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Comparison of Metaraminol and Ephedrine Infusions for Maintaining Arterial Pressure during Spinal Anesthesia for Elective Cesarean Section

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Background: **Although ephedrine is usually recommended as the first-line vasopressor in obstetrics, its superiority over other vasopressors has not been proven in humans.**

Methods: **In a double-blind study, the authors randomized women having elective cesarean section with spinal anesthesia to receive an intravenous infusion of ephedrine, starting at 5 mg/min (n = 25), or metaraminol, starting at 0.25 mg/min (n = 25), titrated to maintain systolic arterial pressure in the target range 90–100% of baseline. Umbilical cord gases, maternal hemodynamics, uterine artery pulsatility index, and Apgar scores were compared.**

Results: **Systolic arterial pressure was maintained more closely in the target range in the metaraminol group compared with the ephedrine group. In the metaraminol group, umbilical arterial *p*H was greater (median and interquartile range, 7.31 and 7.31–7.33 *vs.* 7.24 and 7.14–7.29; $P < 0.0001$), and umbilical venous *p*H was greater (7.36 and 7.35–7.38 *vs.* 7.33 and 7.26–7.34; $P < 0.0001$) compared with the ephedrine group. No patient in the metaraminol group had umbilical arterial *p*H less than 7.2, compared with nine patients (39%) in the ephedrine group ($P = 0.0005$). Apgar scores were similar between groups. Changes in uterine artery pulsatility index were similar between groups.**

Conclusions: **When used by infusion to maintain arterial pressure during spinal anesthesia for cesarean section, metaraminol was associated with less neonatal acidosis and more closely controlled titration of arterial pressure compared with ephedrine.**

THE first-line drug that is usually recommended to treat hypotension associated with regional anesthesia in obstetrics is ephedrine. This is because early animal studies suggested that ephedrine, which is a predominantly β-adrenergic agonist, was better at increasing maternal arterial pressure while preserving uterine blood flow compared with other vasopressors.[1,2] However, despite the wide acceptance of ephedrine as the vasopressor of choice in pregnancy, its superiority over other vasopressors has not been proven in pregnant humans. On the contrary, the use of ephedrine to prevent or treat hypotension associated with regional anesthesia might even worsen fetal acidosis,[3,4] and recent clinical studies have suggested that α-adrenergic agonist drugs may, in fact, be safe alternatives to ephedrine in elective cases.[5–11]

Metaraminol is a mixed α- and β-adrenergic agonist that has predominant α effects at doses used clinically. Early animal studies found that metaraminol increased both maternal arterial pressure and uteroplacental blood flow during spinal anesthesia in pregnant sheep,[12,13] and it was reported that metaraminol was more effective than the pure α agonist methoxamine in correcting fetal deterioration caused by hypotension from spinal anesthesia.[14] Studies in nonpregnant patients have shown metaraminol to be more effective than ephedrine at maintaining arterial pressure during spinal anesthesia.[15] However, few data are available comparing metaraminol with ephedrine in pregnant humans. Therefore, in a randomized, double-blind study, we compared metaraminol with ephedrine for the maintenance of arterial pressure in women receiving spinal anesthesia for cesarean section. The outcomes we compared were umbilical cord blood gases, maternal hemodynamics, uterine artery flow velocity profiles, and Apgar scores.

Materials and Methods

After obtaining approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong, we recruited 50 women with American Society of Anesthesiologists physical status I and II, who had term singleton pregnancies and were undergoing elective cesarean section with spinal anesthesia. All patients gave written informed consent. Patients with preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, known fetal abnormalities, or contraindications to spinal anesthesia were excluded.

Patients were premedicated with 150 mg ranitidine administered orally the night before and on the morning of surgery and 0.3 M sodium citrate 30 ml on arrival to the operating room. Standard monitoring included noninvasive arterial pressure, electrocardiogram, and pulse oximetry. Baseline systolic arterial pressure (SAP) and heart rate (HR) were calculated as the mean of three successive measurements taken 1 min apart after an initial 5–10-min period of stabilization. Baseline uterine artery vascular resistance was estimated by measuring uterine artery pulsatility index (PI). A large bore intravenous catheter was inserted into a forearm vein, and 20 ml/kg lactated Ringer's solution was administered

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over 10–15 min, after which the infusion was slowed to the minimum rate required to maintain vein patency. The patient was then turned to the right lateral position, and spinal anesthesia was administered. After skin infiltration with lidocaine, a 25-gauge Whitacre needle was inserted at the L2–L3 or L3–L4 vertebral interspace, and 2.0 ml of hyperbaric 0.5% bupivacaine and 15 μg fentanyl were injected intrathecally. The patient was then immediately turned supine with left lateral tilt.

Oxygen (5 l/min) was administered by clear face mask until delivery. Arterial pressure was measured at 1-min intervals beginning 1 min after spinal injection. Hemodynamic data were downloaded to a Macintosh computer from the anesthetic machine (Narkomed 4, North American Dräger, Telford, PA) using software developed within our department (*Monitor*, by James L. Derrick, M.B.B.S., F.A.N.Z.C.A., Senior Medical Officer, Prince of Wales Hospital, Shatin, Hong Kong, China§).

After induction of spinal anesthesia, arterial pressure was maintained using intravenous infusion of either 10 mg/ml ephedrine (ephedrine group) or 0.5 mg/ml metaraminol (metaraminol group) using a syringe pump (Terfusion STC-527, Terumo Corporation, Tokyo, Japan) that was connected to the running intravenous line. The ratio of concentrations was based on data from a comparison of ephedrine and metaraminol in nonobstetric patients previously published from our department.[16] Patients were randomly allocated to groups by drawing of shuffled, opaque, coded envelopes that were opened immediately before starting each case. Syringes containing the study drug were prepared by an anesthesiologist not involved with patient assessment. Our target for vasopressor administration was to maintain arterial pressure within the range 90–100% of baseline. Vasopressor was started when SAP decreased to less than 90% of the baseline value. An initial bolus dose of 1 ml (10 mg ephedrine or 0.5 mg metaraminol) was administered, and the infusion was started at 0.5 ml/min (5 mg/min ephedrine or 0.25 mg/min metaraminol). Infusions were adjusted as required after each 1-min measurement of SAP and only stopped if SAP increased above the baseline value. After each measurement, if SAP was less than 80% of the baseline value, the infusion was increased by 0.5 ml/min. If, after stopping, SAP decreased below 90% of baseline again, the infusion was restarted at 0.5 ml/min and titration resumed. The infusion protocol was continued until delivery, after which management was at the discretion of the attending anesthesiologist. Nausea and vomiting not associated with hypotension were treated with 10 mg intravenous metoclopramide.

After 10 min, the upper sensory level of anesthesia was measured by assessing loss of pinprick discrimination, and preparation and surgery were allowed to start. The times of skin incision, uterine incision, and delivery were recorded by stopwatch. After delivery, Apgar scores were assessed at 1 and 5 min by the attending pediatrician, and arterial and venous blood samples were taken from a double-clamped segment of umbilical cord for immediate blood gas analysis using a Ciba-Coring 278 Blood Gas System (Ciba-Corning, Medfield, MA) blood gas analyzer. The total dose of vasopressor used until delivery was recorded from the electronic memory of the syringe pump.

Doppler Ultrasound

Measurements of uterine artery PI were made before induction of anesthesia, 1 min after administration of the initial vasopressor bolus dose, and 2, 5, and 10 min after spinal injection. All Doppler studies were performed on the right uterine artery by a single operator (T. K. L.) using a color duplex pulsed Doppler ultrasound scan (Aloka SSD-5500) with a 5 MHz transabdominal probe (Aloka, Tokyo, Japan). The probe was placed initially on the lower lateral quadrant of the abdomen angled medially.

The external iliac artery was identified, and color Doppler was activated to locate the uterine artery that crossed the external iliac artery.[17] The pulsed Doppler range gate was then placed in the center of the artery to obtain the maximum flow velocity waveform. When at least three consecutive waveforms of the same quality had been obtained, which usually took less than 10 s, the image was frozen and the average of the PI of the three waveforms was calculated as the PI of that artery. PI is defined as $(S - D)/A$, where S is the peak systolic frequency shift, D is the end-diastolic frequency shift, and A is the temporal mean frequency shift over one cardiac cycle.

Statistical Analysis

Prospective power analysis was based on potential differences in umbilical cord blood gases using data from normal deliveries[18] and our own previous studies of patients undergoing cesarean section. This showed that a sample size of 22 patients per group would have 90% power at the 5% significance level to detect a difference in umbilical arterial *p*H of 0.05 units. To allow for possible dropouts, we recruited 25 patients per group.

Intergroup comparisons of single variable data were made using the Student *t* test for parametric data or the Mann–Whitney U test for nonparametric data. Nominal data were compared using the chi-square or Fisher exact test. These analyses were performed using Statview for Windows 4.53 (Abacus Concepts Inc., Berkeley, CA). Serial measurements of SAP, HR, and PI were analyzed using SPSS 10.0 (SPSS Inc., Chicago IL). A repeated-measures analysis of variance model was used to examine group differences in measurements over time. The within-subject factor was measurements taken at inter-

§ Available at http://www.cuhk.edu.hk/med/ans/softwares.htm.

Table 1. Patient Characteristics

	Ephedrine Group (n = 25)	Metaraminol Group (n = 25)	*P*
Age (yr)	32 (3)	33 (4)	0.6
Weight (kg)	66 (10)	67 (8)	0.8
Height (cm)	155 (7)	155 (5)	0.9
Upper level of block (dermatome)	T4 (T1–T9)	T2.5 (T1–T6)	0.6
Intraoperative nausea or vomiting	5 (20%)	1 (4%)	0.3
Induction to uterine incision time (min)	24.8 (18.9–38.2)	28.5 (20.8–49.1)	0.06
Uterine incision to delivery time (s)	88 (30–236)	78 (140–164)	0.9

Values are mean (SD), median [range], or number (%).

vals, the between-subject factor was group, and the interaction between group and measurements was analyzed. The mean of each measurement at each time interval was compared with the mean in the subsequent time interval in the model. The Greenhouse-Geisser procedure was used after checking for variance–covariance matrix sphericity assumptions. $P < 0.05$ was considered statistically significant.

Results

All patients required vasopressor. Spinal anesthesia was initially inadequate for surgery in two patients in the ephedrine group, of whom one patient received repeat spinal anesthesia and one patient received conversion to epidural anesthesia. Data were lost from one patient in the metaraminol group because of software failure in the monitoring module of the anesthetic machine, and from one patient in the metaraminol group in whom severe shivering prevented accurate data collection. Hemodynamic and Doppler velocimetry data were excluded from analysis for these four patients, but because each of these patients did receive the allocated vasopressor, neonatal outcome data were included for analysis on an intention-to-treat basis. Of the remaining patients, we were unable to complete Doppler velocimetry studies in two patients in the ephedrine group and four patients in the metaraminol group for technical reasons. Umbilical arterial blood samples could not be obtained from two patients in the ephedrine group.

Patient demographic characteristics and surgical times were similar between groups (table 1). Four patients in the ephedrine group and one patient in the metaraminol group had intraoperative nausea or vomiting ($P = 0.3$).

Neonatal outcome is summarized in table 2. Umbilical arterial and venous *p*H and umbilical arterial oxygen tension were greater in the metaraminol group compared with the ephedrine group. Umbilical arterial and venous carbon dioxide tensions were lower in the metaraminol group compared with the ephedrine group. Nine patients in the ephedrine group had umbilical arterial *p*H less than 7.2, compared with no patient in the metaraminol group ($P = 0.0005$). Apgar scores were similar between groups.

Changes in SAP, HR, and vasopressor consumption are shown in figure 1 and table 3. Although there was no difference in SAP between groups ($P = 0.3$), there was a significant difference in SAP over time ($P < 0.001$) and a significant interaction between SAP and group ($P = 0.03$). Mean SAP varied significantly between groups from 11 min ($P = 0.03$), when it increased above the target range in the ephedrine group but remained within the target range in the metaraminol group. Ten patients in the ephedrine group and eight patients in the metaraminol group had one or more episodes of a decrease in SAP to less than 80% of the baseline value ($P = 0.6$). There was a significant difference in HR between groups ($P = 0.002$) and HR over time ($P < 0.001$), and a significant interaction between HR and group ($P < 0.001$). Mean HR varied significantly between groups

Table 2. Neonatal Outcome

	Ephedrine Group (n = 25)	Metaraminol Group (n = 25)	*P*
Umbilical arterial blood gases			
*p*H	7.24 (7.14–7.29)	7.31 (7.31–7.33)	< 0.0001
P_{CO_2} (mmHg)	58 (55–68)	51 (49–55)	< 0.0001
P_{O_2} (mmHg)	15 (12–19)	18 (15–21)	0.03
Base excess (mM)	−6.4 (−7.6 to −3.3)	−2.1 (−3.8 to −1.4)	< 0.0001
Patients with umbilical arterial *p*H < 7.2	9 (39%)	0 (0%)	0.0005
Umbilical venous blood gases			
*p*H	7.33 (7.26–7.34)	7.36 (7.35–7.38)	< 0.0001
P_{CO_2} (mmHg)	46 (42–50)	43 (40–46)	0.01
P_{O_2} (mmHg)	32 (28–35)	34 (31–37)	0.2
Base excess (mM)	−4.6 (−5.5 to −3.0)	−1.9 (−2.8 to 0.0)	< 0.0001
Apgar scores < 7 at 1 min	1 (4%)	1 (4%)	1.0
Apgar scores < 7 at 5 min	0 (0%)	0 (0%)	1.0

Values are median (interquartile range) or number (%).

P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

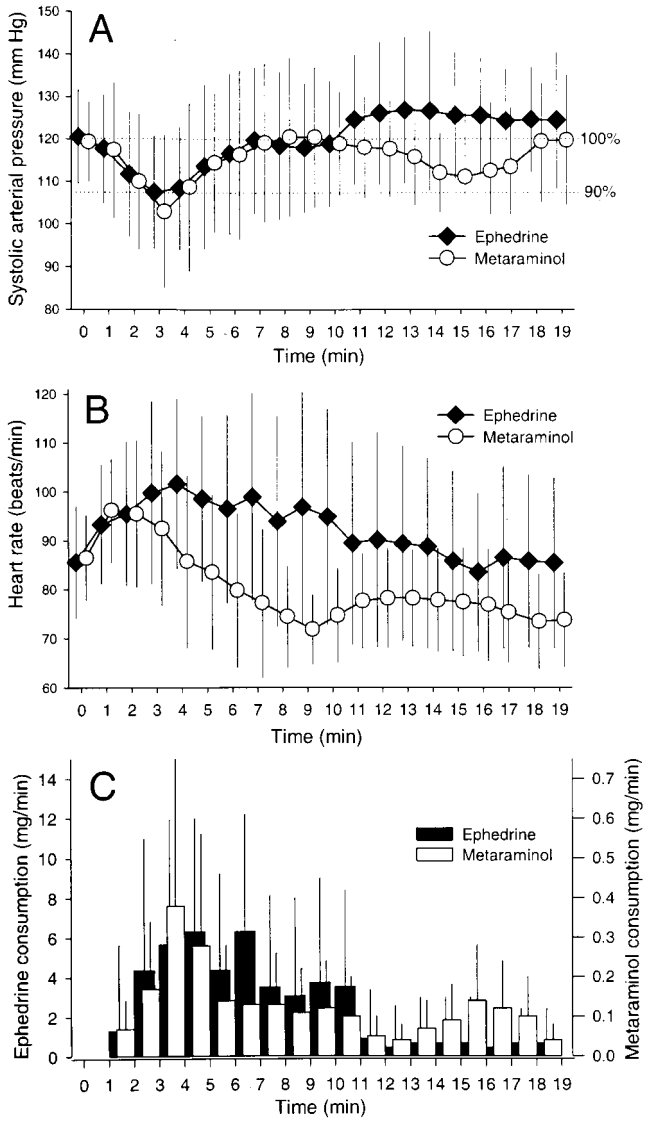

Fig. 1. Changes in systolic arterial pressure (*A*), heart rate (*B*), and vasopressor consumption (*C*) against time. Dotted lines in (*A*) show approximate target range for systolic arterial pressure. There was a significant difference between groups for changes of systolic arterial pressure over time ($P = 0.03$) and changes in heart rate over time ($P < 0.001$).

from 3 min, when it began to decrease in the metaraminol group, whereas it continued to increase in the ephedrine group ($P < 0.001$). Total volume of drug consumption was similar between groups, although there was a trend toward a greater volume in the metaraminol group (mean, 6.2 ml; 95% confidence interval, 5.5–7.0 ml) compared with the ephedrine group (mean, 5.0 ml; 95% confidence interval, 3.9–5.1 ml; $P = 0.06$). Analysis of vasopressor consumption over time showed a trend toward a greater volume of ephedrine consumption in the first half of the period before delivery compared with more uniform metaraminol consumption during the study period ($P = 0.07$).

Changes in uterine artery PI are shown in figure 2. Baseline PI was similar between groups. There was no

Table 3. Incidence of Hypotension, Maximum Changes in Systolic Arterial Pressure, and Total Vasopressor Consumption

	Ephedrine Group (n = 23)	Metaraminol Group (n = 23)	*P*
Number of patients with one or more episodes of SAP < 80% of baseline	10 (44%)	8 (35%)	0.8
Lowest recorded SAP (mmHg)	96 (13) [74–118]	92 (16) [58–120]	0.4
Highest recorded SAP (mmHg)	137 (16) [117–174]	138 (16) [115–171]	0.8
Total vasopressor consumption (ml)	5.0 (2.5)	6.2 (3.1)	0.06
Total vasopressor consumption (mg)	50.0 (25.1)	3.1 (0.9)	

Values are number (%) or mean (SD) [range].
SAP = systolic arterial pressure.

significant change in PI over time ($P = 0.2$), between groups ($P = 0.2$), or between groups over time ($P = 0.3$). Comparison of PI values 1 min after the initial vasopressor bolus dose with baseline values showed no difference for ephedrine (mean, 0.87 [SD, 0.23] *vs.* 0.78 [SD, 0.14]; $P = 0.10$) or metaraminol (1.1 [0.72] *vs.* 0.92 [0.59]; $P = 0.13$).

Discussion

The use of regional anesthesia in obstetrics has increased because it is associated with reduced maternal mortality and morbidity compared with general anesthesia.[19] However, recent reports have suggested that re-

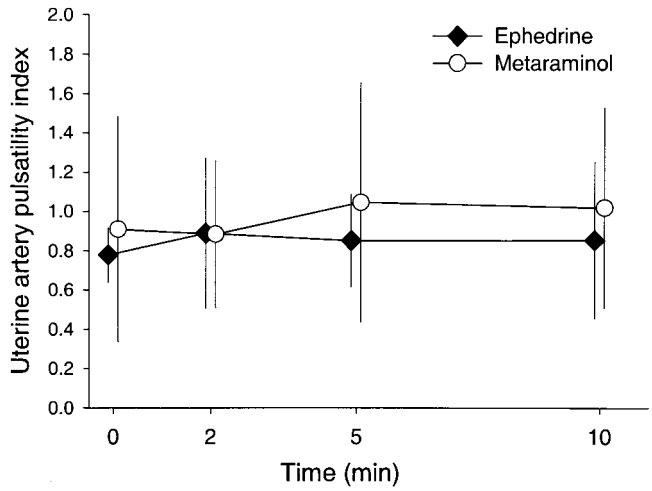

Fig. 2. Changes in uterine artery pulsatility index in the first 10 min after spinal injection. Pulsatility index did not change significantly over time or between groups over time.

gional anesthesia may be associated with a greater incidence of fetal acidosis compared with general anesthesia.[20,21] This is most apparent with spinal anesthesia and is most likely related to hypotension.[22] Lateral uterine displacement and intravenous fluid preload are commonly used to prevent hypotension, but these techniques have limited efficacy, and a vasopressor drug is usually required.[23] Historically, the vasopressor recommended in pregnancy, both during regional anesthesia[22] and in other situations such as trauma,[24] has been ephedrine. During spinal anesthesia for cesarean section, it has been recommended that ephedrine be given by intravenous infusion because this was associated with better control of arterial pressure and less maternal side effects compared with intermittent intravenous bolus doses.[25] However, our results show that, compared with metaraminol, infusion of ephedrine was associated with greater fetal acidosis and was more difficult to titrate to the target maternal arterial pressure.

Our findings are consistent with recent published data on management of maternal hypotension during spinal anesthesia. Several studies have shown that intravenous ephedrine is ineffective in preventing fetal acidosis, and may even worsen it, particularly when large doses are used.[3,4,26] Furthermore, there is evidence that use of ephedrine may be associated with poorer umbilical cord gases compared with phenylephrine[5–8] and angiotensin II.[27,28]

Although our results show that metaraminol has advantages over ephedrine, there are no data directly comparing metaraminol with phenylephrine or other pure vasoconstrictors in humans. Thus, although the magnitude of the differences in umbilical cord blood gases between the ephedrine and metaraminol groups that we found was greater than that reported in studies that compared ephedrine with phenylephrine,[5–8] it is unclear whether this is related to the relatively large doses of vasopressor we used or whether it reflects a true advantage of metaraminol over pure α-adrenergic agonists. Our protocol called for tight control of SAP within a narrow range of 90–100% of baseline. To achieve this, total doses of vasopressor that were greater than those reported in many other studies were required.[29] This may have magnified the relative differences between the drugs. Nonetheless, there is evidence from early animal studies that metaraminol may have advantages over pure α-adrenergic agonists. In three related animal studies, Shnider *et al.*[14,30,31] reported that metaraminol was superior to methoxamine but inferior to ephedrine for correcting fetal deterioration caused by a period of spinal hypotension. They found that ephedrine was effective at restoring maternal arterial pressure and ameliorated fetal acidosis, hypoxia, and hypercarbia,[30] whereas methoxamine restored maternal arterial pressure but was associated with continued fetal deterioration[31]; metaraminol increased both maternal arterial pressure and uterine blood flow and improved fetal hypoxia and hypercarbia but did not arrest progressive fetal acidosis.[14] However, it should be noted that the protocol of these studies included long periods of uncorrected hypotension before administration of vasopressors, and large doses of vasopressors were used; this may limit the applicability of the results to clinical situations.

Why have results of human studies differed from the original comparative evaluations of vasopressors in animals? The animal studies, which were mainly conducted on pregnant sheep and monkeys, found that ephedrine was effective in increasing arterial pressure with better preservation of uteroplacental blood flow compared with other vasopressors.[1,2,32,33] This was explained by the predominant β effect of ephedrine, which caused an increase in arterial pressure by increasing cardiac output rather than by vasoconstriction. More recently, *in vitro* studies showed that direct vasoconstriction of sheep uterine arteries by ephedrine was decreased in pregnancy to a greater extent than that observed with metaraminol, possibly related to an increase in endothelial nitric oxide production.[34,35] However, there are many reasons why it may not be appropriate to extrapolate directly from the animal studies to the clinical setting. These include species differences, omission of intravenous volume expansion, and use of doses greater than those used in clinical practice.[36] In addition, in some of the animal models, vasopressors were used to restore arterial pressure during combined general and spinal anesthesia[2] or to increase arterial pressure to supranormal values in animals who did not have any method of regional anesthesia.[1,37] Therefore, these studies were a poor representation of the conditions seen by the practicing clinician. Furthermore, animal studies do not take into account other practical considerations of clinical use, such as dose, titration, and duration of administration.

The reason why we found that umbilical cord blood gases were worse in the ephedrine group compared with the metaraminol group is uncertain but could be explained by a number of mechanisms. The sympathomimetic effects of ephedrine are largely indirect, arising from release of noradrenaline from postganglionic sympathetic nerve endings.[38] Because of this, ephedrine has a relatively slow onset of action, a relatively long duration of action, and it exhibits marked tachyphylaxis, which is thought to be related to depletion of presynaptic noradrenaline stores or persistent block of adrenergic receptors.[38] These properties of ephedrine reduce its suitability as a drug to be titrated to maintain arterial pressure, as is usually done in clinical practice. In our study, this was reflected by the trend toward large initial requirements of ephedrine in the first 10 min after induction of spinal anesthesia and the associated tendency for SAP to overshoot our target range after 10 min. This tendency to overshoot the target range with ephedrine infusions has been described previously.[28] In contrast, in

the metaraminol group, drug requirement was more evenly distributed through the study period, and SAP was better maintained within the target range. With ephedrine, the large initial drug requirement may have exposed the uteroplacental circulation and fetus to relatively large doses of vasopressor, with a peak effect after 10 min. It has been suggested that ephedrine may have a biphasic dose-related effect on uterine vascular resistance such that with large doses, the effect of ephedrine on uterine vascular resistance may offset the beneficial effects of ephedrine on maternal arterial pressure and cardiac output.[28] Unfortunately, in our study we were unable to investigate this as preparation and surgery were started 10 min after spinal injection, which precluded Doppler velocimetry measurements beyond this time.

We used Doppler velocimetry to assess changes in uterine artery vascular resistance in response to spinal anesthesia and vasopressor administration. However, there are few data available on its sensitivity in this context. It is possible that changes in uteroplacental flow may have occurred that were not reflected in changes in uterine artery PI, and these may have resulted in the neonatal acidosis in the ephedrine group.

Finally, it is possible that ephedrine may have had a direct effect on the fetus that contributed to fetal acidosis. Wright *et al.*[39] showed that ephedrine crossed the placenta and increased fetal HR and beat-to-beat variability, and, although in a study of patients having cesarean section the same group considered that placental transfer of ephedrine was not detrimental to the fetus,[40] they found that umbilical arterial *p*H was lower in patients who received ephedrine compared with those who did not.

In summary, we have found that, when titrated by infusion to maintain arterial pressure during spinal anesthesia for cesarean section, metaraminol was associated with less fetal acidosis and enabled more accurate control of arterial pressure compared with ephedrine. Our findings do not support the role of ephedrine as the vasopressor of choice in pregnancy.

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