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Original Contribution

Cardiac output changes with phenylephrine and ephedrine infusions during spinal anesthesia for cesarean section: A randomized, double-blind trial☆,☆☆

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SUMMARY

Hypotension is a common side effect of spinal anesthesia. Phenylephrine and ephedrine are the two most frequently used vasopressors to treat spinal hypotension during cesarean delivery. In this randomized double-blind study, we aimed to evaluate cardiac output (CO) changes with phenylephrine or ephedrine infusions titrated to maintain baseline systolic blood pressure (bSBP) during spinal anesthesia. Women (n = 40) scheduled for elective cesarean delivery received either phenylephrine 100 μg/min or ephedrine 5 mg/min infusions. Baseline hemodynamics (cardiac output, heart rate, systolic blood pressure) were recorded in the left lateral tilt position before fluid preload, and recorded every minute after spinal anesthesia until delivery. Umbilical cord blood gases were analyzed within 5 minutes of delivery. Good systolic blood pressure control was attained in both groups with minimal periods of hypotension (SBP <80% of bSBP) or hypertension (SBP >120% of bSBP). Cardiac output and heart rate increased over time with ephedrine, but decreased with phenylephrine. The maximum increase in CO from the baseline was 12%, in the ephedrine group, and this occurred 20 minutes after spinal injection. Cardiac output fell by more than 17% in the phenylephrine group, maximal at 10 minutes following spinal injection. Despite good systolic blood pressure control and increased cardiac output with ephedrine, administration of ephedrine was associated with significantly more fetal acidosis [Median (Interquartile range, IQR) UApH – phenylephrine = 7.33 (7.31–7.34) and ephedrine = 7.22 (7.16–7.27), $P < .05$].
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1. Introduction

Spinal anesthesia is the anesthetic technique of choice for cesarean delivery. It is used in 77% and 91% of unplanned and planned cesarean sections respectively, in the UK [1]. The most common undesirable side effect of this technique is hypotension, with an incidence of over 80% without prophylactic management [2]. This can result in significant morbidity for both the mother and fetus. The national institute of health and care excellence (NICE) recommends that women having a cesarean section under regional anesthesia should be offered intravenous ephedrine or phenylephrine, as well as volume pre-loading with crystalloid or colloid, to reduce the risk of spinal-induced hypotension [3].

The ideal vasopressor to treat spinal hypotension during cesarean section has been a subject of much debate. It should maintain maternal blood pressure and placental perfusion, while having minimal adverse effect on the fetus. It is now commonly accepted that phenylephrine is the preferred vasopressor for use on the delivery suite, following concerns

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regarding an association between ephedrine and fetal acidosis. [4-6]. Phenylephrine has been shown to maintain maternal systolic blood pressure effectively. However, it can cause undesirable reflex bradycardia, which could potentially result in a reduction in the maternal cardiac output. In one study, a phenylephrine infusion set to infuse at 100 μg/min to maintain maternal systolic blood pressure, caused up to a 20% reduction in cardiac output [7]. Such a fall in maternal cardiac output could reduce placental perfusion, which in turn may contribute to fetal compromise.

Systolic blood pressure has been widely used as a surrogate for maternal cardiac output. Robson et al suggested that cardiac output, rather than systolic blood pressure, correlated more closely with uteroplacental blood flow [8]. As the fetus depends on the uteroplacental blood flow for its supply of oxygen and nutrients, it is vital to maintain maternal cardiac output under spinal anesthesia during cesarean section. Cardiac output monitoring is not widely used when performing spinal anesthesia for routine elective cesarean delivery, and is mostly reserved for high-risk cases. Therefore, traditionally maternal systolic blood pressure has been used to guide vasopressor treatment.

There are many techniques available to monitor cardiac output during cesarean delivery. New non-invasive techniques, such as suprasternal Doppler, are available to estimate maternal cardiac output reliably and accurately [9]. Suprasternal Doppler, can be used to measure the stroke distance in the aortic arch, providing a linear measure of cardiac output. It has been validated against the volumetric measures derived from thermodilution, and has been used successfully in the pregnant and non-pregnant populations [10,11]. Compared with other devices, it is a truly non-invasive monitor [12,13]. Disadvantages of its use are, that it is an intermittent technique, and therefore, does not allow for continuous monitoring of cardiac output, and anesthesiologists require some training in its use to achieve reproducibility. It can also underestimate cardiac output by approximately 10%. One such example of this device is the SupraQ cardiac function monitor.

Other cardiac output measurement techniques, such as lithium dilution cardiac output monitor (LiDCO), do allow for continuous measurement of cardiac output. However LiDCO requires placement of an invasive arterial line, and so it is usually considered to be a minimally invasive technique. Cardiac output estimation using pressure wave analysis (e.g. LiDCO Plus and Pulse CO) has been reported to have errors up to 33% when used to assess cardiac output during cardiac surgery [14], and is not recommended during times of cardiovascular instability [15].

In this randomized double-blind study, our aim was to study the effect of phenylephrine or ephedrine infusions on maternal cardiovascular stability, by measuring cardiac output changes during spinal anesthesia using the Suprasternal Doppler (SupraQ cardiac function monitor).

2. Methods

After ethics committee (Royal Free London NHS Foundation Trust, London) approval, written informed consent was obtained from 46 women scheduled for elective cesarean delivery under spinal anesthesia, to participate in this prospective, randomized double-blinded study. The study was conducted over a 13 month period from December 2004 to December 2005. All patients were of American Society of Anesthesiologists (ASA) physical status 1 or 2, with term singleton pregnancies. Our exclusion criteria were: cardiac disease, hypertension, preeclampsia, sepsis, medications affecting systolic blood pressure, weight <50 kg or >100 kg, height <152 cm or >183 cm.

Patients were randomized using a computer generated random number table into two patient groups. Randomization assignments were sealed within opaque envelopes. In this way patients were randomly allocated to receive either phenylephrine (100 μg/min) or ephedrine (5 mg/min) infusions, titrated to maintain the maternal baseline systolic blood pressure. Each case required three anesthesiologists: Anesthesiologist 1 was the unblinded anesthesiologist, who prepared the phenylephrine or ephedrine infusions as instructed by the protocol. The phenylephrine syringe contained 50 mL of phenylephrine at a concentration of 50 μg/mL, while the ephedrine infusion contained 50 mL of ephedrine at a concentration of 2.5 mg/mL. Anesthesiologist 1 had no further involvement in clinical care or data collection relating to the trial. Anesthesiologist 2 monitored and recorded the cardiovascular parameters (heart rate and blood pressure measurements), and controlled the vasopressor infusion according to the protocol. Anesthesiologist 2 prepared and administered the rescue medications (10 mL of phenylephrine at a concentration of 50 μg/mL, 10 mL of ephedrine at a concentration of 3 mg/mL and 3 mL of glycopyrrolate at a concentration of 200 μg/mL) to treat hypotension and bradycardia if indicated. Anesthesiologist 3 performed the suprasternal Doppler measurements of cardiac output and the combined spinal epidural anesthesia. The patient and anesthesiologists 2 and 3 were blinded to the vasopressor assignment throughout.

All patients were fasted from midnight and received 150 mg oral Ranitidine pre-medication, the night before, and on the morning of surgery. On arrival in the operating theater, 16G and 20G cannulae were inserted into the non-dominant hand of the patient under local anesthesia. The 16G cannula was attached to one liter of Hartmann's solution (initially turned off), and the 20G cannula to the allocated vasopressor infusion, that had been previously prepared by the unblinded anesthesiologist (Anesthesiologist 1). The vasopressor infusion was placed in a syringe driver (Graseby 3500 Anesthesia Pump, G Medical Ltd., Watford, Herts, UK).

The patient was settled in the supine position with a left lateral 15-degree tilt (a 5 sec push on the operating table electronic control). Anesthesiologist 2 started routine monitoring of heart rate (HR), blood pressure (BP) and oxygen saturation (SpO_2). HR and BP measurements were repeated, until the readings were within 10% of each other. The baseline heart rate and systolic blood pressure (SBP) were taken as the mean of 3 readings within 10% of each other.

At this point, baseline cardiac output measurements using the SupraQ cardiac function monitor (Deltex Medical Ltd., Chichester, UK) were taken by Anesthesiologist 3. Anesthesiologist 3 had undergone training in the use of the suprasternal Doppler, for a minimum of 3 months prior to the start of the study in order to demonstrate the reliability and reproducibility of results. The suprasternal Doppler measurements recorded included: cardiac output (CO), stroke volume (SV), and flow time corrected (FTc). Each cardiac output parameter used for statistical analysis was the mean of 3 measurements, derived from 3 consecutive Doppler complexes at each time interval.

The patient was then pre-loaded with 10 mL/kg of Hartman's solution over 5 minutes, following which further SBP, HR, and Doppler measurements were taken. Anesthesiologist 3 performed a standard combined spinal epidural (CSE) in the sitting position. The skin was infiltrated with 1% lidocaine at the L3/4 level. A 16 g Tuohy needle (Portex® CSEcure, Smiths Medical, Hythe, Kent, United Kingdom) was used to locate the epidural space. After loss of resistance to 0.9% saline, a 27 g Whitacre spinal needle (Portex® CSEcure, Smiths Medical, Hythe, Kent, United Kingdom) was inserted and locked in position. A standard dose of 2.2 mL 0.5% hyperbaric bupivacaine and 15 μg fentanyl was injected intrathecally. An 18 g, closed end, multiport epidural catheter (Smiths Medical, Hythe, Kent, United Kingdom) was then threaded 4 cm into the epidural space.

The vasopressor infusion was commenced at the time of intrathecal injection and ran at 120 mL/hr. for the first 3 minutes, regardless of the SBP recorded. After 3 minutes, a protocol was followed whereby the infusion remained 'on' if the SBP was below baseline values, or turned 'off' if the SBP was at or above baseline. The SBP, HR, and whether the infusion was on or off, were recorded every minute. Hypotension, defined as a reduction in SBP to below 80% of bSBP for 2 consecutive readings, despite the vasopressor infusion running, was treated with 100 μg bolus of phenylephrine. If no improvement was seen after a further 2 consecutive readings, a bolus of 6 mg of ephedrine was administered. A bradycardia (HR 50 < bpm) for 2 consecutive readings was treated by stopping the vasopressor infusion if the SBP was at or above the

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