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Effectiveness of P6 Stimulation for Reduction of Nausea and Vomiting During Caesarean Section Under Combined Spinal-Epidural Anaesthesia: A Randomised Controlled Trial

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Abstract

Objective: Obstetric patients who receive combined spinal-epidural (CSE) anaesthesia for elective caesarean section (CS) frequently experience intraoperative nausea and vomiting (N&V). Prophylactic therapy with antiemetic agents can have multiple adverse effects to the mother and baby. We designed a randomised clinical trial to evaluate the efficacy of electrical P6 stimulation for prophylactic N&V treatment for scheduled elective CS performed under CSE anaesthesia.

Methods: Following the Institutional Review Board approval and informed consent, a total of 180 patients were randomly allocated into three groups: (1) P6 stimulation (via a peripheral nerve stimulator), (2) intravenous (IV) antiemetics (metoclopramide and ondansetron), and (3) control (no IV antiemetic medications and no P6 stimulation), with 60 parturients in each group.

Results: Significantly fewer patients experienced intraoperative N&V in the P6 group (nausea 36.7% and vomiting 13.3%) and IV antiemetic group (nausea 23.3% and vomiting 16.7%) than those in the control group (nausea 73.3% and vomiting 45%; $p<0.001$). In addition, significantly fewer patients required rescue antiemetic medications in the P6 group (35%) and the IV antiemetic group (31.7%) than those in the control group (73.3%; $p<0.001$). There was no significant difference in the overall anaesthetic care satisfaction reported between the three study groups.

Conclusion: Our data suggest that P6 stimulation is as simple and as effective as our routine prophylactic IV antiemetic treatment for prevention of N&V during CS performed under CSE anaesthesia that could be of great interest to patients and obstetric anaesthesiologists who prefer treatments with fewer potential side effects.

Keywords: Antiemetics, caesarean section, combined spinal epidural anaesthesia, nausea, vomiting, P6 stimulation

Introduction

Nausea is an unpleasant physical condition experienced by nearly 80% of parturients who have caesarean section (CS) under combined spinal-epidural (CSE) anaesthesia (1, 2) Intraoperative vomiting causes significant challenges for the obstetrician, such as increased risk of bleeding and surgical duration, inadvertent surgical trauma and aspiration pneumonitis (3, 4) While antiemetic medications have been advocated to prevent intraoperative nausea and vomiting (N&V) during CS, they are not entirely effective and may have multiple adverse effects, including the development of gastrointestinal, renal, neurological, cardiovascular and allergic reactions (3, 5-9).

One non-pharmacological method, stimulation of the P6 acupoint, has been considered as an alternative approach to the utilisation of pharmacological antiemetic medications. It has been found to be effective in the reduction

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of intraoperative nausea (3). However, to our knowledge, no published clinical trial has found this method to be effective in reducing intraoperative vomiting during CS under CSE (3).

In this randomised controlled trial (RCT), we compared the incidence of N&V and rescue antiemetic medication used during CS under CSE in three groups of women, including those who received transcutaneous P6 acupoint stimulation, intravenous (IV) metoclopramide and ondansetron and no prophylactic antiemetic treatment or P6 stimulation. We hypothesised that the incidence of N&V during CS in women under P6 stimulation would be comparable to those who received prophylactic antiemetic treatment but significantly lower than that in parturients without any pharmacological or non-pharmacological antiemetic prophylaxis.

Methods

This randomised clinical trial was approved by the Institutional Review Board (IRB), registered on ClinicalTrials.gov (NCT02959840) and conducted from July 2015 through March 2016. Written consent was obtained from all patients to participate in the study. The study was conducted in accordance with the Consolidated Standards of Reporting Trials guidelines (10). The full trial protocol is available upon request from this manuscript's first author.

Women scheduled for elective CS under CSE, aged 18-45 years old, who met the American Society of Anesthesiologists physical status class 2 criteria were included in the study. Subjects were identified from the operative calendar of the anaesthesiologists participating in the study. During the preoperative assessment, a study coordinator interviewed eligible patients, described the study design and reviewed the IRB-approved consent document. Patients meeting the inclusion criteria were approached for participation except those with a history of placenta accreta, pregnancy-induced hypertension/preeclampsia/eclampsia, chronic medication use, fever ≥38°C, urinary tract infection, pneumonia or otitis media. Eligible patients who signed the informed consent documents were randomised into three groups using a computer-generated randomisation sequence of 1:1:1 (Figure 1): (1) P6 group, (2) IV antiemetic group and (3) control group (no IV antiemetic medications and no P6 stimulation). Parturients assigned to the IV antiemetic group and the control group were not aware whether or not they received IV antiemetic medications. Women were notified during the consent process that if they were to experience nausea and/or vomiting during CS, they would have the option of requesting rescue antiemetic medications despite their group allocation. The anaesthesiologist made the final decision about the rescue medication administration.

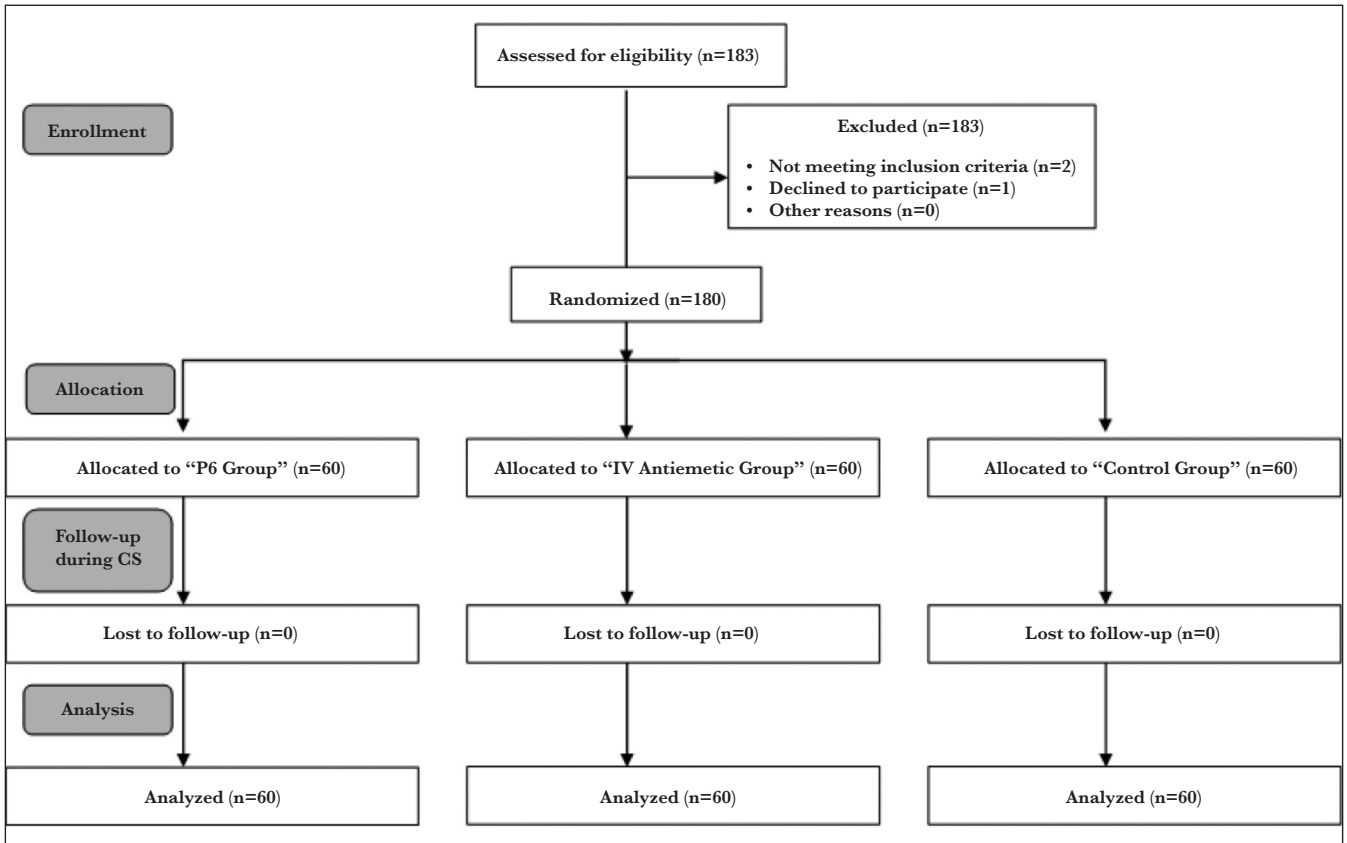

Figure 1. Flow diagram of the study as per the Consolidated Standards of Reporting Trials

All patients received 20 mg IV famotidine, 30 mL sodium citrate/citric acid orally, 2 mg IV cefazolin and 1.5-2 L IV lactated Ringer's solution. The epidural space was located with the loss-of-resistance to air technique. Lumbar CSE anaesthesia to achieve a T2-T4 sensory level was established by using a 17 g Tuohy needle at L4-5 or L3-4 interspace, followed by inserting a 26 g Gertie Marx spinal needle and injection of 2 mL bupivacaine, 0.5% with fentanyl 20 µg and 100 µg epinephrine mixed with 1 mL CSF. Spinal needle was removed, and a 17 g Springwound Epidural Anaesthesia Catheter was directed 5 cm cephalad and secured with sterile dressing to the skin. Sensory level was checked using ice bags. Epidural lidocaine 2% with 5 µg mL^{-1} epinephrine was administered to achieve adequate anaesthesia when needed. A bladder catheter was placed for all patients. During CS, parturients were maintained in supine position with left uterine displacement and were monitored continuously using an automated blood pressure cuff, electrocardiography, capnography and pulse oximetry (11). Oxygen was supplied by a nasal cannula at 4 mL min^{-1} throughout the CS. After the baby was delivered, 20 units of oxytocin were added to two 1000 mL lactated Ringer's bags consecutively. No opioids were administered during CS.

Blood pressure was checked every minute from the arrival to the operating room until induction of CSE, followed by continuously for the next 10 min, and then every 3 min for the duration of the CS. Hypertension was defined as a systolic blood pressure (SBP) >140 mm Hg at any point during the operation (12), and hypotension was defined as an SBP <90 mm Hg at any point (13). In combination, 50 µg IV phenylephrine and 5 mg ephedrine were titrated to avoid and treat hypotension. Following the administration of IV phenylephrine and ephedrine, if blood pressure did not decrease below SBP of 160 and/or diastolic blood pressure of 110 within 3 min, we had the option of administering 10 mg IV esmolol to treat reactive hypertension. Bleeding >1000 mL was defined as excessive blood loss (14). The obstetrician estimated the blood loss based on the amount that was suctioned and the number of absorbent pads that were utilized. Severe hypoxaemia was classified if oxygen saturation as measured by the pulse oximeter (PO_2) was recorded <85% at least once during CS (14).

Peripheral nerve stimulator (EasyMed Instruments Co., Ltd., Foshan, China) was applied to stimulate the P6 point. Two disposable electrodes were placed over their right median nerve prior to the administration of the CSE. The distal electrode was placed approximately one finger breadth cranial to the distal skin crease of the wrist joint between the flexor carpi radialis and palmaris longus muscle tendons. The proximal electrode was placed approximately three finger breadths cranial to the point described above (15). The reusable, battery-powered peripheral nerve stimulator was attached to the two electrodes and provided electrical direct current stimulation at a rate of one pulse per second to the patient. The stimulator output current was adjustable from 0 to 70 mA by a control dial that had 10 different knob settings. The device was turned on gradually to the highest level of intensity tolerated by the patient. The patient continued to receive electrical stimulation from the device from entering the CS room and until arrival to the post-anaesthesia care unit (PACU).

Parturients in IV antiemetic group received 10 mg IV metoclopramide and 8 mg IV ondansetron upon entering the CS room.

Parturients in the control group did not receive IV antiemetic medications or P6 stimulation upon entering the CS room.

Rescue antiemetic therapy, consisting of 10 mg IV metoclopramide and/or 4 mg IV ondansetron, was administered as needed based on the communication between the patient and the anaesthesiologist. The anaesthesiologist made the final decision on whether or not the rescue antiemetic medications would be administered.

In the present study, intraoperative N&V were identified as the primary outcome. Nausea was measured on an ascending numeric rating scale from 0 to 10, where 0 is no nausea and 10 is the worst nausea ever experienced. Objective assessments of whether or not the parturients had vomited were performed. N&V were evaluated separately using the following stages: (1) from the administration of CSE and until eversion of the uterus, (2) after eversion of the uterus and until replacement of the uterus, (3) after replacement of the uterus and to the next 15 min and (4) the rest of the time until arrival at PACU. The need for rescue antiemetic treatment was classified as a secondary outcome. Additional outcome measurement included patient's satisfaction with anaesthetic care during CS. Satisfaction was measured on an ascending numeric rating scale from 0 to 10, where 0 is no satisfaction and 10 is complete satisfaction. Complications and adverse events, such as fever, drowsiness, hypersensitivity reactions, anaphylaxis, neuroleptic malignant syndrome, agitation, QT prolongation and ventricular tachycardia, were also observed. Cardiac arrhythmias were assessed via an intraoperative electrocardiogram.

A previously reported 80% rate of nausea in parturients without antiemetic prophylaxis (2) was used to identify at least 35% reduction of nausea during CS in the treatment groups at the 0.05 level of statistical significance with a power of 0.8. A sample of 180 participants with equal number of subjects in two treatment groups and one control group was found to be sufficient to conduct pairwise comparison in a parallel-group RCT that was designed to compare proportions of nausea in three study groups.

Statistical analysis

Data were analysed using IBM Statistical Packages for the Social Sciences Statistics V22.0 (IBM SPSS Statistics Corp.; Armonk, NY, USA) and Microsoft Excel. One-way ANOVA test was used to analyse continuous variables. Data were presented as mean±standard deviation for continuous variables. Chi-square test was used to analyse categorical variables. Data were presented as number and percentages for categorical variables. The odds ratio (OR) and 95% confidence interval (95% CI) were also calculated. The intention-to-treat analysis was used in the present study. A P value <0.05 was considered statistically significant.

Results

Of the 183 eligible patients (Figure 1), one woman changed her mind about being part of the study prior to coming to the operating room, and two had unsatisfactory CSE; therefore, they received general anaesthesia. There was no significant difference in baseline patient and procedural characteristics across the study groups (Table 1).

Overall, fewer parturients experienced intraoperative nausea in the P6 group (36.7%) than those in the control group (73.3%; OR, 0.21; 95% CI, 0.10-0.46, p=0.0001). Fewer parturients experienced intraoperative nausea in the IV antiemetic group (23.3%) than those in the control group (73.3%; OR, 0.11; 95% CI, 0.05-0.25, p<0.0001). However, the rate of intraoperative nausea experienced in the P6 and IV antiemetic groups was comparable (OR, 1.90; 95% CI, 0.86-4.22, p=0.11). The difference in rate of intraoperative nausea was recorded at stage 1 (p<0.001) (Table 2).

Furthermore, fewer parturients experienced intraoperative vomiting in the P6 group (13.3%) than those in the control group (45%; OR, 0.19; 95% CI, 0.08-0.46, p=0.0003). Fewer parturients experienced intraoperative vomiting in the IV antiemetic group (16.7%) than those in the control group (45%; OR, 0.24; 95% CI, 0.10-0.57, p=0.001). However, the rate of intraoperative vomiting experienced in the P6 and IV antiemetic groups was comparable (OR, 0.77; 95% CI, 0.28-2.11, p=0.61). The difference in incidence of intraoperative vomiting was recorded at stages 1 and 2 (p<0.001) (Table 2).

We found no difference in the frequency of N&V with respect to the hypotension and type of intervention in studied patients (Table 3). Rescue antiemetic medication use was significantly less in the P6 group (35%) than in the control group (73.3%; OR, 0.23; 95% CI, 0.11-0.50, p=0.0002). Parturients in the IV antiemetic group (31.7%) also required significantly less rescue antiemetic medication than those in the control group (73.3%; OR, 0.20; 95% CI, 0.09-0.43, p<0.0001). The need for rescue antiemetic medications was comparable in the P6 and IV antiemetic groups (OR, 0.86; 95% CI, 0.40-1.84, p=0.70) (Table 2).

There was no difference in the satisfaction level with overall anaesthetic care in the three study groups (P6 group: 9.4±0.1, IV antiemetic group: 9.8±0.1 and control group: 9.2±0.2, p=0.08). Patients in the P6 stimulation group received stimulation from the peripheral nerve stimulator device at the average intensity of 36.6±11.6 mA. No patient in the P6 stimulation reported discomfort from this device during CS. Several patients commented that they "enjoyed the stimulator because it helped distract" them about being awake during a surgery. No patient required esmolol for treatment of hypertension. There were no harms or unintended effects of the P6 stimulation or the IV antiemetic medications on any of the patients. No patient in the study had intraoperative fever, drowsiness, hypersensitivity reactions, anaphylaxis, neuroleptic malignant syndrome, agitation, QT prolongation or ventricular tachycardia.

All patients had adequate regional anaesthesia for CS. Very few patients required between 5 and 10 mL rescue epidural lidocaine with epinephrine, but we did not record the number of patients who received this.

Table 1. Patient and procedural characteristics

Characteristics	P6 group (n=60)	IV antiemetic group‡ (n=60)	Control group (n=60)	p
Age (year)	32.3±4.5	33.2±5.6	31.1±4.8	0.08
Gestational age (weeks)	38.4±1.5	38.1±1.3	38.2±2.4	0.6
BMI (kg m^{-2})	33.1±8.2	32.5±6.9	31.6±7.0	0.4
Hypertension, n (%)	33 (55.0)	31 (51.7)	32 (53.3)	0.9
Hypotension, n (%)	33 (36.3)	27 (29.7)	31 (51.7)	0.6
Hypoxia, n (%)	0 (0)	0 (0)	0 (0)	1
Blood loss (mL)	864.4±246.4	838.1±147.8	821.6±279.0	0.6
Duration of surgery (min)	63.8±3.1	64.8±3.0	63.5±2.9	0.9

Continuous variables were expressed as mean±standard deviation, and P values were calculated using the one-way ANOVA test. Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P<0.05 were considered statistically significant.

‡Patients in the IV antiemetic group received 10 mg IV metoclopramide and 8 mg IV ondansetron prior to CSE placement

Table 2. Comparison of nausea and vomiting rate during CS with respect to the group allocation

N&V	P6 group (n=60)	IV antiemetic group‡ (n=60)	Control group (n=60)	p
Nausea, n (%) [NAS mean] {NAS median}				
Overall	22 (36.7)§ [7.9] {8}	14 (23.3)§ [7.6] {9}	44 (73.3) [7.6] {8}	<0.001
Stage 1	14 (23.3)§ [7.8] {9.5}	7 (11.7)§ [8.9] {10}	33 (55.0) [8] {10}	<0.001
Stage 2	5 (8.3) [8.8] {9}	6 (10.0) [7.7] {7}	12 (20.0) [7.3] {8}	0.14
Stage 3	14 (23.3) [7.8] {8}	8 (13.3) [6.9] {9}	16 (26.7) [7.9] {8}	0.18
Stage 4	0 (0)	4 (6.7) [7] {8.5}	3 (5.0) [3.7] {4}	0.16
Vomiting, n (%)				
Overall	8 (13.3)§	10 (16.7)§	27 (45.0)	<0.001
Stage 1	4 (6.7)§	5 (8.3)§	20 (33.3)	<0.001
Stage 2	3 (5.0)§	1 (1.7)§	10 (16.7)	0.01
Stage 3	6 (10.0)	4 (6.7)	9 (15.0)	0.33
Stage 4	0 (0)	2 (3.3)	0 (0)	0.33
Rescue antiemetic medications†	21 (35)§	19 (31.7)§	42 (73.3)	<0.001

Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P values <0.05 were considered statistically significant.

‡Patients in the IV antiemetic group received 10 mg IV metoclopramide and 8 mg IV ondansetron prior to CSE placement.

†Rescue antiemetic therapy consisted of 10 mg IV metoclopramide and/or 4 mg IV ondansetron.

§Statistically significant when compared with the control group.

*Stage 1=from the administration of CSE and until eversion of the uterus.

*Stage 2=after eversion of the uterus and until replacement of the uterus.

*Stage 3=after replacement of the uterus and to the next 15 min.

*Stage 4=the rest of the time until arrival at PACU.

• [NAS mean]=the mean nausea score on the numeric rating scale in patients who experienced nausea

• [NAS median]=the median nausea score on the numeric rating scale in patients who experienced nausea

Table 3. Comparison of nausea and vomiting rates during CS in patients with hypotension

Nausea, n (%)	P6 group (n=31)	IV antiemetic group (n=27)	Control group (n=33)
Yes	26 (83.9)	4 (14.8)	15 (45.5)
p	0.06	0.16	0.12
Vomiting, n (%)			
Yes	16 (51.6)	4 (14.8)	6 (18.2)
p	0.29	0.73	0.22

Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P values <0.05 were considered statistically significant

Discussion

For 20 years, the standard of care at our institution has been to administer IV metoclopramide and ondansetron, apply transcutaneous P6 acupoint stimulation or provide no prophylactic antiemetic treatment or P6 stimulation during elective CS. The parturients would receive one of these three treatments based on the obstetric anaesthesiologist's preference. The obstetric anaesthesiologists who administered the IV antiemetic medications believed that combining the two medications was more effective than the administration of just one of the two medications. Unfortunately, over the years, we had several instances of parturients developing new-onset intraoperative arrhythmias and dystonic reactions when the two IV antiemetic medications were administered togeth-

er. However, the anaesthesiologists who administered those medications felt that the benefits of potentially decreasing the chance of intraoperative N&V outweighed the risks of experiencing these adverse effects. Similar to the reports in the literature, often, the prophylactic IV antiemetic medications were not sufficient, and many patients received rescue antiemetic medication doses. The practice at our hospital has been to administer IV metoclopramide and/or ondansetron as the rescue antiemetic medication, regardless of what prophylactic antiemetic treatment option the anaesthesiologist selected to practice with. In this clinical trial, we studied whether one or more of our current treatment methodologies were better than the other treatment(s).

We chose to evaluate N&V at different stages of the CS to limit the possibility of confounding variables. At different stages of the operation, there are various factors that may cause nausea and/or vomiting, such as rostral spread of fentanyl to the vomiting centre in the medulla, hypotension, ureteral manipulation and vagus nerve stimulation.

Based on our literature search, to the best of our knowledge, this is the first ever three-arm parallel randomised clinical trial that has demonstrated that the administration of either prophylactic P6 stimulation or prophylactic IV antiemetic medications can significantly reduce parturients' experience of both intraoperative N&V during CS under CSE. Moreover, comparable with pharmacological prophylaxis, P6 stimulation significantly reduced the need for rescue antiemetic medications during CS under CSE. Approximately one-third of patients who received IV antiemetic prophylactic prior to CSE were exposed to the additional antiemetic medications during CS.

The exact mechanism of action of P6 stimulation is unknown, but it is based on the belief that a person's well-being depends on the energy balance in the body. It is hypothesised that energy flows within the human body along special paths called meridians, and certain techniques can manipulate these meridians to restore the balance of energy flow (16). An electrical stimulator can send impulses to the Neiguan (P6) acupoint and help with proper energy flow, reducing the chance of N&V (17, 18) without side effects (19). However, a previous systemic analysis of six clinical trials demonstrated that the effectiveness of intraoperative P6 stimulation was inconclusive (3, 20). In 5 of these 6 trials, the P6 acupoint was stimulated via a Sea-Band (1, 21-25), which is a single-sized elastic acupressure band with a plastic button (26). We speculate that these results were inconclusive because the Sea-Band may have not provided sufficient P6 stimulation. The sixth trial applied P6 electrical stimulation at the lowest comfortable level of the parturient without significant reduction of N&V when compared with the control group (27). The researchers believe that they may have had different results if they had applied more electrical stimulation (27). In addition, Habib et al. (27) theorised that their device may have been inadvertently displaced by the patients and was not being applied to the actual P6 point.

We believe that the application of the electrical stimulation at the highest tolerable level contributed to our results. The study by El-Deeb et al. (28) supports our findings; P6 stimulation through the use of acupuncture needles reduced both N&V during CS under spinal anaesthesia. However, the use of needles for P6 stimulation can be less comfortable for the parturient, especially if she wants to hold her newborn during the operation.

In our study, parturients were able to comfortably hold their newborns after the delivery without disruption to the position of the peripheral nerve stimulator. Applying the electrical stimulation at the highest tolerable level had no adverse effects on any of our patients in the present study. Furthermore, we have been utilising this type of stimulation for 20 years at our institution on many of our obstetric and non-obstetric patients and have never had any report of adverse effects from the stimulation.

Study limitations

The lack of complete blinded design is a limitation of the present study although patients in the control and IV antiemetic groups were not aware regarding the IV medications used prior to the initiation of CSE. In addition, a single-blinded randomised clinical trial may reduce the external validity of the current report.

In addition, the anaesthesiologist investigator who made the call for rescue antiemetics was not blinded to the study groups, which brings a potential for biased decision-making.

The combination of the two IV antiemetic medications could be enhancing the risk of adverse effects, but this has not yet been reported in the literature. In addition, the use of a rescue antiemetic medication from a different class of drugs could in theory improve the effectiveness of the antiemetic treatment, but there are minimal data to support this suggestion.

Conclusion

We demonstrated that the intraoperative application of transcutaneous P6 acupoint stimulation is comparable to the administration of IV metoclopramide and ondansetron when applied for N&V during CS with CSE. Both groups of patients had comparable reduction of intraoperative N&V, as well as the use of rescue antiemetic medications during CS. In fact, patients who received the transcutaneous P6 acupoint

stimulation required less total IV antiemetic medications than the pharmacological group. Since transcutaneous electrical P6 stimulation is simple, safe and effective, we hope that other prospective randomised clinical trials will be conducted in the future that will confirm our findings and allow us to recommend the use of transcutaneous P6 acupoint stimulation for intra-caesarean N&V prophylaxis prior to offering prophylaxis with antiemetic medications, such as IV metoclopramide and ondansetron.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of The Rutgers-Robert Wood Johnson Medical School (RWJMS) (Date: 04.08.2014, No: Pro20140000517).

Informed Consent: Written and verbal informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.L., S.C., S.M., G.K., E.P.; Design – D.L., S.C., S.M., G.K., E.P.; Supervision – D.L., S.C., S.M., U.S., G.K., E.P.; Resources – D.L., S.C., S.M., U.S., P.K., A.M., R.Z., G.K., E.P.; Materials – D.L., S.C., S.M., U.S., P.K., A.M., R.Z., G.K., E.P.; Data Collection and/or Processing – D.L., S.C., U.S., P.K., A.M., R.Z.; Analysis and/or Interpretation – D.L., S.C., S.M., U.S., P.K., A.M., R.Z., G.K., E.P.; Literature Search – D.L., S.C., E.P.; Writing Manuscript – D.L., S.C., S.M., U.S., P.K., A.M., R.Z., G.K., E.P.; Critical Review – D.L., S.C., S.M., U.S., P.K., A.M., R.Z., G.K., E.P.

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