A Randomized Trial of Prophylactic Administration of Phenylephrine vs. Ephedrine for Treatment of Hypotension during Combined Spinal-epidural Anesthesia for Cesarean Delivery

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Ephedrine and phenylephrine are useful vasopressors for managing hypotension during caesarean delivery. Fetal arterial cord blood pH and fetal acidosis may be related to the choice of vasopressor. The present study was therefore designed to compare arterial cord blood pH and fetal acidosis rates by vasopressor treatment, while maintaining maternal mean arterial pressure (MAP) near baseline values. Fifty one ASA I-II parturients undergoing cesarean delivery (CD) under combined spinal-epidural anesthesia (CSEA) were randomly assigned to prophylactic infusion (20 mL.hr^{-1}) of phenylephrine (100 µg.ml^{-1}, n=25) or ephedrine (3 mg.ml^{-1}, n=26) prior to CSEA. The infusion, was titrated to maintain mean arterial pressure (MAP) near baseline values. The primary outcome was arterial cord blood pH. Fetal acidosis was defined as pH <7.2; maternal hypotension as MAP <70 mmHg; and maternal bradycardia as heart rate <50 bpm. Arterial cord blood pH was 7.32±0.06 in the ephedrine group vs. 7.32±0.05 in the phenylephrine group, p=0.9. Fetal acidosis occurred in one case (4%) in each study group with similar one- and five-minute Apgar scores (all >7). Hypotension episodes were more frequent in patients given ephedrine (10 patients; 38%) than phenylephrine (three patients; 12%), (p=0.03). We conclude that prophylactic ephedrine as compared to phenylephrine administration was associated with a relatively high incidence of hypotension but with similar cord blood pH.

Keywords: cesarean delivery, combined spinal-epidural anesthesia, hypotension, phenylephrine, ephedrine, fetal pH

Introduction

The incidence of hypotension during spinal anesthesia for cesarean delivery is reported to be as high as 70–80% despite fluid administration and left uterine displacement [1]. Fetal acidosis presumably results from maternal hypotension or as a result of the vasopressor effect, and occurs less frequently during epidural or general anesthesia than during spinal anesthesia [2–3].

Ephedrine and phenylephrine are the two most frequently studied vasopressors in obstetrics. Historically, ephedrine is considered the vasopressor of choice in obstetric anesthesia, but in recent years this has been questioned as phenylephrine has gained popularity. For example, when phenylephrine was used to maintain arterial pressure at 100% of baseline, outcomes for infant and mother were optimal [4]. Compared to ephedrine, prophylactic intravenous infusion of phenylephrine decreased fetal acidosis and maternal nausea and vomiting during spinal anesthesia [5]. Furthermore, even after excluding severely hypotensive, ephedrine-treated patients, the incidence of fetal acidosis has been reported to be eight-fold greater in patients treated with ephedrine compared with those treated with phenylephrine (5), implying an independent, causal association between ephedrine treatment and fetal acidosis. By contrast, in a meta-analysis of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for caesarean delivery, no difference in the incidence of fetal acidosis (pH <7.2) was detected, though ephedrine was associated with lower umbilical cord blood pH6 which can be explained by differences in drug doses among studies. The present study was designed to compare the effects of phenylephrine and ephedrine on fetal cord blood pH, when maintaining blood pressure close to baseline values, following CSEA for Cesarean delivery.

Methods

Following Institutional Research Ethics Committee approval and written informed consent, the present study enrolled 51 patients scheduled for elective cesarean delivery under combined spinal-epidural anesthesia (CSEA) in a prospective, randomized, double-blind study. Eligible participants were parturients with singleton pregnancy, ASA Physical Status I and II, and without a history of pregnancy-induced hypertension, fetal abnormality, or diabetes mellitus.

Before entering the operating room, patients were administered 30 ml of sodium citrate solution orally and a bolus of 10 ml.kg^{-1} of lactated Ringers solution over 30 min. CSEA was performed at the L2–3 or L3–4 intervertebral space, in sitting position with an 18 G epidural needle, 20 G multiport catheter and a 27 G pencil point spinal needle (B. Braun, Melsungen, AG Germany). The needles were inserted with the orifice oriented cephalad. Anesthesia was performed with 10 mg of hyperbaric bupivacaine injected intrathecally (the epidural component of the technique was used when the spinal component was insufficient to provide anesthesia throughout the surgery). The

patient was positioned supine, and the operating table was tilted 15° to the left. Target block height was T4–5. If the target was not obtained, additional 3 mL of bupivacaine was injected epidurally. Sensory level was measured with pinprick, which was assessed every five minutes during the first 30 minutes of anesthesia and thereafter at 15-minute intervals.

Randomization was performed using computer-generated codes that were maintained in sequentially numbered opaque envelopes. Parturients were randomized into two study groups: ephedrine and phenylephrine. The envelopes were opened just before entering the surgical suite. The anesthesiologist responsible for patient care and the patients themselves were blind to vasopressor assignment. The assigned drug was given via coded syringes, each of which contained the same volume. Vasopressor solution was freshly prepared before operation by an anesthesiologist who had no role in the study. Following initiation of spinal anesthesia and supine left tilt (15º) positioning of the patient, prophylactic ephedrine (3 $mg.mL^{-1}$) or phenylephrine (100 $\mu g.mL^{-1}$) per treatment assignment was administered at an initial rate of 20 $ml.h^{-1}$ through an infusion pump (Alaris, Asena, Alaris Medical Systems, Basingstoke, RG 224 BS, UK) and subsequently by titration in an effort to maintain mean arterial blood pressure (MAP) as close as possible to baseline (i.e., pre-anesthetic) levels until delivery. The infusion rate of vasopressors was adjusted for every change of 10 mmHg of MAP that was measured every two minutes. The rate of ephedrine and phenylephrine was doubled or halved accordingly. If blood pressure was still low, a bolus of 100 µg phenylephrine was administered. Baseline blood pressure was measured in the surgical suite after fluid administration, before performing CSE anesthesia. All measurements were performed with the patient in supine position with a left lateral tilt of 15°. The concentration of vasopressor in the test mixture was predetermined based on a previous study [5] and a pilot study. Although the ratio of vasopressors used in our study was much smaller (1:30) than shown previously [4,7] (1:81) for equivalence between phenylephrine and ephedrine, the results of our previous pilot study showed less fetal acidosis with relatively lower concentrations of ephedrine and with clinically insignificant hypotension.

Measurements

Morphometric and demographic characteristics of the patients were recorded. Arterial cord blood pH was the primary endpoint. Fetal acidosis was defined as pH <7.2. Maternal hypotension episode was defined as MAP <70 mmHg and maternal bradycardia as heart rate <50 beats per minute. Systolic, diastolic and mean arterial blood pressures were measured by oscillometry (AS/5TM, Datex Ohmeda Division, Anesthesia Monitor, Instrumentarium Corp., Datex-Ohmeda, Helsinki, Finland) before starting anesthesia and at two-minute intervals throughout surgery. Oxyhemoglobin saturation was measured at the same time intervals.

Cardiac Index (CI) was measured in this study by thoracic bioimpedance (BoMed Medical, MFG, Ltd. Model NCCOM3, Irvine, CA, USA). Measures were taken before anesthesia (baseline), three minutes following anesthetic block, during abdominal incision, at delivery, and after abdominal closure. Systemic vascular resistance index (SVRI) was calculated using the standard formula [8]. All hemodynamic measurements were performed while the patient was in supine position with 15° left lateral tilt.

If maternal blood pressure could not be maintained within baseline MAP of ± 10 mmHg, tilt was increased up to 20º. If this maneuver did not restore baseline blood pressure, phenylephrine was given as required to both groups. Bradycardia when accompanied with decrease of blood pressure was treated by doubling ephedrine rate in the ephedrine group or by 0.5 mg atropine sulfate administration with blood pressure measurements within the baseline range. In the phenylephrine group, bradycardia was treated with 0.5 mg atropine sulfate and the decrease of phenylephrine rate of infusion. Side effects or complications were recorded, including cardiac arrhythmias, nausea, vomiting, or breathing difficulty.

Immediately after delivery, an arterial blood sample was drawn from the clamped segment of the umbilical cord. Apgar scores (one and five min) were recorded, and the need for respiratory or intensive care unit support was also noted. Neonatal condition was not assessed beyond the study period.

Data analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc. Chicago, IL, USA). For continuous variables such as age, laboratory, and hemodynamic values, descriptive statistics were calculated and reported as means ± standard deviations. Normality of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test (cut-off at p=0.01). Categorical variables such as treatment group and symptoms were described using frequency distributions and are presented as frequency (%).

The t test for independent samples was used to compare continuous variables between subjects by treatment group. Multiply-measured continuous variables such as blood pressure were assessed using general linear modeling and repeated-measures analysis. Chi square or Fisher exact tests were used to assess associations between treatment group and other categorical variable. All tests were two-sided and considered significant at $p < 0.05$.

When making multiple measures, the rate of type I error is increased. Therefore, repeated measures analysis is performed first and only if significant overall difference is detected can post hoc, pairwise comparisons be made.

With a sample size of 50 subjects (n=25 in each treatment assignment), our study was designed to have an 80% chance to detect a true, by-treatment difference of 0.03 (0.035) pH points using a t-test for independent samples, assuming a two-sided alpha of 0.05.

Table I. Maternal demographic and neonatal characteristics

Variables	Ephedrine Group n=26	Phenylephrine Group n=25	P value
Age (yr)	32 ± 5	30 ± 4	0.50
Height (cm)	164 ± 50	163 ± 67	0.44
Weight (kg)	81 ± 14	86 ± 14	0.20
Upper thoracic dermatome block (pin prick)	3 (2–4)	3 (2–4)	0.3
Neonatal weight (kg)	3.2 ± 0.5	3.3 ± 0.4	0.84
Apgar score (1 min)*	9 (8–9)	9 (8–9)	0.32
Apgar score (5 min)*	10 (9–10)	10 (9–10)	0.27
Arterial cord blood pH	7.32 ± 0.058	7.32 ± 0.054	0.92
Neonatal acidosis (pH < 7.2)	1 (4)	1 (4)	1.0
Skin incision to delivery time (min)	10.6 ± 4	9 ± 3.5	0.12
Oxyhemoglobin Saturation	98.6 ± 0.4	98.3 ± 0.4	0.09
Anesthetic side effects			
Dyspnea	2 (8)	2 (8)	0.96
Nausea	15 (57)	10 (40)	0.20
Vomiting	4 (15)	1 (4)	0.17

Results

Fifty-one patients were enrolled: 26 patients in the ephedrine group and 25 patients in the phenylephrine group. All completed the study. Maternal demographics and neonatal characteristics were similar in each group. In particular, the groups were well matched for maternal age, height, and weight. Neonatal weight and one and five-minute Apgar scores were similar and satisfactory in each group. Uterine incision to delivery time was similar.

Arterial cord blood pH was 7.32 ± 0.06 in the ephedrine group vs. 7.32 ± 0.05 in the phenylephrine group, p=0.9. Each group experienced one case (4%) of fetal acidosis (pH <7.2) (Table I). No newborn required respiratory support or transfer to the intensive care unit. The maximum cephalad sensory level of anesthesia was similar in each group and average T4 (T3–T5).

No additional epidural local anesthetic dose was required in both study groups.

Hemodynamic characteristics (systolic and diastolic blood pressure, heart rate, cardiac index, stroke volume index and systemic vascular resistance) before and during spinal anesthesia were similar in both ephedrine and phenylephrine treatment groups (Fig 1–4). A significant between-group across-time difference was not observed for any of the hemodynamic variables, therefore, pairwise testing could not be conducted. Hypotension episodes (MAP <70 mmHg) were observed in 10 patients (38%) receiving ephedrine compared to three patients (12%) receiving phenylephrine (p=0.03). All hypotension episodes were controlled with the study vasopressor. No additional phenylephrine was needed in the ephedrine group. One patient (4%) in each group experienced bradycardia (<50 beats per minute) without decreases in blood pressure and each was treated with atropine. Furthermore, cardiac index and SVRI were similar before anesthetic, three minutes after anesthetic block, during incision, at delivery, and after incision closure (Fig. 3 and 4). Oxygen saturation was similar, normal, and stable in each study group (Table I).

Total dose of ephedrine was 16.8 ± 5.6 ml = 50 ± 17 mg, versus phenylephrine which totaled 15.4 ± 4.0 ml = 1.54 ± 0.4 mg, corresponding to a potency factor difference of 32. No patient in either group required a rescue vasopressor. There were no episodes of arrhythmia. The overall incidence of respiratory difficulty was similar between the two groups (Table I). Nausea occurred in 15 patients in the ephedrine group and in 10 patients in the phenylephrine group – p=0.2. Vomiting occurred in four patients

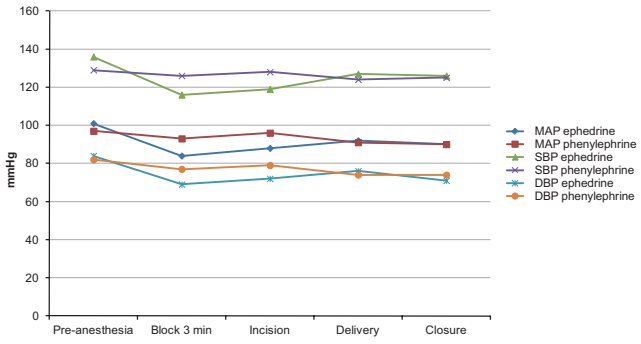

Fig. 1. Mean arterial pressure, systolic and diastolic blood pressure by treatment assignment

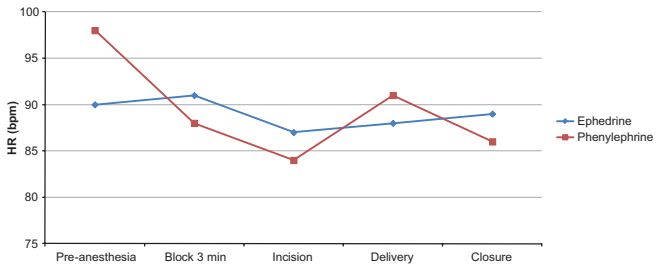

Fig. 2. Heart rate by treatment group

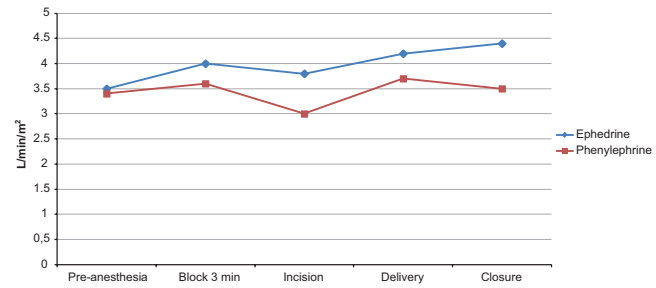

Fig. 3. Cardiac index by treatment assignment

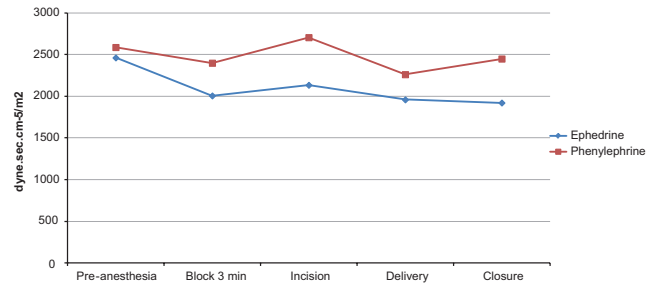

Fig. 4. Systemic vascular resistance by treatment assignment

in the ephedrine group and one patient in the phenylephrine group – p=0.17 (Table I).

Discussion

Cord blood pH during cesarean delivery with spinal anesthesia was similar in parturients receiving prophylactic infusion of ephedrine or phenylephrine at a rate necessary to maintain baseline MAP. Each group experienced 1 case (4%) of fetal acidosis (arterial cord blood pH <7.2) with one and five-minute Apgar scores >7. There were more episodes of hypotension in the ephedrine group (p=0.03). Other secondary endpoints such as nausea, vomiting, bradycardia and dyspnea episodes and Apgar scores were similar between the groups.

Thoracic bioimpedance has been validated for use in pregnancy and during caesarean delivery, as an effective, non-invasive method for continuous measurement of hemodynamic parameters. With superior accuracy than older calculations [9], this technique has also been found to be reliable for determination of stroke volume [10], systemic vascular resistance [8] and cardiac output [11].

Previous studies have reported that umbilical cord blood pH was lower when ephedrine was administered to maintain maternal blood pressure compared with phenylephrine [5,12–14]. Some investigators reasoned that the acidosis was caused by relatively large doses of ephedrine needed to maintain blood pressure [12–14]. This could be further exacerbated by ephedrine-associated tachyphylaxis that leads to noradrenaline release and depletion after repetitive doses [15]. Other possible explanatory mechanisms include the fact that ephedrine is characterized by slow onset and longer duration of action compared to other vasoactive amines [16], or by a direct effects of ephedrine on the fetus [5], although the pH values in the range measured in our study do not correlate with poor clinical outcome. The authors show that, even after exclu-ding severely hypotensive, ephedrine-treated patients, the incidence of fetal acidosis remained greater in ephedrine compared to phenylephrine-treated patients (16% vs. 2%) suggesting that ephedrine is causally linked to fetal acidosis independent of maternal hypotension. By contrast, in a meta-analysis of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery, Lee et al. [6] reported that there was no difference in the incidence of fetal acidosis (pH <7.2), though ephedrine was associated with lower umbilical cord blood pH. Although Lee at all did not show a difference in fetal acidosis (pH <7.2), this was not a primary endpoint of his meta-analysis and it could be explained by different dosage of vasopressors used in different studies. Furthermore, small difference in cord blood pH did not lead to clinically significant lower fetal pH.

An increase in the incidence of fetal acidosis has been observed with ephedrine, but not phenylephrine, when spinal-to-delivery intervals were prolonged [17]. In previous studies [5,17], as with the present one, similar concentrations with a ratio of 1:32–45 of phenylephrine to ephedrine were administered prophylactically by infusion in an attempt to maintain blood pressure near baseline values, although, there is evidence that ephedrine dose equivalence with phenylephrine is approximately 80:1.18 Relatively more ephedrine has been required, with a mean infusion rate of 0.5 $ml.min^{-1}$ and total dose of 34 mg compared to a mean infusion rate of 0.33 $ml.min^{-1}$ and total dose of 0.8 mg for phenylephrine [17]. These results may possibly suggest that excess of ephedrine rather than maternal hypotension per se is the main factor reducing umbilical pH.

Our results show that there were more episodes of hypotension in patients receiving ephedrine. It appears that the dose of the infusion of ephedrine was possibly inadequate for completely avoiding all episodes of hypotension as we administered lower doses of ephedrine than previously reported [18]. We believe however, that an excessive dose of ephedrine was avoided by this and fetal acidosis did not occur.

Whether higher doses of ephedrine would be required to treat hypotension and still not cause fetal acidosis remains to be confirmed by future research, particularly in high risk pregnancies or with pre-delivery fetal distress.

Hemodynamic measures except for the number of episodes of hypotension were similar and stable throughout anesthesia in both the ephedrine and phenylephrine-treatment groups. Heart rate, CI and SVRI were stable, thus, preserving normal neonatal outcome as reflected by both umbilical cord blood pH and Apgar scores. In contrast, Ueland et al. [19] observed that cardiac output increased while SVRI decreased after induction of neuraxial anesthesia for cesarean delivery. However, subjects in the present study were healthy parturients with normal baseline systolic blood pressures and no symptoms of preeclamptic toxemia; thus, they were not at increased risk for hypotension. Further, subjects in the present study were treated prophylactically with vasopressors that stabilized blood pressure and SVRI. The use of CSEA as opposed to single shot spinal, enables employing smaller intrathecal doses (10 mg instead of 12–15 mg) of bupivacaine, thus, reducing the risk of hypotension.

Apgar scores in both treatment groups were similar and >7. Other studies have reported similar findings [6,20,21]. Maternal bradycardia, dyspnea, and nausea/vomiting were also similar between the two treatment groups. One patient (4%) experienced bradycardia in each group. It has been reported that bradycardia is more likely to occur with phenylephrine than ephedrine [5,6] and may be related to a phenylephrine-mediated increase in blood pressure [22]. The low incidence of bradycardia is likely due to administration of the vasopressor via infusion rather than bolus. Also, maternal bradycardia could be due to the Bezold-Jarisch reflex and increased vagal tone associated with reduced cardiac preload [23]. But most likely, this reflex was attenuated or eliminated in some of our patients by preventative administration of vasopressors.

Non-pharmacological techniques for management of maternal hypotension including left lateral tilt and intravenous fluid preload have not proven especially effective [24]. To date, the only effective technique that has been shown is combined high dose phenylephrine infusion and rapid crystalloid cohydration and lower limb wrapping [7,24]. In the present study, flexible dose of prophylactic phenylephrine was administered in patients who received crystalloid prehydration.

Nausea and vomiting is a frequently observed problem during spinal anesthesia and ephedrine administration [5]. for cesarean delivery. In the present study, nausea and vomiting was similar in both groups. However, our study was underpowered for this outcome. An increased incidence of nausea and vomiting has been reported previously in patients who received ephedrine alone or ephedrine in combination with phenylephrine compared to patients who received phenylephrine alone, despite a lack of differences in systolic arterial pressure as patients with hypotension were excluded [5].

A limitation of our study was that our sample size was too small to detect true differences in the incidence of fetal acidosis and nausea and vomiting.

Another limitation may be the use of a lower concentration of ephedrine than previously reported.

Conclusions

In summary, more episodes of hypotension were encountered with prophylactic ephedrine as compared to the phenylephrine infusion. However, both were associated with similar arterial cord blood pH. Additionally, both treatments were associated with infrequent maternal side effects. Apgar scores were comparable, suggesting that neither drug harmed the neonate.

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