Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section

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Background. Comparative studies of ephedrine and phenylephrine in prevention of hypotension after spinal anaesthesia for Caesarean section have lacked a consensus on dose equivalence. The aim of this study was to determine the minimum vasopressor dose for each of these drugs to calculate the dose ratio for clinical equivalence in the prevention of hypotension.

Methods. Patients with a normal singleton pregnancy beyond 36 weeks gestation undergoing elective Caesarean section under spinal anaesthesia were randomized into two groups. The first patient in Group A received 50 mg of ephedrine in saline 0.9% w/v, 500 ml, at 999 ml h⁻¹, the maximum rate possible on the pump and the first patient in Group B received 500 µg of phenylephrine in saline 0.9% w/v, 500 ml, at the same rate. The initial dose for dilution was an arbitrary choice. The dose of vasopressor in the saline bag for every subsequent patient was established by the efficacy of the dose in preventing hypotension in the previous patient according to the technique of up–down sequential allocation. Minimum vasopressor dose for each drug was determined according to the Dixon–Massey formula.

Results. The minimum vasopressor dose in saline 500 ml was 532.9 µg (95% CI 506.0–559.8) for phenylephrine and 43.3 mg (95% CI 39.2–47.3) for ephedrine. The concentration needed for equivalence at an infusion rate of 999 ml h⁻¹ was 1.07 µg ml⁻¹ for phenylephrine and 86.66 µg ml⁻¹ for ephedrine. Mean (SD) dose used for phenylephrine was 496.45 (78.3) µg and for ephedrine 39.64 (6.33) mg.

Conclusion. This study demonstrates a potency ratio of 81.2 (95% CI 73.0–89.7) for equivalence between phenylephrine and ephedrine in prevention of hypotension after spinal anaesthesia for Caesarean section.

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Hypotension after spinal anaesthesia for Caesarean section has an incidence up to 80% without prophylactic management.¹⁻³ Preventive measures include fluid preload, lateral tilt, and use of vasopressors. Traditionally, ephedrine has been recommended in this role,³⁻⁵ but its position has been challenged because of potential complications that include supraventricular tachycardia, tachyphylaxis and fetal acidosis.⁶⁻¹⁰ Advocates of phenylephrine claim better fetal acid–base status, and similar efficacy in blood pressure control,¹¹ but its use is associated with bradycardia,² and serial dilution for i.v. administration is a source of error.¹² Comparative studies claim to use equivalent doses of each drug, the doses chosen on their ability to treat hypotension, but different choices have yielded different results, and there is no consensus on dose equivalence. A recent review¹¹ of randomized trials on the use of vasopressors with spinal anaesthesia analysed seven studies,¹³⁻¹⁸ and concluded that clinical effects were similar between the two drugs in terms of prevention and treatment of hypotension. Ayronide and colleagues¹³ reported that ephedrine
45 mg administered intramuscularly was clinically similar to phenylephrine 4 mg given by the same route, while Moran and colleagues\textsuperscript{14} compared 5–10 mg boluses of ephedrine and 40–80 μg of phenylephrine, considering them equally effective. Ratios used in comparative studies varied from 1:11 to 1:250, and rationalization is needed. The aim of this study was to resolve this issue using sequential allocation to determine the equivalent minimum vasopressor dose, for each of these drugs.

**Methods**

Ethics committee approval was obtained for this prospective, randomized, double-blind, sequential allocation study. After written informed consent, patients older than 18 yr, ASA I or II, weighing 50–120 kg, 150–180 cm tall, and who had a normal singleton pregnancy beyond 36 weeks gestation, undergoing elective Caesarean section under spinal anaesthesia were recruited. Patients with pregnancy-induced hypertension, history of diabetes, cardiovascular and cerebrovascular problems, fetal abnormalities and contraindications to spinal anaesthesia were excluded.

All women received a standardized combined spinal–epidural anaesthetic. Acid prophylaxis with lansoprazole 30 mg was given on the morning of surgery, followed by sodium citrate 0.3 M, 30 ml on arrival in the anaesthetic room. Electrocardiography, non-invasive blood pressure and pulse oximetry were observed throughout. Baseline systolic arterial pressure was measured pre-operatively by averaging two readings taken 5 min apart. I.V. access was established with a 16 G cannula in the non-dominant forearm and saline 0.9% w/v, 500 ml, infusion commenced. An epidural catheter was placed in the second lumbar interspace in the sitting position, using an 18 G Tuohy needle and loss-of-resistance to saline. Subarachnoid injection of a standard dose of hyperbaric bupivacaine 0.5% w/v, 13 mg, with diamorphine 400 μg was made through a 27 G Whitacre needle in the third lumbar interspace. All patients were placed supine with left tilt. Pulse rate and blood pressure were recorded every 3 min until delivery of the baby. The prophylactic vasopressor infusion was started at the time of the subarachnoid injection. All women with levels of block that failed to reach T5 to light touch at 20 min were withdrawn from the study and that dose of vasopressor was repeated for the next patient.

Each patient was allocated to one of two groups according to a computer-generated random code. Both vasopressors were made up in normal saline 500 ml and were infused using a Gemini IMED–PC1 infusion pump (Alaris Medical UK Ltd, Basingstoke, UK). The first patient in Group A received ephedrine 50 mg in saline 0.9% w/v, 500 ml, at 999 ml h\textsuperscript{-1}, the maximum rate possible on the pump. The first patient in the Group B received phenylephrine 500 μg in saline 0.9% w/v, 500 ml, at the same rate. The initial dose for dilution was an arbitrary choice. Vasopressor solutions were freshly prepared at room temperature immediately before Caesarean section by an anaesthetist who had no other role in the study.

An observer blinded to the nature of the vasopressor infusion assessed the efficacy of each solution. The presence of hypotension, tachycardia and bradycardia was recorded until the delivery of the baby, or 30 min after intrathecal injection, whichever was earlier.

Hypotension was defined as a fall in systolic arterial pressure to <75% of baseline value or 100 mm Hg. Tachycardia was defined as a rise in heart rate to >130 beats min\textsuperscript{-1} and bradycardia as a fall to <60 beats min\textsuperscript{-1}. The presence of hypotension, as defined above, during the study period meant that the dose of infusion was classified as ineffective. It was classified as effective if it prevented hypotension during the study period. The dose of vasopressor in the saline bag for the subsequent patient was determined by the efficacy of the dose in the previous patient, according to the technique of up–down sequential allocation. After an effective outcome, the next patient in that group received a dose reduced by 5 mg of ephedrine or 50 μg of phenylephrine. After an ineffective outcome the dose for the next patient was increased by the same amount, in the respective groups.

Hypotension was treated with a bolus of ephedrine 6 mg unless the pulse rate was >100 beats min\textsuperscript{-1}, in which case a bolus of phenylephrine 40 μg was given. Boluses were repeated if needed. Bradycardia was treated with glycopyrronium 0.2 mg i.v. If the systolic arterial pressure exceeded baseline, the infusion was reduced by 100 ml h\textsuperscript{-1} decrement at a time, to maintain normotension.

The Caesarean section was conducted according to established practice. At the end of the operation the patients were observed in the recovery area in a routine manner.

Age, height, weight, gestation, parity, ASA status, baseline systolic arterial pressure and heart rate were recorded.

The primary outcome was the minimum vasopressor dose for ephedrine and phenylephrine in prevention of hypotension between intrathecal injection and delivery of the fetus. Secondary outcomes included uterine arterial pH and standardized base excess, nausea and vomiting scored on a scale of 0–2 (0, no nausea; 1, nausea but no vomiting; 2, nausea and vomiting), need for glycopyrronium, time interval between intrathecal injection and delivery time, dose of vasopressor infused and need for intervention of the non-blinded anaesthetist.

Data were expressed as mean (SD), median [range] and count. These were analysed using Student’s unpaired t-test, Mann–Whitney U-test and Fisher’s Exact tests as appropriate. The sequences were analysed using the up–down method of Dixon and Massey\textsuperscript{19} and with probit regression to estimate the minimum vasopressor dose and 95% CI for each vasopressor. Analyses were performed using Excel 2000 (Microsoft Inc., Redmond, WA, USA), Minitab 14 (Minitab Inc., State College, PA, USA) and GraphPad Prism 4 (GraphPad Software, San Diego, CA, USA). Two-sided \(P<0.05\) was defined as significant.
Personal and obstetric characteristics of the two groups were similar (Table 1). Six patients were withdrawn from the study. Four of them in the ephedrine group and one in phenylephrine group, for whom the block did not reach T5 level, epidural boluses were given. One patient in the phenylephrine group was withdrawn because of infusion pump failure. The up–down sequences of dose against patient for the two drugs are shown in Figures 1 and 2, and the up–down analysis and probit regression in Table 2.

The minimum vasopressor dose for phenylephrine was 532.9 μg (95% CI 506.0–559.8) and for ephedrine was 43.3 mg (95% CI 39.2–47.3), in saline 0.9% w/v, 500 ml. This gave a potency ratio for phenylephrine:ephedrine of 81.2:1 (95% CI 73.0–89.7). The concentration needed for equivalence at an infusion rate of 999 ml h\(^{-1}\) was 1.07 μg ml\(^{-1}\) for phenylephrine and 86.66 μg ml\(^{-1}\) for ephedrine. Mean (sd) dose used for phenylephrine was 496.45 (78.3) mg and for ephedrine 39.64 (6.33) mg, which gave a dose ratio of 1:80.

Time intervals between intrathecal injection and delivery were similar at 33.92 (8.78) min for phenylephrine and 31.65 (8.24) min for ephedrine.

Umbilical arterial blood gas analysis (UApH) showed that pH was significantly (P = 0.01) higher at 7.30 (0.06) for phenylephrine compared with 7.25 (0.09) for ephedrine. Standardized base excess (SBE) was significantly different (P = 0.03) at −0.2 (2.02) mmol litre\(^{-1}\) and −1.59 (2.67) mmol litre\(^{-1}\) for phenylephrine and ephedrine, respectively (Table 3).

Baseline nausea and vomiting scores were similar for both groups. Among the patients with effective blood pressure control there was a similar incidence of nausea and vomiting. However, in the patients with ineffective blood pressure control there was significantly less vomiting (P = 0.01) in the phenylephrine group (Table 4).

No patient required glycopyrronium for the treatment of bradycardia, nor was tachycardia noted. Intervention by the non-blinded anaesthetist was not required.
Discussion

This study achieved its aim and demonstrated a relative potency ratio for phenylephrine:ephedrine of 80:1, when reported to one significant digit, for clinical equivalence in the prevention of post-spinal hypotension. The use of this ratio in future, comparative studies will help avoid dosing bias, which could influence not only the comparative clinical efficacy, but also the incidence of side-effects.

The two vasopressors were titrated to the same clinical endpoint. Despite this, a significant but clinically unimportant difference in fetal acidosis was seen between the groups. SBE was significantly ($P=0.03$) different at $-0.2 \pm 0.2$ (2.02) mmol litre$^{-1}$ for phenylephrine and $-1.59 \pm 2.67$ mmol litre$^{-1}$ for ephedrine, and UApH was significantly ($P=0.01$) higher at $7.30 \pm 0.06$ for phenylephrine compared with $7.25 \pm 0.09$ for ephedrine. SBE and UApH differences between phenylephrine and ephedrine were $1.39 \pm 0.05$ (95% CI 0.057–2.7220) and $0.050 \pm 0.091$, respectively. This suggests that hypotension alone was not responsible for the additional acidosis seen in the ephedrine group. Despite achieving therapeutic equivalence, phenylephrine still produces a better acid–base status than ephedrine. One possible mechanism of fetal acidemia is not related to the uteroplacental or fetoplacental circulation, but to the ephedrine induced fetal β-adrenergic stimulation, as it crosses the placenta and increases fetal catecholamine levels and heart rate.$^{18,20}$ Cooper and colleagues$^{8}$ reported increased umbilical arterial minus venous $PCO_2$ (A–V $PCO_2$) difference after ephedrine administration. β-adrenergic stimulation of fetal lamb with isoproterenol has been shown to produce an initial increase in oxygen consumption, and an increase in blood glucose and lactate concentrations.$^{21}$ However, it is possible that fetal catecholamine stimulation before delivery might be beneficial. When a β-adrenergic agonist is administered before elective Cesarean section, lower respiratory morbidity, better lung function and reduced risk of hypoglycaemia in the newborn infant was found.$^{22}$

Maternal nausea and vomiting is an important problem in obstetric anaesthesia. Among the patients with effective blood pressure control, there was no difference in the amount of nausea and vomiting between the groups. This might suggest that the capacity of both drugs to induce nausea and vomiting is the same. However, in patients with ineffective blood pressure control, phenylephrine was significantly better compared with ephedrine in the prevention of vomiting. Cooper and colleagues$^{8}$ suggest that a possible explanation might be an increase in vagal tone following reduction of preload.$^{23–26}$ Cardiac preload decreases with spinal anaesthesia, but phenylephrine, a pure α-agonist, provides better venoconstriction, reducing the decrease in cardiac preload, and diminishing the vagal reflex. This may explain the higher incidence of vomiting after ephedrine, where the dose was ineffective.

We recognize difficulties in standardizing the speed of administration of intrathecal drugs, time taken to lay the patients flat from the sitting position, speed of onset of sympathetic blockade, adjusting the left lateral uterine tilt position, and timing of fluid and vasopressor infusions. Spinal anaesthesia is an idiosyncratic procedure, and we know that the vasopressor requirement is influenced by technique. We acknowledge that the minimum vasopressor doses measured are valid only for the technique described. This qualification includes the nature and the flow rate of the vasopressor infusion, which reflected the easy availability of infusion hardware and disposables. In all of this, both groups were managed identically, and it is the ratio rather than the absolute doses that was our primary outcome.

Among the weakness of our study design is the failure to record umbilical venous $PCO_2$, which would have enabled us to calculate the A–V difference. With hindsight, we realize this could have added additional interesting data, which might support the idea of increased fetal metabolic rate after ephedrine administration. Although that was not the primary outcome of our study and the procedure was not included during the initial plan, we now regret this omission.

In conclusion, we have established a clinical method to determine the equivalent minimum vasopressor dose of ephedrine and phenylephrine in prevention of hypotension after spinal anaesthesia for Caesarean delivery. We found that phenylephrine is more potent than ephedrine by a factor of 80 for equivalent maternal blood pressure control.

References