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ORIGINAL ARTICLE

Neonatal effects after vasopressor during spinal anesthesia for cesarean section: a multicenter, randomized controlled trial

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ABSTRACT

Background: Placental transfer of ephedrine causes fetal effects when compared with phenylephrine. This study compared their drug effects on neonatal parameters after cesarean delivery under spinal anesthesia.

Methods: Three-hundred-and-fifty-four women undergoing elective cesarean delivery who needed intravenous vasopressor following spinal anesthesia were randomized into two groups. Group E received boluses of ephedrine 6 mg, and Group P phenylephrine 100 μg, titrated to maintain systolic blood pressure near baseline values. Neonatal heart rates at 10 and 30–45 min of age, oxygen saturation and capillary blood glucose at 30 min, and capillary blood lactate and urine metamphetamine were recorded.

Results: Neonatal heart rate at 10 min was significantly higher (mean difference 4.0, 95%CI 0.6 to 7.3, p=0.02) in the Group E versus Group P, but not clinically relevant. There was a linear correlation between neonatal heart rate at 10 min and ephedrine dose in Group E (r^2=0.29, 95%CI 0.22, 0.74, p <0.01). The decremental changes in neonatal heart rate at 10 and 30 min were significantly greater in Group E. Urine metamphetamine tests were positive in 19% of 44 neonatal urine samples. Neonatal heart rates at 30 min, oxygen saturation, capillary blood glucose and the incidence of tachycardia, respiratory problems or abnormal glucose, were not significantly different.

Conclusions: Ephedrine, compared to phenylephrine as a vasopressor during cesarean delivery, was associated with higher neonatal heart rate in the early post-birth period, but without a significant difference in clinical outcomes in uncomplicated pregnancies.

Keywords: Delivery; Caesarean; Vasopressor; Neonate; Outcome

Introduction

Hypotension after spinal anesthesia for cesarean delivery is common and affects uteroplacental blood flow.[1] Ephedrine, which is a mixed direct and indirect-acting sympathomimetic, has been recommended for its therapeutic or prophylactic efficacy to maintain maternal blood pressure, cardiac output and uterine perfusion pressure.[2,3] Recent studies have confirmed placental transfer of ephedrine by its presence in the umbilical vein.[4] Maternal administration of ephedrine induces higher fetal metabolism, lower blood pH, lower blood glucose and higher lactate levels in the neonatal umbilical artery compared to maternal administration of phenylephrine.[5,6] However, no study has compared the differences in hypermetabolic state, focusing on the clinical outcomes such as neonatal tachycardia, hypoglycemia or other abnormalities.

In this study, we conducted a randomized double-blinded controlled clinical trial to compare the effects of these two vasopressors on neonatal heart rate, vital signs and blood glucose concentrations shortly after cesarean delivery under spinal anesthesia.

Methods

The study was approved by the Research Ethics Committee, Faculty of Medicine, Chulalongkorn University (IRB No.003/58, COA No.164/2015), and the Ethics Committee of Chaophrayayommarat Hospital, Suphan Buri province. The inclusion criteria were healthy parturients, aged more than 18 years, and American Society of Anesthesiologists (ASA) physical status 1 and 2 with term singleton pregnancies, undergoing elective cesarean delivery under spinal anesthesia. Parturients who

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required vasopressor medication after spinal anesthesia and before delivery were included. Women with cardiovascular or cerebrovascular abnormalities including cardiac disease, hypertension, arrhythmias, signs of infection, other complicated obstetrics (e.g. placenta previa or abruptio placenta), glaucoma, history of drug abuse, nasal decongestant administration within 24 hours or fetal abnormalities were excluded. Consent was obtained from all patients before entering the operating room and only patients fulfilling the eligibility criteria (i.e. those who needed administration of a vasopressor) were allocated to a treatment group. Patients were allocated to either group E or P using simple randomization based on computer generated random number; sequential codes were kept in sealed opaque envelopes and were opened only when hypotensive treatment was indicated. Data were collected at two institutions, 283 subjects at King Chulalongkorn Memorial Hospital (KCMH), Bangkok and 71 at Chaophrayayommarat Hospital, Suphan Buri province. The study was registered with Thai Clinical Trial Registry (TCTR No. 2015 0609 004).

Maternal blood pressure (BP) was measured the night before surgery, and the baseline systolic BP was defined as the average value of three measurements. On arrival in the operating room, intravenous (IV) cannulation (18 gauge) and standard monitoring were performed. Automatic oscillometric BP monitoring was used on the contralateral arm to the IV cannulation. The cuffed arm was positioned at the level of the right atrium. Maternal BP was recorded each minute until delivery, while electrocardiography and oxygen saturation by pulse oximeter (SpO_2) were monitored continuously. Spinal anesthesia was performed with 2.2 mL (height less than 160 cm) or 2.4 mL (height more than 160 cm) hyperbaric bupivacaine 0.5% with 0.2 mg morphine, via a 27-gauge Quinke spinal needle at the L2–3 or L3–4 vertebral interspace. The parturient was then placed in the supine position with left uterine displacement, using a similarly-sized rolled cloth under the right hip. Cohydration with 500 mL 0.9% normal saline solution was given up to the point of delivery.

The study drugs were prepared by a nurse who was not involved in the study, and the patients were unaware of their treatment allocation. Hypotension was treated so as to maintain systolic BP within 20% of baseline values. The subjects in Group E received a bolus dose of 1 mL of ephedrine (6 mg/mL in water) and those in Group P received 10 mL of phenylephrine (10 μg/mL in water) into running IV fluid. The same drug was repeated every 2–3 min, as needed. To avoid the study drug aggravating bradycardia, we excluded participants in whom the heart rate (HR) was less than 60 beats/min before vasopressor treatment; routine care was given to those excluded. A bolus of 0.6 mg atropine was given intravenously if hypotension with bradycardia (HR <60 beats/min) persisted. The total dose of vasopressor, atropine, anesthetic or vasoactive drug was recorded. Time from intrathecal anesthetic administration to delivery, patient discomfort, degree of meconium-stained amniotic fluid, and any episode of birth difficulty or trauma, were also noted.

After delivery, neonatal Apgar scores were assessed at 1 and 5 min by delivery nurses who were blinded to group allocation. Neonates received standard neonatal care. At 10 min post-delivery, a nurse anesthetist who was blinded to group allocation recorded the 1 min averaged pulse rate (HR_{10}), and SpO_2 (Masimo Radical 8©, Masimo Corporation, Canada). Measurements were taken only when proper contact of the pulse oximeter probe was achieved and the neonate was not crying. If not the case, measurement was delayed for up to 15 min. At 30 min post-delivery, neonatal pulse rate and SpO_2 was monitored continuously for 10 min, with data downloaded every 2 s (Masimo Radical 7®, Masimo Corporation, Canada). These readings were subsequently averaged against time (HR_{30}) (Microsoft Corporation, USA). Neonatal respiratory rate (RR), BP and rectal temperature were recorded as routine care, in addition to capillary blood glucose (CBG) concentration. All non-invasive measurements were recorded by neonatal nurses experienced in their use, and neonatal blood sampling was performed by pediatric residents in the second or third year of their perinatal care rotation. All pediatric residents and nurses were blinded to group allocation.

The following abnormal clinical findings were observed over the first hour: tachycardia (HR >160 beats/min);[7] hypertension (systolic BP >90 mmHg); tachypnea (RR >60 breaths/min); apnea (breathing cessation for 20 s, or less than 20 s with cyanosis or bradycardia); hypoxia (SpO_2 <85%); hyperthermia (temperature >37.5°C); hypoglycemia (CBG <40 mg/dL);[8] hyperglycemia (CBG >125 mg/dL).[9] If these were diagnosed, capillary lactate levels were measured (Accutrend®, Accutrend Data Corp. Inc. United States), and a high lactate level (capillary lactate >4 mmol/L)[10] was recorded. Urine collection bags were attached at the perineum only for neonates in Group E and the first voided urine was tested for metamphetamine by MET test (BlueCROSS®, Blue Cross Biomedical Co, Ltd. Beijing).

Statistical analysis

Sample size calculation was based on a previous study on neonatal HR after cesarean delivery.[11] Assuming a standard deviation (SD) of 26 at 10 min after birth and an anticipated difference of 10 beats/min, we calculated that a sample size of 177 patients per group would be required to have 95% power with a two-sided α-value of 0.05. All continuous variables were described using mean and standard deviation. All categorical variables

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