

# A Randomized Double-Blinded Comparison of Phenylephrine and Ephedrine Infusion Combinations to Maintain Blood Pressure During Spinal Anesthesia for Cesarean Delivery: The Effects on Fetal Acid-Base Status and Hemodynamic Control

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**BACKGROUND:** Phenylephrine and ephedrine are both used to maintain arterial blood pressure during spinal anesthesia for cesarean delivery. Usually, either drug is given alone but several previous studies have described combining the drugs. However, the effect of varying the proportion of vasopressors in such combinations has not been reported.

**METHODS:** One-hundred-twenty-five parturients having spinal anesthesia for elective cesarean delivery were randomized to receive an IV infusion of phenylephrine and ephedrine combined in one of five different concentration ratios. Assuming phenylephrine 100  $\mu\text{g}$  to be approximately equipotent to ephedrine 8 mg, the groups contained the proportional potency equivalent of 100%, 75%, 50%, 25% or 0% of phenylephrine and 0%, 25%, 50%, 75% or 100%, respectively, of ephedrine. The infusions were adjusted to maintain systolic blood pressure (SBP) near baseline until uterine incision. Hemodynamic changes and umbilical cord blood gases were compared.

**RESULTS:** As the proportion of phenylephrine decreased and proportion of ephedrine increased among the groups, the following significant trends were detected: the incidences of hypotension and nausea/vomiting increased, the median magnitude of deviations of SBP above or below baseline and the bias for SBP to be above baseline increased, maternal heart rate was faster, fetal pH and base excess decreased, umbilical arterial oxygen content decreased and umbilical venous  $\text{Po}_2$  increased.

**CONCLUSIONS:** When varying combinations of phenylephrine and ephedrine were given by infusion to maintain arterial blood pressure during spinal anesthesia for cesarean delivery, as the proportion of phenylephrine decreased and the proportion of ephedrine increased, hemodynamic control was reduced and fetal acid-base status was less favorable. Combinations of phenylephrine and ephedrine appear to have no advantage compared with phenylephrine alone when administered by infusion for the prevention of hypotension associated with spinal anesthesia for cesarean delivery.

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**P**henylephrine and ephedrine are both used to maintain maternal arterial blood pressure (BP) during spinal anesthesia for cesarean delivery, but differ in their hemodynamic effects and their effects on the uteroplacental circulation and umbilical cord gases.<sup>1-3</sup>

Usually, either drug is given alone. However, combining both drugs in the same syringe has been described previously.<sup>4-6</sup> Those studies investigated phenylephrine and ephedrine combined in single, fixed ratios. No previous studies have systematically investigated the effect of varying the proportion of the drugs in such combinations.

In this randomized, double-blind study, we compared combinations of phenylephrine and ephedrine that were mixed in one of five different ratios. Our aim

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**Table 1.** Phenylephrine Plus Ephedrine Combinations

|  | Group 1P | Group 2 | Group 3 | Group 4 | Group 5E |
|--|----------|---------|---------|---------|----------|
| Phenylephrine concentration, $\mu\text{g}/\text{mL}$ | 100      | 75      | 50      | 25      | 0        |
| Ephedrine concentration $\text{mg}/\text{mL}$        | 0        | 2       | 4       | 6       | 8        |
| Proportion of phenylephrine by potency equivalent    | 100%     | 75%     | 50%     | 25%     | 0%       |
| Proportion of ephedrine by potency equivalent        | 0%       | 25%     | 50%     | 75%     | 100%     |

Combinations were based on an estimated equipotency ratio for phenylephrine: ephedrine of 80:1 where phenylephrine 100  $\mu\text{g}$  is equivalent in potency to ephedrine 8  $\text{mg}$ .<sup>7</sup>

was to compare the effects of the different combinations on umbilical cord blood gases, maternal BP and heart rate (HR), and the accuracy with which systolic BP (SBP) was maintained near baseline when the solutions were infused using a simple standardized infusion regimen.

## METHODS

Approval was obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, and the trial was registered in the Centre of Clinical Trials Clinical Registry of the Chinese University of Hong Kong (Trial no. CUHK\_CCT00082). All patients gave written informed consent. We recruited 125 ASA physical status 1 and 2 women with term singleton pregnancies scheduled for elective cesarean delivery under spinal anesthesia. We excluded patients who had hypertension (SBP >140 mm Hg or diastolic BP >90 mm Hg), cardiovascular or cerebrovascular disease, known fetal abnormality, contraindications to spinal anesthesia or signs of onset of labor.

Patients received antacid premedication and standard noninvasive monitoring was applied. We allowed patients to rest undisturbed in the left tilted supine position for several minutes, during which BP was measured every 1–2 min. BP measurements were continued until they became consistent (three successive measurements of SBP that had a difference of no more than 10%). Baseline SBP and HR were calculated as the mean of the three recordings.

We then inserted a 16-gauge IV cannula into a forearm vein and connected this using a wide-bore infusion set to a 1-L bag of warmed lactated Ringer's solution. No IV prehydration was given. We induced spinal anesthesia in the right lateral position. After skin infiltration with lidocaine, a 25-gauge pencil-point needle was inserted at what was estimated to be the L3–4 or L4–5 vertebral interspace and hyperbaric 0.5% bupivacaine (10 mg) and fentanyl 15  $\mu\text{g}$  were injected intrathecally. We then returned the patient to the tilted supine position. BP was measured at 1-min intervals beginning 1 min after spinal injection. Hemodynamic data were downloaded to a computer at 5 s intervals.

We randomly allocated patients to 1 of 5 groups (groups 1P, 2, 3, 4, and 5E) according to computer-generated codes contained in opaque, sealed, sequentially numbered envelopes. Each group received a titrated IV infusion of a solution containing one of five

different combinations of phenylephrine and ephedrine. Assuming a potency ratio of 80:1 (phenylephrine 100  $\mu\text{g}$  equivalent to ephedrine 8  $\text{mg}$ ) as described by Saravanan et al.,<sup>7</sup> we varied the concentrations of the drugs so that the mixtures in the five groups contained the proportional potency equivalent of 100%, 75%, 50%, 25% or 0% of phenylephrine and 0%, 25%, 50%, 75% or 100% respectively of ephedrine (Table 1). The vasopressor solutions were prepared in identical 50 mL syringes by an investigator not involved in patient care.

The vasopressors were infused using a syringe pump (Graseby 3500 Anesthesia Pump, Graseby Medical Ltd, Watford, Herts, UK) connected to the IV cannula using a three-way stopcock. Infusion rates were adjusted to maintain SBP near to baseline values using a previously described regimen.<sup>8–10</sup> At intrathecal injection, we started rapid IV fluid infusion (maximum 2 L) by fully opening the valve of the infusion set with the fluid bag suspended 1.5 m above the operating table and commenced the vasopressor at 60 mL/h. For 2 min, the infusion was continued unless SBP was >120% of baseline. Subsequently, until terminating the study at uterine incision, we measured SBP every 1 min and continued the infusion if SBP was  $\leq$  baseline and stopped the infusion if SBP was > baseline. If there were more than two consecutive episodes of hypotension (defined as SBP <80% of baseline) we gave a "rescue" IV bolus of phenylephrine 100  $\mu\text{g}$ . Hypertension was defined as SBP >120% of baseline.

The same investigators recorded the upper level of sensory anesthesia by assessing loss of discrimination of pinprick sensation 5 min after intrathecal injection, surgical times and incidences of nausea (as volunteered by patients) or vomiting (as observed by investigators). Supplemental oxygen was given when oxygen saturation was below 95% by continuous pulse oximetry. Bradycardia (HR <50 bpm) was treated by stopping the vasopressor; if accompanied by hypotension, IV atropine 0.6 mg was given.

Apgar scores were assessed 1 and 5 min after delivery. We took umbilical arterial (UA) and umbilical venous (UV) blood samples from a double-clamped segment of cord for immediate measurement of blood gases using a Rapid Point 400 analyzer (Bayer Diagnostics Mfg [Sudbury] Ltd, Sudbury, UK) and calculation of oxygen content using an IL 682 Co-oximeter (Instrumentation Laboratory, Lexington, MA) with correction for 70% fetal hemoglobin.

## Statistical Analysis

The UA pH was selected as the primary outcome variable on which to base power analysis. We calculated that 23 patients per group were required to detect a difference in UA pH of 0.03 U among groups (two-sided  $\alpha$  0.05,  $\beta$  0.9) based on previous data.<sup>8,9</sup> Sample size was increased to 25 to allow for dropouts. Intergroup comparisons were made using analysis of variance and the Kruskal-Wallis test as appropriate. For *post hoc* analysis, because there was a clear order of groups according to drug concentration, we analyzed trends from group 1P to 5E using Cuzick's test for trend. Nominal data were compared using the  $\chi^2$  test and the  $\chi^2$  test for trend.

To analyze the accuracy of control of BP among groups, we adapted methods described for assessing performance of closed-loop controlled infusion of drugs.<sup>11,12</sup> We calculated the following parameters:

### Percentage Performance Error (PE)

Performance error (PE) was defined as the difference between each measured value of SBP and the baseline value, expressed as a percentage of the baseline value. For each patient until the time of uterine incision, it was calculated as follows:

$$PE_{ij} = \frac{(\text{meaSBP}_{ij} - \text{basSBP}_i)}{\text{basSBP}_i} \times 100 \quad (1)$$

where  $PE_{ij}$  is the percentage PE for the  $i$ th patient at the  $i$ th minute,  $\text{meaSBP}_{ij}$  is the measured SBP for the  $i$ th patient at the  $i$ th minute and  $\text{basSBP}_i$  is the baseline SBP in the  $i$ th patient.

### Median PE (MDPE)

Median PE (MDPE) is a measure of bias and describes whether the measured values for SBP are systematically either above or below the baseline value. For each patient, it is defined as the median of all values of PE and was calculated as follows:

$$MDPE_i = \text{median}\{PE_{ij}, j = 1, \dots, N_i\} \quad (2)$$

where,  $MDPE_i$  is the median performance error for the  $i$ th patient and  $N_i$  is the number of values for PE obtained for the  $i$ th patient.

### Median Absolute PE (MDAPE)

Median Absolute PE (MDAPE) is a measure of inaccuracy and represents an average of the magnitudes of the differences of measured values for SBP above or below the baseline value. For each patient, it is defined as the median of the absolute values of PE and was calculated as follows:

$$MDAPE_i = \text{median}\{ |PE_{ij}|, j = 1, \dots, N_i \} \quad (3)$$

where,  $MDAPE_i$  is the median absolute PE for the  $i$ th patient.

Data were analyzed using SPSS 10.1.4 (SPSS Inc, Chicago, IL), STATA 9.2 (College Station, TX) for trend analysis and Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA) for performance analysis.  $P < 0.05$  was considered significant.

## RESULTS

One-hundred-twenty-five patients consented to participate in the study, were enrolled and were randomly assigned to one of the five study groups. Of these, 122 completed the study protocol; one patient was excluded in group 1P because severe shivering prevented accurate BP measurement; and one patient was excluded (before analysis) in each of groups 2 and 4 because of protocol violations (syringe pump incorrectly set). Insufficient UA blood was obtained for analysis from one patient in each of groups 1P-4 and insufficient UV blood was obtained for analysis from one patient in each of groups 1P, 2 and 4 and 2 patients in Group 3. Values for UA  $PO_2$  were below the minimum limit (10 mm Hg) of the reporting range of the measuring apparatus in 1 sample in group 1P, 4 samples in Group 3, 4 samples in Group 4 and one sample in group 5E; for statistical analysis, these samples were assigned a value equal to the lower limit of the reporting value (10 mm Hg) and comparisons were made by ranks. Two patients in Group 4 and one patient in group 5E required supplemental oxygen ( $P = 0.24$ ). Patient characteristics, the upper level of sensory anesthesia, surgical times and the amount of IV fluid given up to the time of uterine incision are shown in Table 2. The upper sensory level of anesthesia at 5 min was different among groups and there was a significant trend from group 1P to group 5E for the level to increase ( $P = 0.004$ ). There were no other differences among groups.

Vasopressor consumption, hemodynamic changes, and the incidence of nausea and vomiting are summarized in Table 3. The total volume of vasopressor infused was different among groups and there was a significant trend from group 1P to group 5E for volume to decrease ( $P = 0.003$ ). The incidence of nausea or vomiting was different among groups and there was a significant trend from group 1P to group 5E for the incidence to increase ( $P = 0.003$ ).

Figure 1A shows BP recordings from baseline to 15 min after induction, which was the time of uterine incision of the patient with the shortest induction-to-uterine incision interval. There was no difference overall in the incidence of hypotension among groups (Table 3); however, the  $\chi^2$  test for trend showed that there was a significant trend from group 1P to group 5E for the incidence to increase ( $P = 0.019$ ). The time to the minimum recorded SBP was different among groups and there was a significant trend from group 1P to group 5E for intrathecal injection-minimum BP interval to be shorter ( $P <$

**Table 2.** Patient Characteristics, Upper Level of Sensory Anesthesia, Surgical Times and Intravenous Fluid

|   | Group 1P<br>(n = 24) | Group 2<br>(n = 24) | Group 3<br>(n = 25) | Group 4<br>(n = 24) | Group 5E<br>(n = 25) | P    |
|---|----------------------|---------------------|---------------------|---------------------|----------------------|------|
| Age, yr <sup>a</sup>                                      | 32 (4)               | 31 (3)              | 30 (5)              | 32 (4)              | 32 (4)               | 0.35 |
| Weight, kg <sup>a</sup>                                   | 64 (7)               | 70 (10)             | 70 (9)              | 68 (9)              | 68 (10)              | 0.24 |
| Height, cm <sup>a</sup>                                   | 158 (5)              | 157 (6)             | 159 (6)             | 157 (6)             | 158 (6)              | 0.69 |
| Upper level of sensory anesthesia, dermatome <sup>b</sup> | T7 [T6–T8]           | T6 [T5–T6.5]        | T6 [T4–T7]          | T5 [T4–T7.5]        | T5 [T4–T6]           | 0.03 |
| Induction to delivery interval, min <sup>b</sup>          | 28 [24–31]           | 28 [24–32]          | 27 [25–30]          | 28 [24–30]          | 28 [24–32]           | 0.86 |
| Incision to delivery interval, min <sup>b</sup>           | 9 [7–12]             | 9 [8–12]            | 8 [6–10]            | 8 [7–11]            | 8 [6–11]             | 0.65 |
| Uterine incision to delivery interval, s <sup>b</sup>     | 90 [68–121]          | 86 [55–135]         | 98 [52–171]         | 90 [63–116]         | 90 [54–116]          | 0.91 |
| Total intravenous fluid given, mL <sup>b</sup>            | 1925 [1615–2018]     | 1910 [1463–2020]    | 1900 [1175–2000]    | 1925 [1488–2020]    | 1850 [1650–2015]     | 0.63 |

Values are mean (standard deviation) or median [interquartile range].

<sup>a</sup> Intergroup differences compared using analysis of variance.

<sup>b</sup> Intergroup differences compared using the Kruskal-Wallis test.

**Table 3.** Vasopressor Consumption, Hemodynamic Changes and Maternal Symptoms

|   | Group 1P<br>(n = 24) | Group 2<br>(n = 24) | Group 3<br>(n = 25) | Group 4<br>(n = 24) | Group 5E<br>(n = 25) | P      |
|---|----------------------|---------------------|---------------------|---------------------|----------------------|--------|
| Total volume of vasopressor given, mL                     | 8.9 [6.5–11.0]       | 9.1 [6.6–10.2]      | 8.2 [7.2–9.2]       | 6.8 [5.3–8.1]       | 6.7 [5.3–8.9]        | 0.012  |
| Total phenylephrine dose, μg <sup>a</sup>                 | 890 [650–1085]       | 679 [660–765]       | 410 [360–460]       | 169 [131–204]       | 0 [0–0]              | <0.001 |
| Rescue phenylephrine bolus required                       | 1 (4%)               | 1 (4%)              | 1 (4%)              | 1 (4%)              | 5 (20%)              | 0.12   |
| Phenylephrine infusion rate, μg/min <sup>b</sup>          | 34 [28–41]           | 25 [29–32]          | 17 [15–19]          | 7 [5–9]             | 0 [0–0]              | <0.001 |
| Total ephedrine dose, mg                                  | 0 [0–0]              | 18 [15–20]          | 33 [29–37]          | 41 [32–49]          | 54 [42–71]           | <0.001 |
| Ephedrine infusion rate, mg/min                           | 0 [0–0]              | 0.7 [0.6–0.9]       | 1.3 [1.2–1.5]       | 1.7 [1.2–2.1]       | 2.0 [1.7–3.3]        | <0.001 |
| Nausea or vomiting  | 0 (0%)               | 4 (17%)             | 0 (0%)              | 5 (21%)             | 10 (40%)             | <0.001 |
| Hypotension   | 1 (4%)               | 3 (13%)             | 3 (12%)             | 2 (8%)              | 8 (32%)              | 0.05   |
| Hypertension  | 12 (50%)             | 13 (54%)            | 9 (36%)             | 8 (33%)             | 15 (60%)             | 0.17   |
| Minimum systolic blood pressure, mm Hg                    | 107 [100–114]        | 106 [96–114]        | 105 [97–110]        | 106 [102–119]       | 96 [85–116]          | 0.31   |
| Time to minimum systolic blood pressure, min <sup>c</sup> | 9.0 [7.8–14.5]       | 12.0 [7.5–20.0]     | 8.0 [5–14.0]        | 5.5 [3.0–8.5]       | 5.0 [3.0–8.0]        | <0.001 |
| Maximum systolic blood pressure, mm Hg                    | 137 [132–147]        | 138 [130–150]       | 132 [130–147]       | 137 [132–143]       | 144 [129–155]        | 0.77   |
| Bradycardia   | 3 (13%)              | 1 (4%)              | 1 (4%)              | 0 (0%)              | 1 (4%)               | 0.37   |
| Minimum heart rate, bpm                                   | 59 [53–67]           | 59 [53–66]          | 64 [59–71]          | 71 [62–77]          | 73 [65–84]           | <0.001 |
| Maximum heart rate, bpm                                   | 100 [89–108]         | 102 [92–117]        | 106 [95–119]        | 117 [101–129]       | 129 [119–137]        | <0.001 |

Values are median (interquartile range) or number (%). Intergroup differences were analyzed using the Kruskal-Wallis test or the chi-square test.

<sup>a</sup> Total dose of phenylephrine includes rescue boluses.

<sup>b</sup> Averaged over study period.

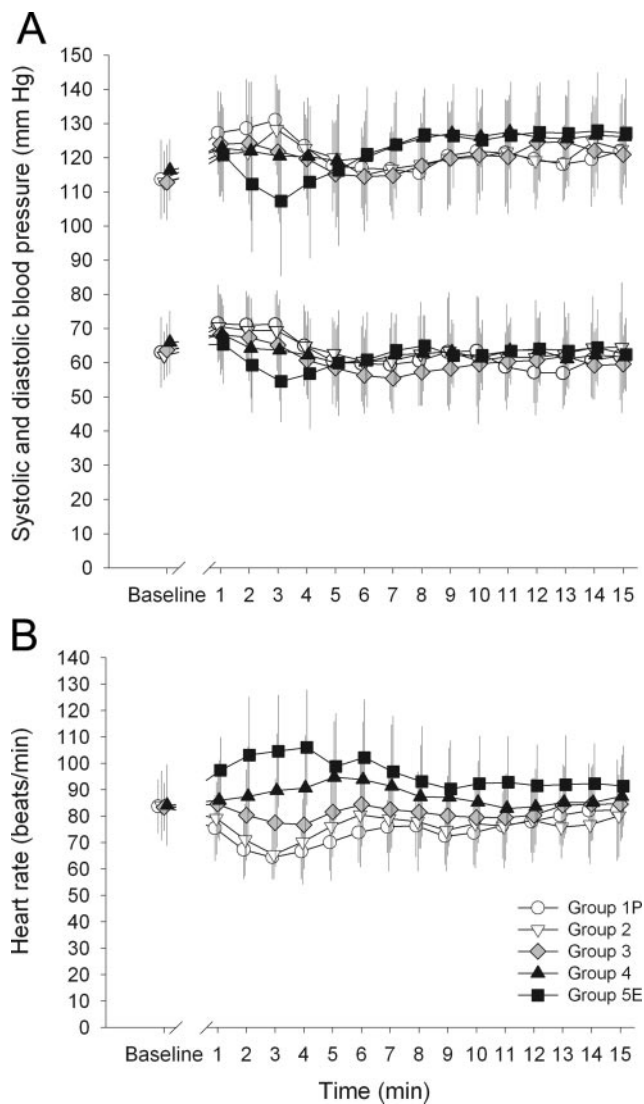
<sup>c</sup> From time of intrathecal injection.

0.001). The incidence of hypertension and the minimum and maximum recorded values for SBP were similar among groups.

Figure 1B shows HR recordings from baseline to 15 min after induction. The median value from 1 to 15 min for each patient was different among groups ( $P < 0.001$ ), and there was a significant trend from group 1P to group 5E for values to increase ( $P < 0.001$ ). The minimum recorded HR was different among groups, and there was a significant trend from group 1P to group 5E for values to increase ( $P < 0.001$ ). However, there was no difference among

groups in the incidence of bradycardia and no patient required atropine. The maximum recorded HR was different among groups, and there was a significant trend from group 1P to group 5E for the values to increase ( $P < 0.001$ ).

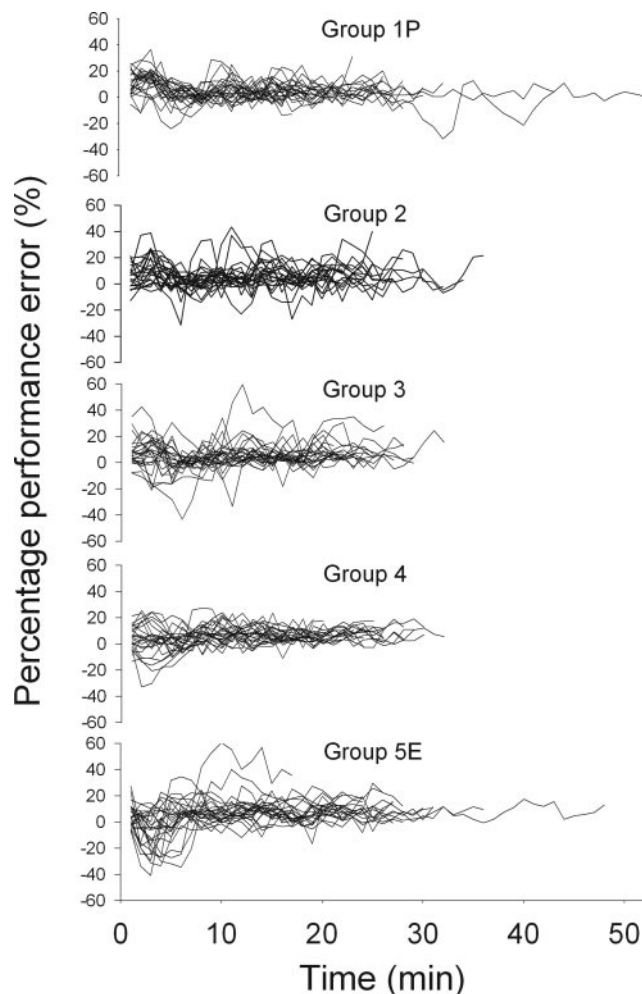
Figure 2 shows, for each group, the calculated values for PE for all patients versus time. MDPE was calculated for each patient and the data for each group are shown as boxplots in Figure 3A. The median value was above zero for all groups. MDPE was different among groups ( $P = 0.02$ ), and there was a significant trend from group 1P to group 5E



**Figure 1.** Systolic and diastolic blood pressure (A) and heart rate (B) versus time. Data are shown as mean and standard deviation. Time 0 is intrathecal injection.

for the values to increase ( $P = 0.001$ ). MDAPE was calculated for each patient and the data for each group are shown as boxplots in Figure 3B. MDAPE was different among groups ( $P = 0.019$ ), and there was a significant trend from group 1P to group 5E for the values to increase ( $P = 0.002$ ).

All Apgar scores were  $\geq 7$  at 1 min and  $\geq 9$  at 5 min. Results of analysis of umbilical cord blood are shown in Table 4. For UA blood, pH,  $P_{CO_2}$ ,  $P_{O_2}$ , base excess, and oxygen content were different among groups; there were significant trends from group 1P to group 5E for pH, base excess, and oxygen content to decrease ( $P < 0.001$ ,  $P < 0.001$  and  $P = 0.001$  respectively) and for  $P_{CO_2}$  to increase ( $P < 0.001$ ). No significant trend among groups for  $P_{O_2}$  was found ( $P = 0.073$ ). The proportion of patients with UA pH  $< 7.2$  was different among groups and there was a significant trend from group 1P to group 5E for the proportion to increase ( $P < 0.001$ ). For UV blood, pH,  $P_{O_2}$ , and base excess were significantly different among groups; there were

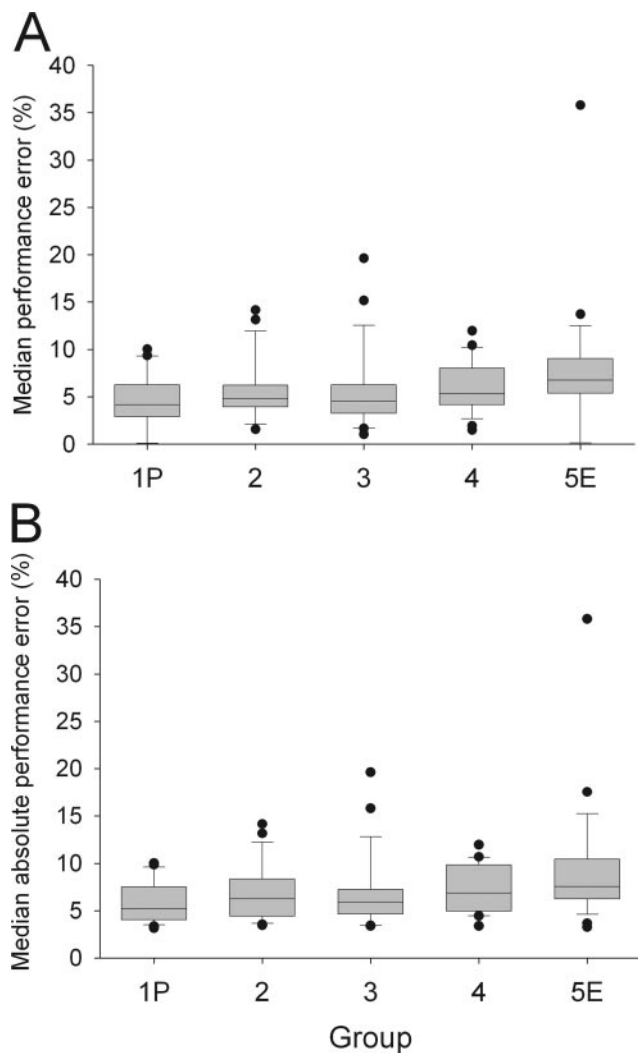


**Figure 2.** Percentage performance error (PE) plotted for each patient versus time. PE was calculated as the difference between systolic blood pressure and the baseline value, expressed as a percentage of the baseline value. Time 0 is intrathecal injection.

significant trends from group 1P to group 5E for pH and base excess to decrease (both  $P < 0.001$ ) and for  $P_{O_2}$  to increase ( $P = 0.003$ ).

## DISCUSSION

In this study we found that, using the chosen infusion protocol, as the proportion of phenylephrine in the groups decreased and the proportion of ephedrine increased, hemodynamic stability decreased, as evidenced by the significant trends for the minimum recorded SBP to occur earlier and for the incidences of hypotension and nausea and vomiting to be more frequent. These findings likely reflect pharmacologic differences between phenylephrine and ephedrine. Because ephedrine is mainly an indirect-acting drug, it has a relatively slow onset of action which makes it less effective at preventing the rapid hypotension that typically occurs soon after spinal injection. Furthermore, we found that as the proportion of ephedrine in the groups increased, there was an increasing bias for SBP to be maintained above baseline level (increasing



**Figure 3.** (A) Boxplots showing median performance error (MDPE) for the patients in each group. The 25th, 50th, and 75th percentiles are displayed as lines on a bar centered about the mean, whiskers above and below the box indicate the 90th and 10th percentiles and data beyond the 10th and 90th percentiles are displayed as individual points. (B) Boxplots showing median absolute performance error (MDAPE) for the patients in each group. The 25th, 50th, and 75th percentiles are displayed as lines on a bar centered about the mean, whiskers above and below the box indicate the 90th and 10th percentiles and data beyond the 10th and 90th percentiles are displayed as individual points.

positive MDPE) and increasing inaccuracy of control (increasing MDAPE). These findings are consistent with ephedrine having a relatively longer duration of action compared with phenylephrine; accurate titration of drugs is normally more easily achieved with short-acting drugs. Although there was a trend towards slower HR as the proportion of phenylephrine increased, this was not a clinical problem since no patient required treatment.

The trends for UA pH and base excess to decrease as the proportion of ephedrine increased are consistent with previous studies that have shown that ephedrine is associated with lower fetal pH and/or base excess compared with phenylephrine,<sup>5,7</sup> although

in our study this may also have been contributed to by the trend from group 1P to group 5E for the incidence of hypotension to increase. Depression of fetal pH and base excess with ephedrine has been postulated to be related to ephedrine-induced stimulation of fetal metabolism.<sup>5,13</sup> Consistent with this, our results showed that UA Pco<sub>2</sub> increased and UA oxygen content decreased as the proportion of ephedrine increased without changes in the corresponding UV values, suggesting an increase in fetal CO<sub>2</sub> excretion and O<sub>2</sub> extraction. Conversely, UV Po<sub>2</sub> decreased as the proportion of phenylephrine increased. It is possible that this could reflect phenylephrine having a greater vasoconstrictive effect on the uteroplacental circulation as was suggested by early animal studies,<sup>14</sup> since reduction in uteroplacental blood flow has been shown to correlate directly with decreases in fetal Po<sub>2</sub>.<sup>15,16</sup> However, because there was no difference among groups in UV O<sub>2</sub> content, O<sub>2</sub> delivery to the fetus is unlikely to have been greatly affected. Although not all studies comparing phenylephrine and ephedrine have shown differences in UA and UV Po<sub>2</sub>, this could reflect the comparatively large vasopressor doses used in the present study. Overall, when considering the effects of vasopressors on the fetus, effects on both oxygen demand and O<sub>2</sub> supply should be considered. The balance between these should be reflected by fetal acid-base status which in our study was better as the proportion of phenylephrine increased and the proportion of ephedrine decreased.

We calculated MDPE and MDAPE to assess the differences among groups in the precision of BP maintenance using a previously described infusion regimen. This infusion algorithm was originally developed for titrating phenylephrine. It is possible that different algorithms could be more suited to the characteristics of ephedrine and might result in different performance characteristics among groups. Additionally, the on-off algorithm was originally developed for ease of manual titration. It is possible that variable rate infusions could improve the precision of BP control. Some anesthesiologists prefer to administer ephedrine by intermittent bolus; however we previously reported a frequent incidence of hypotension and fetal acidosis with this technique.<sup>17</sup> Although the calculated performance parameters are useful measures of precision of hemodynamic control, it is also important to consider other clinical values such as highest and lowest values and the different measures of fetal wellbeing when considering differences among groups.

The ratios of phenylephrine: ephedrine in our groups assumed a potency ratio of 80:1 as reported by Saravanan et al.<sup>7</sup> However, because there were significant trends from group 1P to 5E for the total dose of vasopressor to decrease and for SBP to be more than baseline (increasing MDPE), our results suggest that the actual potency ratio is lower. Although there was a trend from group 1P to 5E for the incidence of hypotension to increase, this can be explained by the

**Table 4.** Umbilical Cord Blood Analysis

|                                | Group 1P            | Group 2             | Group 3             | Group 4             | Group 5E            | P      |
|--------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|--------|
| <b>Umbilical arterial</b>      |                     |                     |                     |                     |                     |        |
| n                              | 23                  | 23                  | 24                  | 23                  | 25                  |        |
| pH                             | 7.29 [7.28–7.30]    | 7.28 [7.23–7.30]    | 7.26 [7.21–7.29]    | 7.24 [7.20–7.28]    | 7.21 [7.12–7.25]    | <0.001 |
| pH <7.2                        | 0 (0%)              | 3 (13%)             | 6 (24%)             | 7 (29%)             | 12 (48%)            | 0.02   |
| PCo <sub>2</sub> , mm Hg       | 53 [50–56]          | 55 [52–60]          | 57 [50–67]          | 62 [54–66]          | 62 [55–75]          | <0.001 |
| Po <sub>2</sub> , mm Hg        | 16 [14–19]          | 18 [15–20]          | 14 [11–16]          | 15 [12–18]          | 14 [13–19]          | 0.01   |
| Base excess, mM                | -2.3 [-3.5 to -1.2] | -2.8 [-3.6 to -1.8] | -3.1 [-5.6 to -2.0] | -4.0 [-5.6 to -2.3] | -5.1 [-8.1 to -4.0] | <0.001 |
| Hemoglobin concentration, g/dL | 15.4 [14.6–16.1]    | 14.4 [13.6–15.9]    | 14.3 [13.8–16.0]    | 14.5 [13.8–15.2]    | 15.0 [14.2–15.6]    | 0.14   |
| Oxygen content, mL/dL          | 7.3 [5.6–8.6]       | 7.2 [6.1–8.2]       | 4.9 [3.2–7.0]       | 5.3 [3.9–6.4]       | 4.7 [3.5–7.8]       | 0.001  |
| <b>Umbilical venous</b>        |                     |                     |                     |                     |                     |        |
| n                              | 23                  | 23                  | 23                  | 23                  | 25                  |        |
| pH                             | 7.34 [7.33–7.35]    | 7.34 [7.32–7.37]    | 7.32 [7.29–7.35]    | 7.32 [7.29–7.34]    | 7.30 [7.25–7.33]    | 0.001  |
| PCo <sub>2</sub> , mm Hg       | 45 [42–49]          | 45 [42–47]          | 45 [41–51]          | 47 [42–50]          | 45 [41–51]          | 0.88   |
| Po <sub>2</sub> , mm Hg        | 27 [24–30]          | 30 [27–33]          | 28 [26–33]          | 29 [26–31]          | 32 [29–34]          | 0.008  |
| Base excess, mM                | -2.7 [-3.4 to -1.3] | -2.2 [-3.6 to -1.2] | -3.2 [-4.8 to -2.0] | -3.6 [-5.6 to -2.5] | -4.9 [-6.9 to -4.0] | <0.001 |
| Hemoglobin concentration, g/dL | 15.3 [14.6–16.2]    | 14.7 [13.9–15.9]    | 14.4 [13.9–16.6]    | 14.7 [14.1–15.8]    | 15.0 [14.5–16.3]    | 0.41   |
| Oxygen content, mL/dL          | 13.9 [11.8–14.9]    | 14.0 [12.6–15.1]    | 13.8 [12.5–15.1]    | 13.0 [12.3–14.1]    | 14.5 [12.9–15.5]    | 0.35   |

Values are median [interquartile range] or number (%). Intergroup differences were analyzed using the Kruskal-Wallis test or the  $\chi^2$  test.

slower onset of ephedrine which makes early hypotension more likely despite higher mean values for BP. If a potency ratio of 60:1 is assumed, conversion of doses to phenylephrine equivalents results in similar median total doses of 890, 979, 960, 852, and 900  $\mu\text{g}$  for groups 1P to 5E respectively. Our findings alone and in comparison with those of Saravanan et al.<sup>7</sup> highlight the difficulties in comparing potencies of two drugs that differ in speed of onset and duration of action.

There was a significant trend from group 1P to group 5E for the upper level of sensory block at 5 min to increase. This is consistent with a previous report by Cooper et al.<sup>18</sup> who described higher blocks in patients who received infusions of ephedrine compared with phenylephrine. This may be considered a confounding factor in our results because higher cephalad extent of sensory anesthesia is likely to be associated with greater degrees of sympathetic block. However, from group 1P to group 5E, despite the trend towards higher block, less vasopressor was required and SBP was higher overall. Furthermore, we believe that our results provide a valid representation of clinical conditions since any effect of a vasopressor on block height should be integrated into the assessment of the overall response to that drug.

In summary, this study showed that when infusions of solutions containing a mixture of phenylephrine and ephedrine were used to maintain BP during spinal anesthesia for cesarean delivery, hemodynamic control was better with increasing proportion of phenylephrine and decreasing proportion of ephedrine. Umbilical cord blood gas analysis suggested that ephedrine and phenylephrine have differing effects on

O<sub>2</sub> supply and demand, but analysis of fetal acid-base status showed that, overall, phenylephrine has the more favorable net effect. The results of this study support the use of phenylephrine over ephedrine when administered by infusion for the prevention of hypotension associated with the initiation of spinal anesthesia for cesarean delivery. Combinations of phenylephrine and ephedrine appear to have no advantage over phenylephrine alone when given by prophylactic infusion.

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