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Fetal and Maternal Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery

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Background: **In our routine practice, we observed a reduced incidence of fetal acidosis (umbilical artery *p*H < 7.20) at cesarean delivery during spinal anesthesia when a combination of phenylephrine and ephedrine was used as first line vasopressor therapy, compared with using ephedrine alone.**

Methods: **The study was randomized and double blind. It compared phenylephrine 100 μg/ml (phenylephrine group), ephedrine 3 mg/ml (ephedrine group), and phenylephrine 50 μg/ml combined with ephedrine 1.5 mg/ml (combination group), given by infusion, to maintain maternal systolic arterial pressure at baseline during spinal anesthesia for elective cesarean delivery.**

Results: **Fetal acidosis was less frequent in the phenylephrine group (1 of 48) (*P* = 0.004) and less frequent in the combination group (1 of 47) (*P* = 0.005) than in the ephedrine group (10 of 48). The mean systolic arterial pressure was similar for the three groups: Phenylephrine group median 98% (IQR 94–103) of baseline, ephedrine group 100% (96–106) and combination group 101% (97–108) (*P* = 0.11). The mean heart rate was higher in the ephedrine group (median 107% [IQR 99–118] of baseline) than in the phenylephrine group (88% [82–98]) (*P* < 0.0001), or the combination group (96% [86–102]) (*P* < 0.0001). Nausea and vomiting were less frequent in the phenylephrine group (nausea 17%, vomiting 0%) than in the ephedrine group (nausea 66%, vomiting 36%) (*P* < 0.0001), or the combination group (nausea 55%, vomiting 18%) (*P* < 0.0001).**

Conclusions: **Giving phenylephrine alone by infusion at cesarean delivery was associated with a lower incidence of fetal acidosis and maternal nausea and vomiting than giving ephedrine alone. There was no advantage to combining phenylephrine and ephedrine because it increased nausea and vomiting, and it did not further improve fetal blood gas values, compared with giving phenylephrine alone.**

SPINAL anesthesia for elective cesarean delivery has been associated with a higher incidence of fetal acidosis at delivery than epidural or general anaesthesia.[1–4] The increased incidence of fetal acidosis associated with spinal anesthesia is likely to be secondary to maternal hypotension, or to be a side effect of drugs used in the prevention or treatment of hypotension.

Ephedrine is an indirectly acting α- and β-adrenergic agonist. A recent survey found that it was used as the sole vasopressor by 95% of consultant obstetric anesthetists in the United Kingdom.[5] α-Adrenergic agents, such as phenylephrine, were used much less frequently. This is probably because earlier work in pregnant ewes found the treatment of hypotension with α-adrenergic agonists to be associated with reduced uteroplacental perfusion, compared with ephedrine.[6] More recent work in pregnant ewes has found phenylephrine to be safe.[7] Tachyphylaxis can occur with ephedrine and prophylactic ephedrine has been associated with fetal acidosis.[8–10] A quantitative, systematic review of trials of ephedrine *versus* phenylephrine has recently been published.[11] It found blood pressure control to be similar with both vasopressors, but phenylephrine was associated with a higher umbilical artery *p*H at delivery than ephedrine. However, there was no difference in the incidence of fetal acidosis (umbilical artery *p*H < 7.20), or APGAR (appearance, pulse, grimace, activity, and respiration) score of less than 7 at 1 and 5 min.

In our routine practice, we observed that giving a combination of phenylephrine and ephedrine as first line vasopressor therapy was associated with a lower incidence of fetal acidosis at delivery than when ephedrine was used as first line therapy.[12] This study was designed to compare the incidence of fetal acidosis at elective cesarean delivery when an infusion of phenylephrine, or ephedrine, or a combination of both, was given to maintain maternal systolic arterial pressure at baseline during spinal anesthesia. Maternal nausea and vomiting during spinal anesthesia were also compared with the three infusions.

Materials and Methods

The local hospital ethics committee approved this randomized, double-blind study. After obtaining written informed consent, we studied American Society of Anesthesiologists physical status I and II patients scheduled for elective cesarean section under spinal anesthesia. Only women with a singleton pregnancy, with no known fetal abnormality, and no history of preeclampsia or diabetes mellitus, were included.

Before coming to the anesthetic room patients had three blood pressure and heart rate readings recorded with an automated oscillometer, at 3-min intervals, while sitting in bed. The lowest of the three readings was recorded as the baseline value for the maternal systolic arterial pressure and heart rate. The highest nausea and vomiting score was recorded for 30 min before spinal

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anesthesia was induced. Nausea and vomiting were scored: 0 = none, 1 = nausea without vomiting, 2 = vomiting.

Patients were randomly allocated by envelope selection to one of three vasopressor solutions to maintain maternal systolic arterial pressure during spinal anesthesia. The patients, anesthetists, nurses, and midwives involved with patient care were blinded to the patient grouping. The phenylephrine group received phenylephrine 100 μg/ml, the ephedrine group, ephedrine 3 mg/ml, and the combination group, phenylephrine 50 μg/ml combined with ephedrine 1.5 mg/ml. These concentrations were based on unpublished pilot work performed at our hospital to find solutions of similar potency. Immediately before anesthesia, three intravenous solutions were prepared by one of the investigators in three identical unlabelled syringes containing phenylephrine 4 mg, ephedrine 120 mg, or phenylephrine 2 mg combined with ephedrine 60 mg. Each solution was in the same total volume. The syringes were placed on trays labeled for each of the trial solutions in the cupboard of a room adjacent to the anesthetic room. A third party, not involved with the study, opened an envelope containing the code for the patient group and gave the investigator the relevant unlabelled syringe. The solution was then diluted with saline to a total volume of 40 ml.

The anesthetist giving the anesthetic was allowed to choose the spinal anesthetic technique that he or she was most familiar with from one of four standard spinal anesthetic techniques. The reason for not using one standard technique was to address concerns that anesthetists had about using a technique and/or patient position that they did not use routinely. To avoid bias, randomization was stratified by using a separate set of randomization envelopes for each of the standard spinal anesthetic techniques. Technique 1: 2.5 ml of spinal hyperbaric 0.5% bupivacaine with 20 μg of fentanyl, given in the sitting position. Technique 2: 2 ml of spinal levobupivacaine 0.5% with 20 μg of fentanyl, given in the sitting position before an epidural catheter was inserted. Technique 3: 2 ml of spinal levobupivacaine 0.5% with 20 μg of fentanyl, given in the left lateral position before an epidural catheter was inserted. Technique 4: 2.5 ml of spinal levobupivacaine 0.5% with 10 μg of fentanyl, given in the left lateral position before an epidural catheter was inserted. The height of neural blockade to cold sensation was measured using ethyl chloride spray at 10-min postspinal and at skin incision. The target block height was above T5. An epidural top-up, using 0.5% levobupivacaine, was only used predelivery if neural blockade was not sufficiently high or dense with spinal anesthesia alone.

Immediately before spinal anesthesia, a preload of 10 ml/kg of Hartmann solution was rapidly infused. Immediately following the spinal injection the infusion of intravenous vasopressor solution was started, using a Graseby Medical 3400 Anesthesia Pump (Graseby Medical Limited, Colonial Way, Watford, Herts, WD2 4LG, United Kingdom), and adjusted according to a standard protocol. The patients were then placed in the supine position with standard left lateral tilt. Systolic arterial pressure and heart rate were measured every minute following spinal anesthesia using the same automated oscillometer that was used for the baseline blood pressure. The trial solution was given *via* a Y-connector into the same intravenous cannula as the Hartmann solution. The Hartmann solution was infused at approximately 4 ml/min following the preload and a one-way valve prevented reflux of trial solution into the intravenous fluid line. The trial solution was started at 20 ml/h (equating to phenylephrine 33 μg/min for the phenylephrine group, ephedrine 1 mg/min for the ephedrine group, or half the dose rate of each for the combination group). The rate was doubled or halved as necessary to maintain systolic arterial pressure at baseline. The maximum infusion rate in the protocol was 40 ml/h and the minimum rate 1.3 ml/h (it was then discontinued and recommenced as necessary). If more than 40 ml/h of trial solution was required, 1 or 2 ml boluses of trial solution could be given by the syringe driver. If the systolic arterial pressure increased above 1.25 times baseline the infusion was stopped and recommenced at half the rate when the systolic arterial pressure decreased below 1.25 times baseline again. If the systolic arterial pressure decreased below 0.75 times baseline the infusion rate was doubled and a 1 ml bolus given. If the investigator was not able to maintain the systolic arterial pressure above 0.75 times baseline using the trial solution at 40 ml/h, with additional 2 ml boluses as required, the patient was placed in the full left lateral position. If this did not restore systolic arterial pressure above 0.75 times baseline, or hypotension recurred when the patient was returned to the supine position with left tilt, then the code was broken and the vasopressor solution altered as necessary. These patients were analyzed on an "intention to treat" basis.

The study continued until delivery of the fetus. Maternal heart rate was continuously measured with a pulse oximeter. Intravenous glycopyrrolate 200 μg was given for inappropriate or severe bradycardia according to a protocol that included systolic arterial pressure. It was given if maternal heart rate was less than 60 beats/min, and systolic arterial pressure was less than 0.75 of baseline, or if heart rate was less than 50 beats/min, and systolic arterial pressure was less than 1.00 of baseline, or if heart rate was less than 45 beats/min, whatever the systolic arterial pressure. The maximum nausea and vomiting score between spinal and delivery was recorded. At delivery one of the investigators obtained umbilical artery and vein blood samples from a segment of umbilical cord double-clamped before the baby's first breath. A Bayer Rapidlab 248 blood gas analyser (Bayer plc, Bayer

Table 1. Maternal and Fetal Demographic Data

	Phenylephrine Group (n = 48) (%)	Ephedrine Group (n = 50) (%)	Combination Group (n = 49) (%)
Age (yr)	30 (26–35)	29 (27–32)	31 (27–34)
Height (cm)	162 (160–168)	160 (158–166)	160 (155–168)
Weight (kg)	76 (68–89)	80 (70–90)	78 (71–89)
Previous cesarean section	44	46	37
Gestation (weeks)	39 (38–39)	39 (38–39)	39 (38–39)
Breech presentation	35	24	24
Fetal weight (kg)	3.50 (3.27–3.95)	3.37 (2.99–3.76)	3.43 (3.19–3.80)

Data are expressed as a proportion or median (IQR).

House, Strawberry Hill, Newbury, Berkshire, RG14 1JA, United Kingdom) was used for blood gas analysis. Supplemental oxygen was not given to the mother prior to childbirth (giving oxygen to the mother was not routine practice). APGAR scores recorded at 1 and 5 min by a midwife, and the need for tracheal intubation and ventilation, or admission to the special-care baby unit, were recorded. Newborn infants were not studied beyond the immediate postdelivery period.

Statistical Analysis

The study was designed to have an 80% chance of detecting a 15% incidence of fetal acidosis (umbilical artery $p\mathrm{H} < 7.20$) in the ephedrine group, and to have an 80% chance of detecting a difference of 0.03 in the mean umbilical artery *p*H, at $P = 0.05$ (two-sided). The Kruskal-Wallis test was used to compare the three groups. If a difference was found with the Kruskal-Wallis test, pairs of groups were then compared using the Mann–Whitney U test. The Wilcoxon signed-rank test and Spearman rank test were also used to analyze data. The Wilcoxon signed-rank test was used to compare data within a group. $P < 0.05$ was considered significant.

Results

Forty-eight patients were studied in the phenylephrine group, 50 in the ephedrine group and 49 in the combination group. It was not possible to study blood gases for four fetuses: In three (two ephedrine group and one combination group) arterial and venous samples were almost identical, suggesting that both were either arterial or venous, and in one (combination group), it was not possible to obtain umbilical blood samples. These four patients were included for analysis of other variables. The groups were well matched for age, height, weight, gestation, breech presentation, previous cesarean delivery, and birth weight (table 1). The trial infusions were controlled, and all data were collected by one of four investigators (table 2). The groups were well matched for the spinal anesthetics given ($P = 0.99$), for the

Table 2. Operative Data

	Phenylephrine Group (n = 48) (%)	Ephedrine Group (n = 50) (%)	Combination Group (n = 49) (%)
Spinal technique	—	—	—
Technique 1	50	46	47
Technique 2	27	28	29
Technique 3	16	16	16
Technique 4	8	10	8
Investigator	—	—	—
One	31	48	47
Two	35	32	22
Three	23	16	24
Four	10	4	6
Epidural top-up before delivery	4	4	10
Block height at 10 min	T3 (T2–T5)	T3 (T1–T4)	T3 (T2–T6)
Block height at skin incision	T3 (T2–T3)	T2 (C8–T3)	T2 (T2–T3)
Spinal-skin incision (min)	19 (17–23)	20 (18–23)	19 (17–22)
Spinal-delivery (min)	27 (23–30)	27 (24–30)	26 (24–31)
Skin incision-delivery (min)	7 (6–9)	7 (6–8)	7 (5–10)
Uterine incision-delivery	—	—	—
1-min	55	35	55
2-min	32	48	34
3-min	11	10	9
4-min	2	6	2

Data are expressed as a proportion or median (IQR).

Table 3. Baseline and Spinal-delivery Data

	Phenylephrine Group (n = 48) (%)	Ephedrine Group (n = 50) (%)	Combination Group (n = 49) (%)	P Value
Baseline values				
Systolic arterial pressure (mmHg)	115 (109–128)	114 (109–127)	113 (105–128)	$P = 0.63$
Heart rate (beats/min)	88 (78–93)	84 (77–92)	87 (75–95)	$P = 0.73$
Nausea and vomiting				$P = 0.46$
None	75	84	73	
Nausea without vomiting	23	12	24	
Vomiting	2	4	2	
From spinal-delivery				
Fetal acidosis	2	21	2	$P = 0.0007$
1-min APGAR score	9 (9–9)	9 (9–9)	9 (9–9)	$P = 0.53$
5-min APGAR score	9 (9–9)	9 (9–10)	9 (9–10)	$P = 0.35$
Mean systolic arterial pressure as proportion of baseline	98 (94–103)%	100 (96–106)%	101 (97–108)%	$P = 0.11$
Hypotension (systolic arterial pressure $<$ 80% of baseline)	48	68	57	$P = 0.13$
Mean heart rate as proportion of baseline	88 (82–98)	107 (99–118)	96 (86–102)	$P < 0.0001$
Glycopyrrolate required	4	10	2	$P = 0.18$
Nausea and vomiting				$P < 0.0001$
None	83	34	45	
Nausea without vomiting	17	30	37	
Vomiting	0	36	18	
Mean infusion rate (ml/min)	0.33 (0.24–0.47)	0.50 (0.27–0.65)	0.34 (0.24–0.47)	$P = 0.01$

Baseline data for systolic arterial pressure, heart rate, and nausea and vomiting. Spinal-delivery data for fetal acidosis (umbilical pH < 7.20), APGAR scores, mean systolic arterial pressure, hypotension (systolic arterial pressure $<$ 80% of baseline), heart rate, glycopyrrolate, nausea and vomiting, and vasopressor infusion rates. Results expressed as a proportion or median (IQR). (Kruskal-Wallis test).

investigator collecting the data ($P = 0.77$), and for the uterine incision-delivery interval ($P = 0.10$) (table 2). Results are expressed as median (IQR).

Overall, the mean systolic arterial pressure from spinal until delivery was similar for all three groups (table 3). The systolic arterial pressure was also similar over time for the three groups (fig. 1). However, there was a small but statistically significant difference between 20 and 25 min postspinal anesthesia when the mean systolic arterial pressure was lower in the phenylephrine group than in the ephedrine and combination groups (fig. 1). The incidence of hypotension (systolic arterial pressure $<$ 80% of baseline) was similar for the three groups (table 3). However, there were small but statistically significant differences between the three groups for the lowest systolic arterial pressure recorded ($P = 0.04$), and for the proportion of systolic arterial pressure readings below 80% of baseline ($P = 0.02$). The lowest systolic arterial pressure recorded was higher in the phenylephrine group (80% [73–88] of baseline) than in the ephedrine group (73% [61–87] of baseline) ($P = 0.02$), but the combination group (77% [69–86] of baseline) was not significantly different from the phenylephrine ($P = 0.14$) and ephedrine ($P = 0.25$) groups. The proportion of systolic arterial pressure readings below 80% of baseline was lower in the phenylephrine group (0% [0–8]) ($P = 0.007$) and in the combination group (4% [0–10]) ($P = 0.04$) than in the ephedrine group (8% [0–20]), but there was no difference between the phenylephrine and combination groups ($P = 0.55$). The code had to be broken for two patients in the ephedrine group who had a systolic arterial pressure less than 0.75 times baseline, despite treatment with ephedrine and the full left lateral position. Each of these patients was given 100 μg of phenylephrine, which increased the systolic arterial pressure above 0.75 times baseline, and allowed subsequent control of the systolic arterial pressure in the left tilt position with ephedrine given alone.

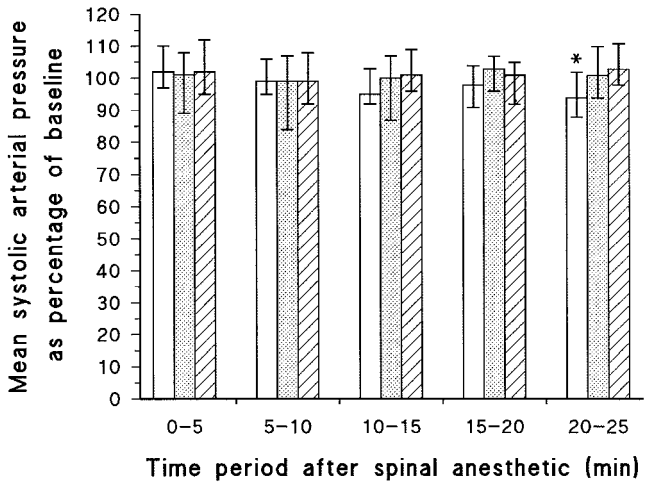

Fig. 1. Mean systolic arterial pressure during spinal anesthesia for the phenylephrine group (open bar), the ephedrine group (shaded bar) and the combination group (cross-hatched bar). Data are expressed as median (IQR). There was a difference between the groups between 20 and 25 min ($P = 0.0001$) (Kruskal-Wallis): The mean systolic arterial pressure was lower in the phenylephrine group than in the ephedrine ($P = 0.0008$) or combination ($P = 0.0001$) groups, but there was no difference between the ephedrine and combination groups ($P = 0.54$) (Mann–Whitney).

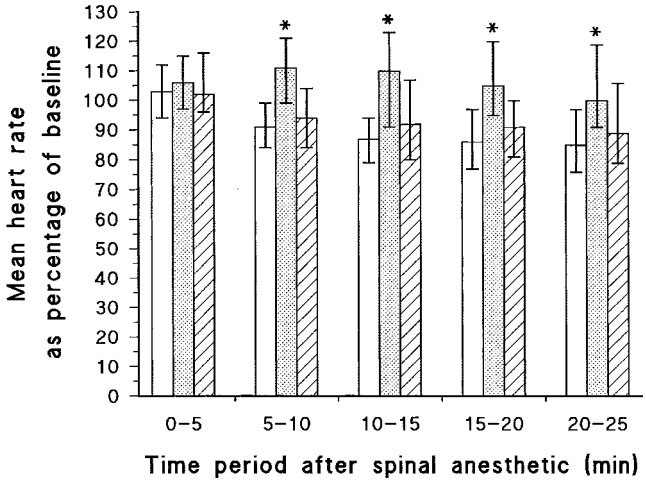

Fig. 2. Mean heart rate during spinal anesthesia for the phenylephrine group (open bar), the ephedrine group (shaded bar) and the combination group (cross-hatched bar). Data are expressed as median (IQR). From 5-min onward there was a difference between the groups ($P < 0.0001$) (Kruskal-Wallis): The mean heart rate was higher in the ephedrine group than in the phenylephrine ($P < 0.0001$) and combination ($P < 0.001$) groups, but there was no difference between the phenylephrine and combination groups for these 5 min intervals ($P > 0.07$).

From 5-min onward, the mean heart rate was higher in the ephedrine group than in the phenylephrine and combination groups (fig. 2). Overall, the mean heart rate in the combination group was lower than in the ephedrine group ($P < 0.0001$) and higher than in the phenylephrine group ($P = 0.008$) (table 3). The highest heart rate recorded differed between the groups ($P < 0.0001$): It was higher in the ephedrine group (137% [124–156] of baseline) than in the phenylephrine group (115% [108–128] of baseline) ($P < 0.0001$) and the combination group (122% [109–140] of baseline) ($P = 0.004$), but there was no difference between the phenylephrine and combination groups ($P = 0.051$). There was no difference in the need to give glycopyrrolate for bradycardia (table 3). One phenylephrine group, no ephedrine group and one combination group patient received glycopyrrolate for a heart rate less than 45 beats/min. One phenylephrine group, one ephedrine group, and no combination group patient received glycopyrrolate for a heart rate less than 50 beats/min with a systolic arterial pressure less than 1.0 times baseline. No phenylephrine group patient, four ephedrine group patients and no combination group patient received glycopyrrolate for a heart rate less than 60 beats/min with a systolic arterial pressure less than 0.75 times baseline.

Fetal acidosis was less frequent in the phenylephrine group (1 of 48) ($P = 0.004$) and less frequent in the combination group (1 of 47) ($P = 0.005$) than in the ephedrine group (10 of 48) (table 3). There was no difference in the incidence of fetal acidosis between the phenylephrine and combination groups ($P = 0.99$). However, 1-min and 5-min APGAR scores were good for all three groups (table 3), and no newborn infant required tracheal intubation, or admission to the special care baby unit, in the immediate postdelivery period. Blood gas values for the three groups are shown in table 4. Blood gas values were similar for the phenylephrine and combination groups. However, the ephedrine group had a lower umbilical artery *p*H than the phenylephrine group ($P = 0.002$), or the combination group ($P = 0.009$), and a lower umbilical vein *p*H than the phenylephrine group ($P = 0.04$), or the combination group ($P = 0.003$). There was no difference in the umbilical vein P_{CO_2} between the groups, but the ephedrine group had a higher umbilical artery P_{CO_2} than the phenylephrine group ($P = 0.004$). This resulted in a greater umbilical arterial minus venous (A − V) P_{CO_2} difference in the ephedrine group than in the phenylephrine group ($P = 0.002$). Table 5 shows the blood gas values for the acidotic fetuses. In the ephedrine group, fetal acidosis was a mixed metabolic and respiratory acidosis. Two fetuses, both in the ephedrine group, had a base deficit of more than ten (11.2 mM and 11.4 mM, respectively).

To investigate the mechanism for the increased acidosis in the ephedrine group, blood gas values have been further analyzed. In the ephedrine group, decreasing umbilical artery *p*H (fetal acidemia) did not correlate with umbilical vein P_{O_2} ($r^2 = 0.00$, $P = 0.71$). However, in the ephedrine group, decreasing umbilical artery *p*H

Table 4. Umbilical Blood Gas Values

	Phenylephrine Group ($n = 48$)	Ephedrine Group ($n = 48$)	Combination Group ($n = 47$)	*P* Value
Arterial *p*H	7.31 (7.29–7.33)	7.29 (7.23–7.31)	7.31 (7.28–7.32)	$P = 0.004$
Venous *p*H	7.37 (7.35–7.38)	7.36 (7.32–7.37)	7.37 (7.35–7.39)	$P = 0.009$
V − A *p*H difference	0.05 (0.05–0.07)	0.07 (0.06–0.10)	0.07 (0.05–0.08)	$P = 0.003$
Arterial P_{O_2} (mmHg)	14 (9–17)	12 (10–15)	11 (8–15)	$P = 0.17$
Venous P_{O_2} (mmHg)	28 (23–31)	24 (21–28)	25 (22–29)	$P = 0.12$
Arterial P_{CO_2} (mmHg)	52 (48–56)	57 (50–64)	54 (50–58)	$P = 0.01$
Venous P_{CO_2} (mmHg)	40 (37–44)	42 (38–44)	41 (37–43)	$P = 0.17$
A − V P_{CO_2} difference (mmHg)	11 (9–13)	14 (11–17)	13 (10–16)	$P = 0.006$
Arterial base deficit (mM)	1.8 (0.0–2.9)	2.2 (0.6–4.6)	1.4 (0.4–2.9)	$P = 0.16$
Venous base deficit (mM)	2.6 (1.4–3.4)	2.8 (1.7–3.9)	2.2 (0.9–3.3)	$P = 0.12$

Umbilical artery and vein *p*H, P_{O_2}, P_{CO_2}, base deficit, venous minus arterial (V − A) *p*H difference and arterial minus venous (A − V) P_{CO_2} difference, expressed as median (IQR). (Kruskal-Wallis test).

Table 5. Blood Gas Values for the Acidotic Fetuses (Umbilical Artery *p*H < 7.20)

	Phenylephrine Group (n = 1)	Ephedrine Group (n = 10)	Combination Group (n = 1)
Arterial *p*H	7.16	7.17 (7.01–7.19)	7.18
Venous *p*H	7.25	7.29 (7.13–7.36)	7.37
Arterial P_{O_2} (mmHg)	14	10 (6–24)	8
Venous P_{O_2} (mmHg)	27	23 (19–39)	33
Arterial P_{CO_2} (mmHg)	75	69 (58–89)	56
Venous P_{CO_2} (mmHg)	56	47 (36–58)	33
Arterial base deficit (mM)	5.0	4.8 (2.6–11.4)	8.5
Venous base deficit (mM)	4.0	4.8 (2.8–6.8)	8.4

Data are expressed as median (range) for the ephedrine group.

correlated strongly with increasing A − V P_{CO_2} difference (fig. 3). The umbilical A − V P_{CO_2} difference was 77% greater in the acidotic than in the nonacidotic ephedrine group fetuses (median A − V P_{CO_2} difference 23 (16–26) mmHg, compared with 13 (10–16) mmHg, respectively) ($P = 0.0001$). In the ephedrine group, increasing A − V P_{CO_2} difference correlated strongly with increasing mean ephedrine dose (fig. 4), but it did not correlate with the mean systolic arterial pressure ($r^2 = 0.06$, $P = 0.09$), or with the lowest systolic arterial pressure recorded ($r^2 = 0.07$, $P = 0.07$). In the phenylephrine group there was no correlation between umbilical A − V P_{CO_2} difference and the mean phenylephrine dose ($r^2 = 0.05$, $P = 0.12$), the mean systolic arterial pressure ($r^2 = 0.03$, $P = 0.26$), or the lowest systolic arterial pressure recorded ($r^2 = 0.00$, $P = 0.73$).

Baseline nausea and vomiting scores were similar for the three groups (table 3). There was no change in the nausea and vomiting score from baseline for the phenylephrine group ($P = 0.30$), but the nausea and vomiting score increased from baseline in the ephedrine group ($P < 0.0001$), and in the combination group ($P = 0.007$).

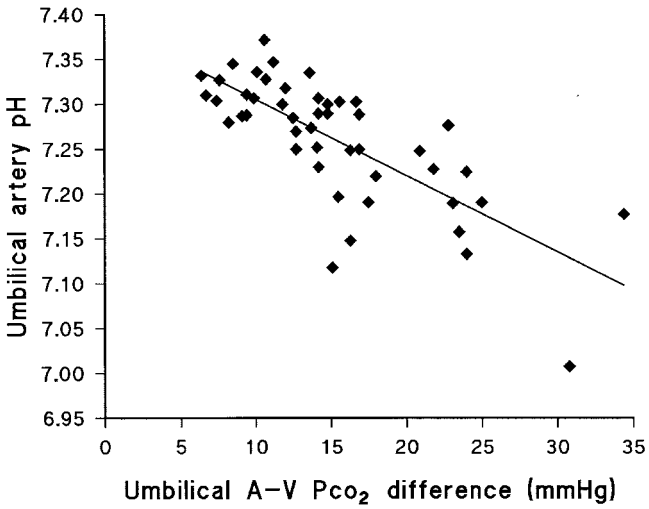

Fig. 3. Association between umbilical artery pH and umbilical arterial minus venous (A − V) P_{CO_2} difference for the ephedrine group: $r^2 = 0.55$, $P < 0.0001$.

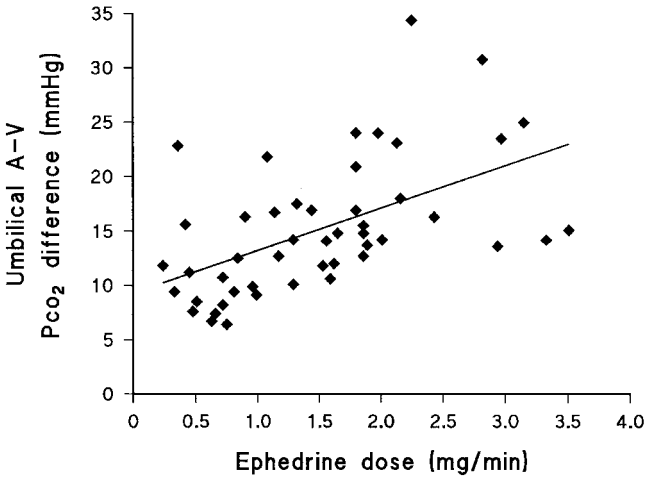

Fig. 4. Association between umbilical arterial minus venous (A − V) P_{CO_2} difference and ephedrine dose: $r^2 = 0.28$, $P = 0.0001$.

The nausea and vomiting score was lower in the phenylephrine group than in the ephedrine ($P < 0.0001$) or combination ($P < 0.0001$) groups, but there was no significant difference between the ephedrine and combination groups ($P = 0.09$). In the ephedrine group, vomiting was associated with decreased systolic arterial pressure, decreased heart rate, and increased ephedrine dose. For the ephedrine group patients who vomited (n = 18) and those ephedrine group patients without nausea or vomiting (n = 17), the lowest systolic arterial pressures recorded were 62% (54–71) and 87% (75–93) of baseline, respectively ($P = 0.0002$), the lowest heart rates recorded were 71% (66–80) and 92% (81–103) of baseline, respectively ($P = 0.0006$), and the mean ephedrine doses were 1.8 (1.3–2.9) and 0.9 (0.5–1.4) mg/min, respectively ($P = 0.002$). There was no difference in the block height at 10-min, or at skin incision, for the ephedrine group patients who vomited, compared with the ephedrine group patients without nausea or vomiting ($P = 0.57$ and $P = 0.36$, respectively).

If patients in the ephedrine group with the most severe hypotension (lowest systolic arterial pressure recorded < 60% of baseline) were excluded from analysis, there was no difference in the mean systolic arterial pressure, or in the incidence, severity, or duration of hypotension, between the groups (table 6). However, the ephedrine group still had the highest incidence of fetal acidosis, and the phenylephrine group still had the lowest nausea and vomiting score (table 6).

Discussion

This study found that the incidence of fetal acidosis at cesarean delivery under spinal anesthesia was reduced by giving phenylephrine, alone, or in combination with ephedrine, compared with giving ephedrine alone. Only 1 of 48 phenylephrine group fetuses, and 1 of 47 com-

Table 6. Effect of Excluding the Most Severely Hypotensive Ephedrine Group Patients from Analysis

	Phenylephrine Group (n = 48)	Ephedrine Group (n = 40)	Combination Group (n = 49)	P Value
Fetal acidosis	2%	16%	2%	$P = 0.01$
Nausea and vomiting				$P < 0.0001$
None	83%	43%	45%	
Nausea without vomiting	17%	30%	37%	—
Vomiting	0%	28%	18%	—
Mean systolic arterial pressure as proportion of baseline	98 (94–103)%	100 (98–107)%	101 (97–108)%	$P = 0.051$
Hypotension (systolic arterial pressure < 80% of baseline)	48%	60%	57%	$P = 0.48$
Lowest systolic arterial pressure as proportion of baseline	80 (73–88)%	77 (66–91)%	77 (69–86)%	$P = 0.50$
Systolic arterial pressure readings < 80% of baseline	0 (0–8)%	4 (0–15)%	4 (0–10)%	$P = 0.50$

Fetal acidosis, nausea and vomiting, and systolic arterial pressure control, when ephedrine group patients with the most severe hypotension (lowest systolic arterial pressure recorded < 60% of baseline) (n = 10) were excluded from analysis. Data are expressed as proportion or median (IQR). (Kruskal-Wallis).

bination group fetuses were acidotic, compared with 10 of 48 in the ephedrine group. The fetal acidosis was mixed; a metabolic and respiratory acidosis. Two fetuses, both in the ephedrine group, had a severe metabolic component to the acidosis (base deficit more than ten).

The increased incidence of fetal acidosis associated with giving ephedrine alone could have been caused by reduced uteroplacental perfusion from decreased maternal artery pressure, reduced uteroplacental perfusion from ephedrine-induced uteroplacental vasoconstriction, or by a direct fetal effect of ephedrine. Uteroplacental resistance or flow were not measured directly, but there is indirect evidence which suggests that reduced uteroplacental perfusion was not the main mechanism for the increased incidence of acidosis in the ephedrine group. The mean systolic arterial pressure was similar for the three groups throughout the study, but there was a small increase in the severity and duration of hypotension in the ephedrine group. However, if the ephedrine group patients with severe hypotension were excluded from analysis, there was no difference in the incidence, severity, or duration of hypotension between the three groups, yet the incidence of fetal acidosis in the ephedrine group remained higher than in the phenylephrine and the combination groups. It is therefore unlikely that reduced uteroplacental perfusion secondary to reduced uterine artery perfusion pressure was the main mechanism for the increased acidosis in the ephedrine group. It is also unlikely that reduced uteroplacental perfusion secondary to ephedrine-induced uteroplacental vasoconstriction was the main mechanism. Work in pregnant ewes has shown ephedrine to be a less potent uterine artery vasoconstrictor than α-adrenergic agonist agents.[13] A recent study comparing the α agonist metaraminol with ephedrine during spinal anesthesia for elective cesarean section did not find a difference in uterine artery blood flow using Doppler ultrasound.[14] Furthermore, a reduction in uteroplacental perfusion sufficient to cause fetal acidosis would have been expected to decrease the umbilical vein Po_2 by reducing delivery of oxygen to the placenta. However, in the ephedrine group, there was no association between fetal acidemia (decreasing umbilical artery pH) and umbilical vein Po_2.

Analysis of the umbilical arterial and venous blood Pco_2 provides indirect evidence for a fetal mechanism for the increased acidosis in the ephedrine group. A study has found that a profound reduction in uteroplacental perfusion secondary to abruptio placentae, sufficient to cause severe fetal acidosis (median pH 6.87 [IQR 6.78–7.05]), was not associated with a high umbilical arterial minus venous (A − V) Pco_2 difference (median difference 13 [IQR 6–15] mmHg).[15] However, in our study, acidemia was strongly associated with an increasing umbilical A − V Pco_2 difference: The A − V Pco_2 difference for ephedrine group fetuses without acidosis (an umbilical arterial pH $\geq$ 7.20) was median 13 (IQR 10–16) mmHg, whereas for those with acidosis (pH < 7.20) it was 23 [16–26] mmHg ($P = 0.0001$). A possible fetal mechanism for fetal acidosis is umbilical vessel constriction secondary to α-adrenergic stimulation. Reduced umbilical vessel blood flow does produce acidosis that is associated with an increase in umbilical A − V Pco_2 difference: Severe fetal acidosis (median pH 7.05 [IQR 6.98–7.07]) secondary to cord prolapse was associated with a high umbilical A − V Pco_2 difference (median difference 40 [23–44] mmHg).[15] However, it is unlikely that reduced umbilical vessel blood flow was the reason for the increased fetal acidosis with ephedrine in our study. This is because ephedrine has less α-adrenergic activity than phenylephrine, β-adrenergic stimulation has been shown to increase umbilical vessel blood flow,[16] and both vasopressors have been shown to have a minimal effect on umbilical artery pulsatility index.[17]

Ephedrine-induced β-adrenergic stimulation of the fetus is a possible mechanism for fetal acidemia that does not involve the uteroplacental or fetoplacental circula-

tions. β-Adrenergic stimulation of the fetal lamb with isoproterenol produces an initial increase in oxygen consumption, and an increase in glucose and lactic acid concentrations.[16] The authors proposed that β-adrenergic stimulation increased anaerobic glycolysis because basal oxygen delivery to the fetus was at or near maximum. In humans, ephedrine given to the mother has fetal effects. It can increase fetal heart rate and fetal catecholamine levels.[18,19] Giving a β2-adrenergic stimulant to the mother for 2 h prior to delivery of the fetus by elective cesarean section can cause fetal metabolic acidemia.[20] In our study, the umbilical vein P_{CO_2} was similar in the ephedrine and phenylephrine groups, but the umbilical artery P_{CO_2} was higher in the ephedrine group than in the phenylephrine group. Provided that the umbilical vessel blood flow was no lower in the ephedrine group than in the phenylephrine group, this is evidence of increased CO_2 production by the fetus, supporting an increase in fetal metabolic rate in the ephedrine group. In the ephedrine group, the A − V P_{CO_2} difference was 77% greater in the acidotic fetuses, suggesting that the metabolic rate was greater in the acidotic, than in the nonacidotic, ephedrine group fetuses. We therefore believe that increased fetal metabolic rate, secondary to ephedrine-induced β-adrenergic stimulation, was the most likely mechanism for the increased incidence of fetal acidosis in the ephedrine group. The addition of phenylephrine to ephedrine allowed a two-thirds reduction in the dose of ephedrine, which probably explains the low incidence of fetal acidosis in the combination group.

Our results are supported by the findings of two recent studies. They found that using vasopressor infusions with a greater degree of α-adrenergic receptor activity than ephedrine decreased fetal acidosis at cesarean delivery. The first study compared metaraminol with ephedrine.[14] The second study compared a combination of phenylephrine and ephedrine, with ephedrine.[21] The study comparing metaraminol and ephedrine found that ephedrine was associated with more acidosis even though there was no difference in hypotension between the groups.[14] There is further evidence that ephedrine itself can produce fetal acidosis. Giving prophylactic ephedrine during epidural or spinal anesthesia can increase fetal acidosis, despite a reduction in hypotension.[8–10] However, this does not necessarily mean that the use of α-adrenergic agonists is better for the fetus than ephedrine. Current evidence supports APGAR scores as a better predictor of neonatal outcome than measurement of umbilical artery pH.[22] In our study, APGAR scores were good for all newborn infants, and none required tracheal intubation and ventilation, or admission to the special care baby unit, in the immediate postdelivery period. There may even be benefits from fetal catecholamine stimulation before delivery. A study has found that maternal administration of a β2-adrenergic agonist prior to delivery by elective cesarean section can increase dynamic lung compliance, decrease airway resistance, decrease respiratory rate and reduce the risk of hypoglycemia in the newborn infant.[20] Further work is required to examine possible hemodynamic respiratory and metabolic effects on newborn infants when phenylephrine and/or ephedrine are given to the mother during elective cesarean delivery. It is possible that fetuses with preexisting compromise may not tolerate the decrease in *p*H that can occur with ephedrine as well as the low-risk fetuses did in our study. Further work is therefore also required to compare fetal outcome when phenylephrine and/or ephedrine are used during cesarean delivery where there is a higher risk of preexisting fetal compromise.

Maternal nausea and vomiting is a significant problem during spinal anesthesia for cesarean delivery. In our study, significant differences in nausea and vomiting occurred between groups despite similar systolic arterial pressure control. When phenylephrine was given alone, spinal anesthesia was not associated with a change in nausea and vomiting from baseline, even though hypotension did occur. In contrast, when ephedrine was given alone, or in combination with phenylephrine, spinal anesthesia was associated with a highly significant increase in nausea and vomiting from baseline, and with more nausea and vomiting than with giving phenylephrine alone. The differences in nausea and vomiting between the phenylephrine and combination groups occurred even though there were no differences in systolic arterial pressure control. The differences in nausea and vomiting between the phenylephrine and ephedrine groups persisted even if those ephedrine group patients with the most severe hypotension were excluded from analysis, thereby eliminating the small differences in hypotension. This suggests that a difference in hypotension was not the main reason for the difference in nausea and vomiting between the groups. The nausea and vomiting may have been a direct effect of ephedrine, but this is unlikely because ephedrine has been shown to have antiemetic properties following gynecological surgery.[23] Nausea and vomiting may have been secondary to an absolute, or relative, increase in vagal tone. There is evidence for a vagal mechanism causing nausea during spinal anesthesia. Atropine has been found to be more effective at treating nausea associated with high spinal anesthesia than vasopressors.[24] More recently, glycopyrrolate has been found to reduce nausea during spinal anesthesia for cesarean delivery.[25] In our study, in the ephedrine group, vomiting was associated with a decrease in systolic arterial pressure, but it was also associated with a decrease in heart rate. This provides evidence of an increase in vagal tone in the ephedrine group patients who vomited. However, there was no evidence that this was because of more extensive neural blockade. A possible alternative explanation is a reflex increase in vagal tone that can occur following a reduction in cardiac preload.[26–29] There is evidence that this

vagal reflex is more likely to occur if there is also β-adrenergic stimulation.[27–29] Reduced preload is a major feature of spinal anesthesia for cesarean delivery because of vasodilatation and caval compression. In our study, giving phenylephrine alone may have reduced the risk of a reflex increase in vagal tone by producing more effective venoconstriction, thereby increasing preload, and by avoiding excessive β-adrenergic stimulation. This may explain why we found highly significant differences in nausea and vomiting between groups when there was no significant difference in systolic arterial pressure control.

All three vasopressor solutions were similarly effective at maintaining the mean systolic arterial pressure near baseline. However, two women in the ephedrine group did require the code to be broken because of hypotension, not responding to ephedrine, and full left lateral tilt. Only 100 μg of phenylephrine was required for each of these women, in conjunction with the ephedrine infusion, to treat the hypotension and to allow the left tilt position to be resumed. This supports the use of phenylephrine for hypotension resistant to treatment with ephedrine. There were significant differences in maternal heart rate between the groups. The mean maternal heart rate was lowest for the phenylephrine group and highest for the ephedrine group. However, the need to give glycopyrrolate for severe or inappropriate bradycardia was similar for the three groups.

This study found that using an infusion of phenylephrine to maintain systolic arterial pressure during spinal anesthesia for elective cesarean delivery can decrease fetal acidosis, and maternal nausea and vomiting, compared with using ephedrine alone. There was no advantage in combining phenylephrine and ephedrine because it increased maternal nausea and vomiting, and it did not further improve fetal blood gas values, compared with using phenylephrine alone.

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