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ORIGINAL ARTICLE

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A randomised comparison of bolus phenylephrine and ephedrine for the management of spinal hypotension in patients with severe preeclampsia and fetal compromise

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ABSTRACT

Background: Studies in healthy patients undergoing elective caesarean delivery show that, compared with phenylephrine, ephedrine used to treat spinal hypotension is associated with increased fetal acidosis. This has not been investigated prospectively in women with severe preeclampsia.

Methods: Patients with preeclampsia requiring caesarean delivery for a non-reassuring fetal heart tracing were randomised to receive either bolus ephedrine (7.5–15 mg) or phenylephrine (50–100 μg), to treat spinal hypotension. The primary outcome was umbilical arterial base excess. Secondary outcomes were umbilical arterial and venous pH and lactate concentration, venous base excess, and Apgar scores.

Results: Among 133 women, 64 who required vasopressor treatment were randomised into groups of 32 with similar patient characteristics. Pre-delivery blood pressure changes were similar. There was no difference in mean [standard deviation] umbilical artery base excess (−4.9 [3.7] vs −6.0 [4.6] mmol/L for ephedrine and phenylephrine respectively; P=0.29). Mean umbilical arterial and venous pH and lactate concentrations did not significantly differ between groups (7.25 [0.08] vs 7.22 [0.10], 7.28 [0.07] vs 7.27 [0.10], and 3.41 [2.18] vs 3.28 [2.44] mmol/L respectively). Umbilical venous oxygen tension was higher in the ephedrine group (2.8 [0.7] vs 2.4 [0.62]) kPa, P=0.02). There was no difference in 1- or 5-min Apgar scores, numbers of neonates with 1-min Apgar scores <7 or with a pH <7.2.

Conclusions: In patients with severe preeclampsia and fetal compromise, fetal acid-base status is independent of the use of bolus ephedrine versus phenylephrine to treat spinal hypotension.

Keywords: Ephedrine; Fetal compromise; Phenylephrine; Preeclampsia; Spinal hypotension; Vasopressor

Introduction

Spinal hypotension during caesarean delivery remains a significant clinical challenge; maternal nausea and vomiting and fetal compromise may result. Ephedrine and phenylephrine are commonly used to prevent and treat spinal hypotension. In healthy patients with no fetal compromise, ephedrine is associated with more fetal acidosis than phenylephrine.[1] The clinical significance of this difference is likely to be minimal unless large doses are administered.[2] One study suggests that acidosis may arise after low doses of ephedrine in genetically susceptible individuals.[3] There are limited data regarding vasopressor use in mothers with a compromised fetus or placental function.[4–7] In these women it is possible that the unfavourable oxygen supply–demand ratio caused

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by an ephedrine-induced increase in fetal metabolic rate may be deleterious.

In women with preeclampsia, spinal anaesthesia is associated with less hypotension than in healthy patients.[8] Typically, spinal anaesthesia causes modest afterload reduction, which may be beneficial to women with preeclampsia and raised systemic vascular resistance.[9] However, clinically significant hypotension may occur in some patients. A retrospective comparison of the use of phenylephrine and ephedrine during spinal anaesthesia for caesarean delivery in women with preeclampsia included women with both maternal and fetal indications for delivery.[6] There were no between-group differences in umbilical arterial (UA) pH.[6]

The present trial is the first to compare the use of bolus ephedrine and phenylephrine for the treatment of spinal hypotension in women with severe preeclampsia with a non-reassuring fetal heart tracing and undergoing caesarean delivery. The primary outcome variable was the UA base excess. Secondary outcomes were UA and venous (UV) pH and lactate concentration, venous base excess, and Apgar scores at 1- and 5-min. Overall results for the entire cohort of recruited patients, including those not requiring vasopressor pre-delivery, are also presented.

Methods

The study commenced after the approval of the Health Science Faculty Human Research Ethics Committee of the University of Cape Town. It was registered on the South African National Clinical Trial Registry (DOH -27-111-3888), and performed at the New Groote Schuur Hospital Maternity Centre, from January 2011 until May 2013.

Informed written consent was obtained immediately after the patient was scheduled for caesarean delivery. Fetal cardiotocography was interpreted by the obstetricians, according to the guidelines of the Royal College of Obstetricians and Gynaecologists.[10] Patients with severe preeclampsia requiring caesarean delivery for a non-reassuring fetal heart tracing were recruited.

Recent recommendations are that proteinuria is no longer an absolute requirement for the diagnosis of preeclampsia, and a new nomenclature, "preeclampsia with severe features", has been advocated.[11] At the time of initiation of the present study, preeclampsia was diagnosed if the diastolic blood pressure after 20 weeks' gestational age was equal to or greater than 90 mmHg on two separate occasions at least 4 h apart, and there was proteinuria of 2+ on urine Dipstix in two clean mid-stream samples taken at least 4 h apart, or greater than or equal to 300 mg protein per 24 h. Preeclampsia was defined as severe if the systolic blood pressure exceeded 160 mmHg and/or the diastolic blood pressure exceeded 110 mmHg, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (severe headache, visual disturbance, epigastric pain, hyperreflexia), or proteinuria on urine Dipstix of 3+ or more.

Maternal exclusion criteria were patient refusal, any contraindication to spinal anaesthesia, body mass index greater than 40 kg/m^2, clinical signs of hypovolaemia, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopaenia (platelet count $<75 \times 10^9$/L), pulmonary oedema, local or generalised sepsis, spinal deformity, umbilical cord prolapse, prior non-obstetric abdominal surgery, more than two previous caesarean deliveries, or patients who were human immunodeficiency virus positive and had an acquired immune deficiency syndrome defining disease at the time of recruitment. Fetal exclusion criteria were persistent fetal bradycardia or any other fetal condition contraindicating spinal anaesthesia, gestational age <28 weeks, estimated fetal weight <900 g, and twin pregnancy. Patients were excluded from data analysis if initiation of spinal anaesthesia took longer than 20 minutes; in this case, the patient received general anaesthesia and failure of the technique was recorded.

Antepartum management followed the established protocols of our institution: if the patient was in established labour, an intravenous line was inserted, and a balanced crystalloid solution was administered at less than 100 mL/h. Patients not in labour were allowed free oral fluids. Magnesium sulphate ($MgSO_4$) seizure prophylaxis was administered to patients with severe preeclampsia (intravenous loading dose of 4 g followed by 1 g/h). Dihydralazine was administered intravenously for additional blood pressure control according to a standardised protocol. Prior use of other agents (alpha methyldopa, morphine and dexamethasone) was recorded.

When a decision was made to proceed to caesarean delivery, the patient was placed in the left lateral position before transfer to the operating theatre; 40% oxygen was delivered by a Venturi face-mask at 10 L/min.

All patients received 30 mL oral sodium citrate in theatre, and 1 g intravenous cefazolin prior to induction of spinal anaesthesia. Monitoring consisted of electrocardiograph, non-invasive blood pressure and pulse oximetry. Baseline mean arterial pressure (MAP) was recorded as the mean of two non-invasive blood pressure readings not differing by more than 10%, measured in the five minutes prior to induction of spinal anaesthesia in the left lateral position. After calculation of the mean baseline blood pressure, the target value for administration of vasopressor was calculated. Thereafter an intravenous fluid preload of 300 mL 6% hydroxyethyl starch (Voluven®, Port Elizabeth, South Africa) was rapidly administered. Haemodynamic data were recorded every minute after initiation of spinal anaesthesia until delivery; thereafter the time intervals for