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ORIGINAL ARTICLE

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Ephedrine versus ondansetron in the prevention of hypotension during cesarean delivery: a randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: Maternal hypotension is common after spinal anesthesia for cesarean delivery. We compared the effects of prophylactic ephedrine with ondansetron on post-spinal blood pressure.

Methods: One hundred and sixty-eight term, singleton parturients were enrolled in this prospective, double-blind, placebo-controlled trial. Patients were randomized to receive either prophylactic intravenous ephedrine 10 mg (Group E), ondansetron 8 mg (Group O) or normal saline (Group P) immediately after spinal anesthesia. The primary outcome was maternal blood pressure between spinal block and delivery; secondary outcomes were nausea and vomiting scores, Apgar scores, numbers requiring intraoperative vasoconstrictors and the dose of vasoconstrictors required.

Results: Fifty-six patients were recruited to each group, but two in Group P were excluded from the analysis owing to protocol violations. There were no significant differences between the groups in maternal systolic, diastolic or mean arterial pressures, or the proportion of patients experiencing hypotension. The proportion of patients in Group E requiring intraoperative ephedrine or any vasoconstrictor (ephedrine and/or norepinephrine) was significantly lower than that in Group P (P=0.023 and 0.034, respectively). The proportion of patients in Group O requiring intraoperative norepinephrine was significantly lower than that in Group P (P=0.02). There was no difference in the proportions of patients in Groups E and O requiring any vasoconstrictors (P=0.34).

Conclusions: There was no significant difference in maternal blood pressure in women administered prophylactic ephedrine or ondansetron after spinal anesthesia for cesarean delivery compared with placebo. Ephedrine reduced the proportion of patients requiring a rescue vasoconstrictor before delivery.

Keywords: Cesarean delivery; Anesthesia; Spinal; Hypotension; Ephedrine; Ondansetron

Introduction

Spinal anesthesia is the technique of choice for parturients undergoing cesarean delivery, owing to its rapid onset of action, reliability, superior postoperative pain control and lower mortality rate when compared to general anesthesia.[1] One of the most important complications is maternal hypotension, which may result in maternal nausea and vomiting, physical discomfort or headache, and consequences for the fetus such as hypoxia and acidosis.[2–5] The primary causes of hypotension are the reduction in vascular resistance from sympathetic blockade after spinal anesthesia- and aortocaval compression. Ephedrine or phenylephrine are often administered as systemic vasoconstrictors to prevent maternal hypotension.[2–4]

Several studies have shown that ondansetron, a serotonin (5-HT_3) receptor antagonist, can prevent hypotension after spinal anesthesia in pregnant[6–9] and non-pregnant women.[10] A recent meta-analysis concluded that ondansetron effectively reduces the incidence of hypotension induced by spinal anesthesia.[11] The mechanism of action is believed to be inhibition of the Bezold-Jarisch reflex (BJR). This reflex is mediated through vagal afferents, which, when activated, cause hypotension and bradycardia.[12] Triggering of chemoreceptors sensitive to serotonin in the intracardiac wall by a reduction in blood volume may lead to increased vagal nerve activity, followed by bradycardia and vasodilatation.[12–14]

The effect of prophylactic ondansetron on blood pressure after spinal anesthesia has not been compared

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in a clinical trial with that of a vasoconstrictor. We compared ephedrine and ondansetron for the prevention of maternal hypotension after spinal anesthesia for elective cesarean delivery. The primary outcome was maternal blood pressure from spinal block to delivery. Secondary outcomes included the number of patients requiring a vasoconstrictor, the dose of vasoconstrictor required, maternal symptoms and Apgar scores.

Methods

The study was a randomized, double-blind, placebo-controlled trial. It was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (protocol approval number 810/2556(EC2)) and the protocol was registered with www.clinicaltrials.gov (NCT02194192). Inclusion criteria were: age >18 years; American Society of Anesthesiologists physical status I or II; term, singleton pregnancy; elective cesarean delivery under spinal anesthesia; and a full understanding of all aspects of the study protocol. Patients with a history of diabetes mellitus other than gestational diabetes, hypertension, body mass index >40 kg/m^2, complicated pregnancy, allergy to study drugs, long QT syndrome, and/or contraindication to spinal anesthesia were excluded from the study. Data collection took place from July 2014 to March 2015.

Patients were evaluated the day before surgery by an anesthesiologist. Written informed consent was obtained from all participants. Patients were randomized using a computer-generated randomization table into one of three groups: those in Group E were administered intravenous ephedrine 10 mg diluted in 10 mL 0.9% saline; Group O, ondansetron 8 mg diluted in 0.9% saline 10 mL; and Group P was a control group who received 0.9% saline 10 mL as a placebo. Patients, attending anesthesiologists and postoperative data collectors were blinded to group allocation.

On the morning of surgery, patients were premedicated with oral ranitidine 150 mg. Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded in the supine position before arrival in the operating room, and an intravenous infusion of lactated Ringer's solution 500 mL started. Monitoring with pulse oximetry, non-invasive blood pressure measurement and electrocardiogram was established. Spinal anesthesia was administered in the lateral position at L2–3 or L3–4 with a 25-gauge Whitacre spinal needle (Becton Dickinson, Franklin Lakes, NJ, USA), or a 26- or 27-gauge Quincke spinal needle (Becton Dickinson, Franklin Lakes, NJ, USA). When free-flowing cerebrospinal fluid was observed, 0.5% hyperbaric bupivacaine 11 mg with morphine 200 μg was injected intrathecally. Study drugs, which had been prepared and sealed in an envelope by a nurse anesthesiologist who had no further study involvement, were given by a nurse anesthesiologist or second anesthesiologist who were unaware of the patient's randomization status. The patient was then positioned supine on the operating table with a roll positioned under the right flank to facilitate left uterine displacement.

Systolic blood pressure, DBP, MAP and HR were recorded every minute until delivery. The level of sensory block was evaluated with cold sensation 5 min after spinal anesthesia. Hypotension was defined as a decrease in SBP >20% of baseline, or SBP <90 mmHg. If hypotension developed, ephedrine 5–10 mg or norepinephrine 4–8 μg were given intravenously; this is normal practice at our institution, but the drug and dose used were at the discretion of the attending anesthesiologist. Heart rate <50 beats/min was treated with intravenous atropine 0.6 mg. The severity of nausea and/or vomiting before delivery was graded according to the following four-point grading system: 0, no symptoms; 1, nausea; 2, vomiting 1–2 times; 3, vomiting >2 times. Delivery time, Apgar score at 1 and 5 min, estimated blood loss and total volume of intravenous fluid administered were recorded. Patients who required general anesthesia or another drug likely to influence blood pressure before delivery were withdrawn from the study. Metoclopramide 10 mg was administered intravenously to patients complaining of nausea or vomiting in the first 6 h postoperatively. Thereafter, intravenous ondansetron 8 mg or metoclopramide 10 mg were given every 8 h as required. Nausea and vomiting score, dose of antiemetic drugs and patient satisfaction were recorded by a nurse anesthesiologist who visited the patient 24 h postoperatively.

Statistical analysis

Sample size calculation was based on the findings of Sahoo et al.,[6] in which MAP of patients who received ondansetron was 87.5 mmHg compared with 80.4 mmHg in patients who received placebo (standard deviation (SD) 11.3 mmHg). Sample size calculation using nQuery Advisor® Version 5 (Statistical Solutions Ltd., Cork, Ireland) with a two-sided test, 90% test power and an alpha level of 0.05 indicated 55 subjects were required in each group. Fifty-six women were included in each group to compensate for possible subject loss during the study. All analyses were performed using PASW statistics (SPSS) Version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical data are presented as the number and proportion, expressed as a percentage. The chi-squared test was used to analyze categorical data. Continuous data were analyzed using analysis of variance and the Kolmogorov–Smirnov test, and reported as the mean ± SD. Corrections for multiple comparisons were made using the Bonferroni correction. The areas under the curve (AUC) of MAP were compared using MedCalc® for Windows (trial version,