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OBSTETRICS

Effect of i.v. phenylephrine or ephedrine on the ED50 of intrathecal bupivacaine with fentanyl for Caesarean section

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Background. Prophylactic infusion of phenylephrine to prevent hypotension at Caesarean section has been shown to decrease the rostral spread of intrathecal plain levobupivacaine and intrathecal hyperbaric bupivacaine by a median of two dermatomes compared with ephedrine. The aim of this study was to determine the median effective dose (ED50) of intrathecal bupivacaine required to achieve a block to touch at the xiphisternum in patients undergoing Caesarean section when phenylephrine or ephedrine are used to prevent hypotension.

Methods. Seventy women were randomized in two groups to receive either phenylephrine at a rate of 16.6 μg min^{-1} (concentration 1 μg ml^{-1}) or ephedrine at a rate of 1.5 mg min^{-1} (concentration 90 μg ml^{-1}). Patients received varying doses of hyperbaric bupivacaine with fentanyl 25 μg using a double-blinded, up-down sequential allocation design. Effective doses were defined as anaesthesia to touch with ethyl chloride spray to the xiphisternum within 20 min.

Results. The ED50 estimates of bupivacaine were similar in the two groups: 7.8 mg [95% confidence interval (CI) 6.7–8.9] with phenylephrine and 7.6 mg (95% CI 6.8–8.4) with ephedrine. Systolic blood pressure control was similar (P=0.18) with vasopressors but heart rate was higher with ephedrine (P=0.0014).

Conclusions. Under the conditions of this study, we have shown that when phenylephrine or ephedrine were used to prevent post-spinal hypotension, the dosing requirement of hyperbaric bupivacaine was similar for intrathecal anaesthesia.

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Spinal anaesthesia for Caesarean section is associated with an 80% incidence of hypotension without prophylactic measures.[1–3] Several strategies are promoted to prevent hypotension such as uterine displacement, i.v. fluid preload, and the use of vasopressors. Historically, ephedrine has been the vasopressor of choice because it has been shown to have a more protective effect on uterine blood flow and perfusion pressure than α-adrenergic agonists in gravid ewes and in humans.[4 5] However, more recent evidence has supported the use of alpha agonists, with phenylephrine demonstrating better acid–base status and similar efficacy in blood pressure control.[6–9]

Two studies have shown that use of i.v. phenylephrine compared with ephedrine can result in a decreased rostral spread of intrathecal local anaesthetic. Cooper and colleagues[10] demonstrated a decreased rostral spread of intrathecal plain levobupivacaine by a median of two dermatomal levels, and in a more recent paper Ngan Kee and colleagues[11] showed the same effect with hyperbaric bupivacaine. However, another study by Cooper and colleagues[12] failed to demonstrate this effect with hyperbaric bupivacaine. Saravanan and colleagues[13] have demonstrated that phenylephrine is more potent than ephedrine, by a factor of 80 [95% confidence interval (CI) 73–90], for the prevention of hypotension after spinal anaesthesia for Caesarean delivery.

The aim of this study was to determine whether the choice of vasopressor used to treat spinal-induced

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hypotension affected the dose of intrathecal local anaesthetic required for Caesarean section. We wished to do this by estimating the ED50 of intrathecal hyperbaric bupivacaine with fentanyl required to achieve a block to the xiphisternum in patients undergoing elective Caesarean section with phenylephrine or ephedrine, using a potency ratio similar to that described by Saravanan to prevent hypotension.

Methods

Ethics committee approval was obtained for this prospective, randomized, double-blind sequential allocation study (REC Ref: 05/Q0406/167 EudraCT No. 2005-005 415-25). After obtaining written informed consent, patients of ASA physical status I or II, weighing 50–120 kg, 150–180 cm tall, and who had a normal singleton pregnancy beyond 37 weeks gestation and booked to deliver by elective Caesarean section were recruited. Patients with pregnancy-induced hypertension, a history of diabetes mellitus, cardiovascular or cerebrovascular problems, fetal abnormalities, and contra-indications to spinal anaesthesia were excluded.

Antacid prophylaxis was administered with metoclopramide 10 mg and ranitidine 150 mg orally the night before and a second dose of oral ranitidine on the morning of surgery. Before being transferred to the operation theatre, a baseline systolic arterial pressure (SAP) and heart rate (HR) recording taken in the sitting position, were calculated from the mean of two readings taken 5 min apart, which had less than a 10% variation. Electrocardiography, non-invasive blood pressure (NIBP), and pulse oximetry were observed throughout. I.V. access was established with a 16G cannula in the non-dominant arm and Hartmann's solution, 500 ml, commenced slowly to maintain patency of the cannula. All women received a standardized combined spinal epidural (CSE) technique. Skin was infiltrated with 2% w/v lignocaine and a 16G Tuohy needle used to identify the epidural space with loss of resistance to no more than 3 ml of saline at the L3–4 interspace with the parturient in the sitting position. A 27G Whitacre spinal needle was then passed via the Tuohy needle with the orifice pointing cephalad. The study solution was injected over 10–15 s and cerebrospinal fluid (CSF) aspirated before and after injection to confirm intrathecal placement. The spinal needle was then removed and the epidural catheter immediately threaded into the space. All patients were then placed in the left lateral position within 30 s of the spinal injection and the epidural catheter secured. Three minutes after the intrathecal injection, all parturients were then moved to the right lateral position until a block to the xiphisternum to touch was established. As is our routine, continuous cardiotocogram (CTG) monitoring was instituted 5 min before the intrathecal injection and continued until the start of surgery. HR and NIBP were recorded every minute until the delivery of the baby and subsequently at 5-min intervals.

Subjects were randomized in pairs using sealed opaque envelopes into two groups to receive either phenylephrine (1 mg in 1000 ml 0.9% w/v saline) or ephedrine (90 mg in 1000 ml 0.9% w/v saline) and run at a rate of 16.6 μg min^{-1} and 1.5 mg min^{-1}, respectively, using a Baxter Colleague® Volumetric infusion pump (Baxter Healthcare Corporation, IV Systems Division, Deerfield, IL, USA). Vasopressor solutions were freshly prepared at room temperature immediately before use by the unblinded anaesthetist performing the CSE.

An up–down sequential allocation technique was used to allocate the bupivacaine dose to each parturient with the first patient in each group receiving 6 mg hyperbaric bupivacaine at room temperature with 25 μg fentanyl. The starting dose of bupivacaine was derived from a previous study in our unit where the ED50 of intrathecal bupivacaine with 25 μg fentanyl for Caesarean section was found to be 6.1 mg.[14] An observer was blinded to the dose of bupivacaine and also to the nature of the vasopressor used. This was achieved by covering up the infusion bag and positioning the cardiovascular monitor out of sight of the observer. The observer assessed the efficacy of the block to light touch using ethyl chloride spray bilaterally. An effective dose was defined as one that resulted in a sensory block to the xiphisternum within 20 min of the intrathecal injection. After an effective outcome, the next patient in that group received a dose reduced by 1 mg of hyperbaric bupivacaine and the dose of fentanyl remained constant throughout the study. For subjects who received an intrathecal dose that was ineffective by 20 min, small incremental doses of 0.5% w/v bupivacaine were used to top up via the epidural catheter before surgery was allowed to commence and the study period was concluded. The dose of intrathecal hyperbaric bupivacaine was increased by 1 mg for the next patient in that group.

Blood pressure was managed by the unblinded anaesthetist according to a strict protocol. The prophylactic vasopressor infusion was started at the time of the intrathecal injection and continued if the SAP was at or below baseline. The infusion was turned off if SAP was above baseline. In the presence of hypotension, defined as a decrease in the SAP to $<80\%$ of baseline for two consecutive readings despite the infusion running, then a bolus of the same vasopressor as being infused was given from pre-prepared syringes (ephedrine 6 mg or phenylephrine 75 μg). If there was no improvement in SAP after a further two consecutive readings then a repeat bolus dose was given. At any time if there was a further decrease in the SAP or no improvement another vasopressor was used, the parturient was excluded, and the intrathecal dose of hyperbaric bupivacaine repeated for the next patient in that group. Bradycardia was defined as a HR of <50 beats min^{-1}. The vasopressor infusion was stopped in the presence of

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