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 \( \mu \text{g} \text{min}^{-1} \) (concentration 1 \( \mu \text{g} \text{ml}^{-1} \)) or ephedrine at a rate of 1.5 \( \mu \text{g} \text{min}^{-1} \) (concentration 90 \( \mu \text{g} \text{ml}^{-1} \)). Patients received varying doses of hyperbaric bupivacaine with fentanyl 25 \( \mu \text{g} \) 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.


Keywords: anaesthetic techniques, subarachnoid; surgery, Caesarean section; sympathetic nervous system, phenylephrine; sympathetic nervous system, ephedrine

Accepted for publication: March 27, 2009

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 \( \alpha \)-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
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. 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
bradycardia for two consecutive readings but with a normal SAP. However, a bradycardia with hypotension, as defined above, on two consecutive readings was treated with 200 μg glycopyrrolate and the vasopressor continued. Delivery of the baby marked the end of the study period for those subjects who received an effective dose. Age, height, weight, gestation, ASA status, baseline SAP, HR, Apgar scores at 1 and 5 min, and birth weight were recorded.

The primary outcome was the ED50 of intrathecal hyperbaric bupivacaine with 25 μg fentanyl required to achieve a block to light touch to the xiphisternum within 20 min. Secondary outcomes included umbilical arterial and venous pH and standardized base excess. In addition, time between intrathecal injection and delivery, uterine incision to delivery time, the number of patients requiring boluses of vasopressor, and the need for glycopyrrolate were also recorded.

**Statistical analysis**

Data are presented as means (sd), medians (range), and counts. Means were analysed using Student’s t-test, medians using Mann–Whitney U-test and counts using Fisher’s exact and χ² tests. Up-down analysis of independent paired reversals was used to estimate ED50 with 95% CIs. Analyses were carried out using Excel 2000 (Microsoft Inc., Redmond, WA, USA), Number Cruncher Statistical Software (NCSS Inc., 2004, Kaysville, UT, USA), and GraphPad Prism 5.0 (GraphPad Inc., San Diego, CA, USA). Significance was defined as P < 0.05 (two-sided). Sample size estimations were based on data from a previous study which showed that a minimum of 60 subjects would be required to find a difference of 2 mg as significant (sd 2 mg) with 80% power.⁴

**Results**

Seventy patients were recruited (Fig. 1). Eight were excluded: two because of a failure of the blood pressure cuff, one because of a failed infusion pump, one because of an inadvertent dural puncture with the Tuohy needle, and one because a patient with an effective block required an epidural top-up before delivery owing to surgical delay. The dose of hyperbaric bupivacaine had to be repeated on three occasions because of hypotension unresponsive to treatment within the protocol, one dose in the ephedrine group and two doses in the phenylephrine group.

The groups were similar in age, height, ASA class, gestation, baseline SAP, and HR (Table 1). There were differences in mean weight (P = 0.04) between the phenylephrine [74 (sd 14) kg] and ephedrine groups [80 (17) kg]. This was reflected in differences (P = 0.03) in mean BMI of 26 (sd 7) and 29 (sd 5) kg m⁻² for the phenylephrine and ephedrine groups, respectively.

The up-down sequences of doses of hyperbaric bupivacaine for each vasopressor are shown in Figure 2. The ED50 (95% CI) estimates of hyperbaric bupivacaine were similar at 7.8 (6.7–8.9) mg and 7.6 (6.8–8.4) mg in patients receiving phenylephrine or ephedrine, respectively.

For the effective blocks, mean (sd) SAP (Table 2 and Fig. 3) was similar: 110 (7) mm Hg and 114 (9) mm Hg in the phenylephrine and ephedrine groups, respectively (P = 0.18) confirming that blood pressure control between groups was equivalent. Within-subject variabilities (sd) were similar at 10 and 12 mm Hg for phenylephrine and ephedrine, respectively. Mean dose of vasopressor given between intrathecal injection and delivery of the baby was 494 μg phenylephrine and 35 mg ephedrine. HR was
Phenylephrine and ED50 of bupivacaine for Caesarean section

**Table 2** Haemodynamic data expressed as mean (SD) and number of patients requiring rescue boluses. *P=0.001

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phenylephrine (n=15)</th>
<th>Ephedrine (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>80 (13)</td>
<td>95 (9)*</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>110 (7)</td>
<td>114 (9)</td>
</tr>
<tr>
<td>Rescue bolus</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

significantly (P=0.0014) slower in the phenylephrine group compared with the ephedrine group [80 (13) vs 95 (9) beats min⁻¹] (Table 2 and Fig. 3). Two patients in the phenylephrine group required glycopyrrolate for the treatment of bradycardia associated with hypotension.

Time intervals between intrathecal injection and uterine incision, and uterine incision to delivery were similar at 35 (5) and 2.1 (1) min for the phenylephrine group and 36 (4) and 2.5 (1) min for the ephedrine group (Table 3). Although blood-gas analysis showed that there was no significant difference in umbilical artery pH (UApH) between the two groups, there was a lower incidence of babies born with UApH < 7.20 in the phenylephrine group compared with the ephedrine group (Table 3). This was not statistically significant. The standardized base excess (SBE) was significantly different (P=0.01) at −2.3 (2) and −5.1 (3) for phenylephrine and ephedrine groups, respectively. Fetal birth weight and Apgar scores were similar between groups (Table 3).

**Discussion**

In this study the ED50 estimates of intrathecal hyperbaric bupivacaine with fentanyl required for elective Caesarean

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**Table 3** Operative and fetal data presented as mean (SD) or number.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phenylephrine (n=15)</th>
<th>Ephedrine (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection – uterine incision (min)</td>
<td>35 (6)</td>
<td>36 (4)</td>
</tr>
<tr>
<td>Uterine incision – delivery (min)</td>
<td>2.1 (1)</td>
<td>2.5 (1)</td>
</tr>
<tr>
<td>Umbilical arterial pH</td>
<td>7.26 (0.1)</td>
<td>7.21 (0.1)</td>
</tr>
<tr>
<td>Umbilical arterial pH&lt;7.20</td>
<td>1</td>
<td>5*</td>
</tr>
<tr>
<td>Umbilical artery SBE (mmol litre⁻¹)</td>
<td>−2.3 (2)</td>
<td>−5.1 (3)</td>
</tr>
<tr>
<td>Umbilical vein pH</td>
<td>7.33 (0.1)</td>
<td>7.29 (0.1)</td>
</tr>
<tr>
<td>Umbilical vein SBE (mmol litre⁻¹)</td>
<td>−2.2 (2.4)</td>
<td>−4.4 (2.7)</td>
</tr>
<tr>
<td>Fetal weight (kg)</td>
<td>3.4 (0.4)</td>
<td>3.6 (0.2)</td>
</tr>
<tr>
<td>1-min Apgar score</td>
<td>9 (7–10)</td>
<td>9 (8–10)</td>
</tr>
<tr>
<td>5-min Apgar score</td>
<td>10 (9–10)</td>
<td>10 (9–10)</td>
</tr>
</tbody>
</table>

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Fig 2 Up–down sequences for phenylephrine and ephedrine with ED50 (95% CI) estimates at 7.8 (6.7–8.9) and 7.6 (6.8–8.4) mg, respectively.

Fig 3 Heart rate and blood pressure data expressed as mean (SD).
section were similar when phenylephrine or ephedrine were used to prevent hypotension.

Two previous studies have shown that i.v. phenylephrine can decrease the rostral spread of intrathecal local anaesthetic by a median of two dermatomes compared with ephedrine, one using plain levobupivacaine, and another hyperbaric bupivacaine. Pregnancy is associated with epidural vein engorgement and a reduction in lumbosacral CSF volume. Cooper and colleagues speculated that phenylephrine may constrict engorged lumbar epidural veins to a greater extent than ephedrine, thereby increasing the compliance of the epidural space, lowering intrathecal pressure, and reducing the spread of an intrathecal injection. However, in a subsequent study using hyperbaric bupivacaine the same group showed no effect on block height with the usage of phenylephrine.

The results of our study, and those of these three other studies, have generated conflicting findings and this may be owing to differences in methodology. For example, in the studies of Cooper and colleagues, one used plain levobupivacaine with a CSE technique and 10 ml epidural volume extension, and the second used hyperbaric bupivacaine with a single shot spinal technique, placing patients from sitting to supine with left lateral tilt. This makes comparisons between studies more difficult. Another reason for conflicting results might be because phenylephrine and ephedrine have been used in different ratios. The three previous studies used phenylephrine and ephedrine infusions at different potency ratios (30:1, 45:1, and 80:1) to achieve equivalent blood pressure control. Saravanan and colleagues have shown that the relative potency ratio for phenylephrine and ephedrine to be 80:1 to prevent post-spinal hypotension. They suggested that further comparative studies on clinical efficacy and side-effects between phenylephrine and ephedrine should be made using this potency ratio. This is why we decided to use a potency ratio of 90:1 for our study as it fell within the 95% CI quoted by Saravanan and proved convenient for preparing infusions. However, the recent study of Ngan Kee and colleagues would suggest that this ratio may underestimate the potency of ephedrine and that a potency ratio of 60:1 is more appropriate. Nevertheless, when studies previously have used ratios with as wide a variation as 11:1 to 250:1, comparative studies using ratios ranging from 60:1 to 90:1 are now much more informative.

Using a potency ratio of 80:1, Ngan Kee and colleagues demonstrated a decrease in rostral spread of hyperbaric bupivacaine by a median of two dermatomes. These findings are in direct contrast to the findings of our own study, also using hyperbaric bupivacaine with phenylephrine and ephedrine used in a similar potency ratio of 90:1.

Why did we fail to demonstrate a difference in ED50 for intrathecal hyperbaric bupivacaine? First, our study design used doses closer to the ED50 of intrathecal bupivacaine rather than ED95 doses. Consequently, the haemodynamic changes and vasopressor requirements may have been reduced, and so the chance of a difference being induced. Secondly, the dose rate that we chose was approximately one-sixth that of the study of Ngan Kee. However, had we chosen a higher dose of phenylephrine, using the potency ratio of 90:1 may have increased the ephedrine dose to an unacceptably high level causing significant maternal tachycardia and fetal acidosis. Thirdly, we used full left and right lateral positioning rather than supine position with left lateral tilt. This may have more effectively eliminated the venous engorgement in the epidural space resulting from aorto-caval compression and hence reduced the vasopressor influence on epidural vein engorgement and lumbosacral CSF volume. Finally, the changes in maternal positioning from sitting to left lateral and then to right lateral after intrathecal injection may create gross CSF dynamic changes which might override the possibly more subtle changes resulting from the choice of vasopressor. We suspect that this was the main reason for failing to demonstrate a difference in ED50.

In this study the block assessor was blinded to the dose of bupivacaine and also to the nature of the vasopressor used. Although the assessor was not able to see the cardiovascular monitor, for safety reasons the audible aspects of the monitoring were not silenced and it may have been possible to distinguish between a slower or faster HR and thus the vasopressor used. In order to make a valid comparison between the ED50 estimates, BP control between the two groups should be equivalent. In this study, control of the prophylactic vasopressor solution was not blinded but each vasopressor was titrated according to a stringent protocol so as to eliminate any bias. SAPs were similar in groups during the 20 min after intrathecal injection. A mean difference of only 4% with 95% CIs of the ratio not exceeding 10%, was well within the 80–125% interval for equivalence as defined by international standards, and confirms that clinically important differences were excluded. As expected there was a significant difference in HR between the two groups, at 80 and 95 beats min$^{-1}$ for phenylephrine and ephedrine, respectively ($P=0.0014$). Of 15 patients in the phenylephrine group with an effective block, only seven episodes occurred where the HR was <50 beats min$^{-1}$ and, as dictated by the protocol, only two required treatment with glycopyrrolate. We believe that the administration of phenylephrine as an infusion resulted in a low incidence of bradycardia requiring treatment.

Ephedrine is no longer the ‘gold standard’ for prophylaxis and treatment of hypotension after spinal anaesthesia for Caesarean delivery. Though our study was not powered to detect a difference in fetal blood gases, consistent with other studies we found a trend (though not statistically significant), towards better fetal blood gases in the phenylephrine group (UApH=7.26) compared with the ephedrine group (UApH=7.21). This was reflected in the uterine artery base excesses, which did reach statistical significance ($P=0.01$) at $-2.3$ and $-5.1$ in the phenylephrine and ephedrine groups, respectively.
We excluded one subject in the study even though she had an effective block because she required an epidural top-up before delivery as a consequence of surgical delay. For primary outcome analysis she could have been included but the need for epidural top-ups and the prolonged spinal to delivery time may have affected the secondary outcome data, and so we decided she should be excluded. In terms of the study we believe that this made little difference to the results because the next patient in that group received the same dose as the excluded patient.

Women in the ephedrine group tended to be heavier and have larger BMI measurements. Increased BMI has been shown to reduce the minimum local anaesthetic concentration of bupivacaine for epidural analgesia in labour and local anaesthetic requirements for spinal anaesthesia are reduced to 75–80% of normal with an increase in BMI.18

Had the groups been of equal weight one might have expected the ED50 of the ephedrine group to be higher than that of the phenylephrine group. To assess the effect of possible confounding factors, logistic regression was used to test the effects of age, height, weight, and BMI independently and the effect of vasopressor remained insignificant (P>0.20) in all models. This suggests that the differences in baseline patient characteristics are unlikely to have affected the results.

In conclusion, under the conditions of this study, we have shown that hyperbaric bupivacaine with fentanyl and ephedrine to prevent hypotension in patients undergoing elective Caesarean sections under CSE.

Funding
The authors are grateful for the support of the UK National Institute for Health Research Biomedical Research Centre Funding Scheme and to the Obstetric Anaesthetists Association for a research grant.

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