operation), and IV granisetron 1mg (> 6 hours post operation).The patients' charts were assessed at the end of 24 hours for anti-emetic requirements.

The postoperative analgesia regimen is standardized, rectal diclofenac 100mg will be given at the end of the surgery and continue with tablets paracetamol 1g 4 times per day and tablets diclofenac acid 50mg 3 times per day.

In this study, even though the principle investigator is a subspecialized obstetric anaesthesiologist given privilege to perform acupuncture, she will perform all the acupuncture procedure only, she will be independent and will not interfere with any of the anesthesiology clinical decision made on the subject.

There will be no cessation of medication if patient is on any or medication not permitted in this study. But those drugs which known to affect nausea vomiting and have to be given to the patient to ensure patient comfort (antiemetic, opioid usage) preoperatively or intraoperatively, patient will be excluded from the study (inclusion, exclusion and withdrawal criterion)

Safety monitoring of subjects- Patient's vital signs will be monitored once patient is given spinal anesthesia including continuous electrocardigraphy, continuous heart rate, continuous oxygenation saturation, non-invasive blood pressure every 2 minutes, patient is awake and able to communicate with investigators throughout the whole surgery, pain at needle insertion site with be monitored time to time. Needle will be removed once operation is done. Post operatively, patient will be observed in the ward for 24hours. Other than that, fetal heart rate will be monitored using doppler fetal monitor before and after acupuncture is performed.

Adverse effect and management- As the puncture site is safe (over the hand, away from main vessels) and the needle is tiny, it can rarely cause serious adverse event. The most serious event will be syncopal which happens in needle phobia patient (who will be not be included in the study during recruitment) and interference with pacemaker (exclusion criteria in this study), the most common drawback of the

acupuncture practice couple using electroacupuncture machine will be pain and hematoma at the needle insertion site but is usually transient and self-limiting. Furthermore it is done in a controlled environment (operation theatre) with resuscitation equipment and experience personnel further ensure the safety of subjects. In the cases of study related injury, patient will receive necessary treatment in Hospital Raja Permaisuri Bainun until recover.

Sample Size

Objective 1:

For this study, it is expected the incidence of IONV in granisteron group to be 52%, whereas for electroacupuncture and granisetron group, 22%.

Power and Sample size Program, ScalexProp version 1.0.2 (Naing, 2016) is used to estimate the sample size for this objective. It is planned that this study consists of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.52. If the true failure rate for experimental subject is 0.22, 37 experimental (electroacupuncture+granisetron) subjects and 37 control (granisetron alone) subjects will be needed to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Including 20% potential drop out rate, the sample size needed for this study is 88 patients (44 for electroacupuncture+granisetron arm and 44 for granisetron arm).

Objective 2:

No prior research was done using a recommended dose 1mg of granisetron in ceaserean section patient for reduction in incidence of PONV up to 24 hours However there is a RCT done in 2017 by Chang Yen Yin et al comparing the efficacy of acupuncture plus ondansetron versus ondansetron after bupivacainie-morphine spinal anesthesia, this study showed that the incidence of PONV up to 24 hours were 43% in ondansetron group versus 16% in acupuncture plus ondansetron. Since most of the literature stated the 5HT3 antagonist drugs (4mg IV ondansetron and 1mg IV granisetron) have similar efficacy to prevent PONV.

For this study, it is expected that the incidence of PONV in granisteron group to be 43%, whereas for electroacupuncture and granisetron group, 16%.

Power and Sample size Program, ScalexProp version 1.0.2 (Naing, 2016) is used to estimate the sample size for this objective. We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.43. If the true failure rate for experimental subject is 0.16, we will need to study 41 experimental (electroacupuncture+granisetron) subjects and 41 control (granisetron alone) subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Including 20% potential drop out rate, the sample size needed for this study is 98 patients (49 for electroacupuncture+granisetron arm and 49 for granisetron arm).

Data Collection

Postoperative data collection shall be done by trained APS team.The details to be filled in the form include patient general demographic datas (Age, gender, weight), anaesthetic regime (dosage of heavy bupivacaine 0.5%), indication of caesarean section (breech presentation, one previous scar refuse vaginal birth), intraoperative exteriorization of uterus, as well as duration of surgery in minutes.

Nausea and vomiting are then assessed intraoperatively in operating theatres and post operatively in recovery room and ward. Retrospective assessment will be done by study team in ward to assess nausea and vomiting incidence at 0-12 Hrs post operation and 12-24 hrs post operation.

Pain score will be assessed as well using the numeric rating scale. The Numeric Rating Scale is a well-established tool in pain measurement. The presence of nausea and vomiting will be assessed using a four-point scale adapted from a study done by Y Fuji et al.

The scale used was:

I. None

II. Nausea only

III. vomiting/retching only

IV. Nausea and vomiting/retching

Study Instruments

1. Sterile acupuncture needles for single use.

2. Electroacupuncture machine

(Medical Device Authority registration number: GB82707425017)

Validity Date of Registration 13/11/2017-12/11/2022

Electronic acupuncture treatment device uses low frequency pulse to stimulate the acupoints of human body.