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A randomized double-blind study comparing prophylactic norepinephrine and ephedrine infusion for preventing maternal spinal hypotension during elective cesarean section under spinal anesthesia

A CONSORT-compliant article

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Abstract

Background: Studies have shown the efficacy of norepinephrine in the treatment of maternal hypotension during cesarean section by comparing it to treatment with phenylephrine. However, few studies have compared the efficacy of norepinephrine to ephedrine.

Methods: Ninety-seven women undergoing elective cesarean section were administered norepinephrine at 4 μg/minute (group N; n = 48) or ephedrine at 4 mg/minute (group E; n = 49) immediately postspinal anesthesia, with an on-off titration to maintain systolic blood pressure (SBP) at 80% to 120% of baseline. A rescue bolus of 8 μg norepinephrine was given whenever SBP reached the predefined lower limit. Our primary outcome was the incidence of tachycardia. Secondary outcomes included the incidence of bradycardia, hypertension, hypotension, severe hypotension, hypotensive episodes, number of rescue top-ups, hemodynamic performance error including median performance error (MDPE), and median absolute performance error (MDAPE). Neonatal Apgar scores and umbilical arterial (UA) blood gas data were also collected.

Results: Women in group N experienced fewer cases of tachycardia (4.2% vs 30.6%, $P = .002$, odds ratio: 0.11 [95% confidence interval, CI: 0.02–0.47]), a lower standardized heart rate (HR) (70.3 ± 11 vs 75 ± 11, $P = .04$, difference: 4.7 ± 2.2 [95% CI: 0.24–9.1]), and a lower MDPE for HR (1.3 ± 9.6 vs 8.4 ± 13.5 bpm, $P = .003$, difference: 3.1 ± 1.8 [95% CI: −0.6–6.7]). In addition, the lowest or the highest HR was lower in group N compared to group E (both $P < .05$). Meanwhile, the standardized SBP in group N was lower than that in group E ($P = .04$). For neonates, the UA blood gas showed a higher base excess (BE) and a lower lactate level in group N compared to E (both $P < .001$). Other hemodynamic variables, maternal, and neonatal outcomes were similar.

Conclusion: Infusion of 4 μg/minute norepinephrine presented fewer cases of tachycardia, less fluctuation and a lower HR compared to baseline values, as well as a less stressed fetal status compared to ephedrine infusion at 4 mg/minute. In addition, norepinephrine infusion presented a lower standardized SBP compared to ephedrine.

Abbreviations: BE = base excess, BP = blood pressure, CI = confidence interval, HR = heart rate, IQR = interquartile range, MDAPE = median absolute performance error, MDPE = median performance error, PE = performance error, SBP = systolic blood pressure, UA = umbilical artery.

Keywords: cesarean section, efficacy, ephedrine, norepinephrine, safety

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1. Introduction

At present, spinal anesthesia is a widely accepted technique for cesarean section; however, it can lead to maternal spinal hypotension. Severe or sustained hypotension contributes to various maternal side effects including nausea, vomiting, dizziness, and even a compromise of uteroplacental perfusion. A decrease of peripheral vascular resistance is acknowledged as a significant contributor to maternal spinal hypotension[1]; therefore, the administration of vasopressors owing to their vasoconstrictor properties is a rational drug treatment for maternal hypotension.

For many years, ephedrine has been considered the first choice for the treatment of maternal hypotension during cesarean section. It has α and β-adrenergic receptor agonist activity and is favorable for the preservation of uteroplacental perfusion.[2] However, certain side effects need to be considered when administering ephedrine such as tachyphylaxis, reactive hypertension, tachycardia, and increased myocardial contractility and myocardial oxygen demand.[3] Ephedrine can easily cross the placental barrier and stimulate fetal metabolism, leading to fetal acidemia.[4] Severe fetal acidemia, or fetal acidosis, typically defined as a pH <7.20 in the umbilical artery (UA), can predict poor neonatal outcomes.[5]

Recently, another traditional vasopressor norepinephrine has attracted increasing attention in obstetric anesthesia. Norepinephrine is an α-receptor agonist; however, it is a weak β-receptor agonist, making it less likely to increase heart rate (HR) and thus reduces the risk of tachycardia related maternal arrhythmia. Furthermore, norepinephrine does not cross the placental barrier easily, with only $11.6\% \pm 0.6\%$ transfer in a dual perfused human placental system in vitro.[6] Furthermore, the available evidence highlights an onset time shorter than 60 s for norepinephrine,[7] much faster than the 2 to 3 minutes onset time of ephedrine, thus norepinephrine may correct hypotension at a faster rate. There have been several studies suggesting the efficacious and safe use of norepinephrine to treat maternal hypotension with diverse dosing regimens and administration protocols; however, the majority have been conducted in comparison to phenylephrine.[8–11] There is little data available comparing norepinephrine and ephedrine for the treatment of maternal spinal hypotension.

Considering the limited available research, this study was performed to compare prophylactic norepinephrine and ephedrine infusion for preventing maternal hypotension in parturients undergoing cesarean section with spinal anesthesia. We investigated and analyzed the maternal hemodynamics, as well as maternal side effects and neonatal outcomes in parturients treated with norepinephrine or ephedrine.

2. Methods

2.1. Subjects and ethics

This randomized, double-blind study was approved by the Clinical Research Ethics Committee of Nanjing Medical University, Nanjing, China. This study was registered in the Chinese Clinical Trial Registry (ChiCTR1900021084). This trial was conducted between July and December, 2018 at a maternal and child health care hospital in Nanjing, China.

2.2. Inclusion criteria

The inclusion criteria were as follows: American Society of Anesthesiologists (ASA) grade I or II, singleton, nonlaboring, scheduled for elective cesarean section with spinal anesthesia. All eligible women were invited to join the study when they entered the operating room.

2.3. Exclusion criteria

Parturients were excluded in the following situations: twin or multiple gestations, known fetal abnormalities, suspected fetal compromise, chronic hypertension, chronic hypertension comorbid with preeclampsia, preeclampsia, diabetes mellitus, cardiovascular or cerebrovascular disease, failed spinal anesthesia, infusion pump malfunction, or unexpected use of other vasopressors such as phenylephrine throughout the study.

2.4. Randomization assignment

Eligible parturients were randomized into 2 groups to receive norepinephrine (group N) or ephedrine (group E) and each was assigned a computer-generated number. The numbers were sealed in an opaque envelope and kept by one study member. Just before spinal anesthesia, the number would be allocated to determine which vasopressor would be infused. If one patient dropped out, the assigned number would be automatically allocated to the next one. Both the anesthesiologist and patient were blinded to the group allocation.

2.5. Intraoperative monitoring and patient management

After written informed consent was obtained, each parturient was placed in the supine position with a wedge under their right buttock to obtain a nearly 30° tilt for left uterine displacement. Then, the antecubital vein was opened with an 18G indwelled needle and the hemodynamic parameters including blood pressure (BP), HR, and pulse oximetry were detected, with the average of 3 successive values taken as baseline values.

We performed spinal anesthesia with parturients placed in a left lateral position using 2.5 to 2.7 mL of 0.6% hyperbaric ropivacaine through a 25-G spinal needle at the intervertebral space L2–3 or L3–4. Immediately preceding intrathecal injection, each parturient was rapidly infused with 10 mL/kg of lactated Ringer solution to a maximum volume of 2 L between the interval of induction and delivery, and after delivery the fluid was slowly maintained.

BP and HR were recorded every 2 minutes until delivery. Consistent with group allocation, norepinephrine or ephedrine was continuously infused at a dose of 4 μg/minute and 4 mg/minute for hemodynamic management beginning from the intrathecal injection until delivery. Of note, an additional 8 μg (4 μg/mL) of norepinephrine was given whenever hypotension was observed, defined as a systolic blood pressure (SBP) lower than 80% of the baseline. The dose of 8 μg of norepinephrine was determined based on a previous dose-finding study, which was equivalent to the commonly used 100 μg of phenylephrine used to rescue the first episode of hypotension.[12] In addition, the pump was stopped in the presence of hypertension (SBP $>120\%$ of baseline), and restarted when it fell into the defined normal range ($80\% < \text{SBP} < 120\%$). The infusion protocol was performed until delivery; thereafter, the hemodynamic management was determined by the attending anesthesiologist. Either norepinephrine (Norepinephrine Bitartrate, Grand Pharmaceutical Co., Ltd, China) or ephedrine (Ephedrine Hydrochloride, Northeast Pharm, China) was prepared by one specific study

member, who did not participate in the patient anesthesia or the following data collection and analysis. In case of bradycardia (HR <60 bpm) comorbid with hypotension or significant bradycardia (HR <50 bpm) irrespective of SBP, 0.5 mg intravenous atropine was injected. For blood gas analysis (GEM, Premier 3000, Instrumentation Laboratory, Badford, Massachusetts), a UA blood sample was taken from a double-clamped cord. Neonatal Apgar scores at 1 and 5 minutes were also recorded.

The primary outcome was the incidence of maternal tachycardia (HR >100 bpm). Secondary outcomes included incidences of bradycardia (HR <60 bpm), hypertension (SBP >120% of baseline), hypotension (SBP <80% of baseline), and severe hypotension (SBP <60% of baseline); the number of hypotensive episodes, number of rescue top-ups; and the precision of hemodynamic control via performance error (PE) calculation including the median performance error (MDPE) and the median absolute performance error (MDAPE).[13] MDPE is calculated as the median of all PE values, acting as a measure of bias to reflect whether the detected values are above or below the baselines. Meanwhile, MDAPE is calculated as the median of all absolute values of PE, acting as a measure of inaccuracy to represent an average of the magnitudes of the differences of detected values above or below the baselines.

Drug consumption until delivery, together with maternal side effects including headache, nausea, vomiting, dizziness, chest pain, shortness of breath, shivering, and neonatal outcome encompassing Apgar scores, umbilical arterial (UA) blood gas, and pH were collected as well.

Sensory block of the dermatome was tested by pinprick with surgery permitted if it reached T5. All parturients breathed air spontaneously throughout anesthesia and surgery; additional oxygen was only given when the pulse oximeter was lower than 95%.

2.6. Sample size calculation

An undesired side effect of ephedrine treatment is tachycardia. In the statistical analysis of 30 parturients, tachycardia (defined as HR >100 bpm) occurred at a ratio of 3.3% and 23.3% after norepinephrine and ephedrine infusion, respectively. Using α set at 0.05, β at 0.20, along with the power of test (1–β) at 0.80, a number of 45 subjects per group were required to detect an intergroup difference. Further, considering potential dropouts or data missing, the expected sample size was set at nearly 50 in either group.

2.7. Statistical analysis

Data are presented as mean ± standard deviation, median (interquartile range, IQR), or number (percentage). Statistical analysis in this trial was conducted using GraphPad Prism v.7.0 (GraphPad Inc., San Diego, CA) and Microsoft Excel 2010 (Microsoft Corporation, Washington). A $P < .05$ was considered to be statistically significant. Univariate data were first examined for normality with D'Agostino–Pearson omnibus normality test and then compared with an unpaired *t* test or a nonparametric Mann-Whitney *U* test. In addition, nominal data between groups were compared with a chi-square test or Fisher exact test. Standardized SBP and HR between the 2 groups were compared via a two-step summary protocol described by Matthews et al.[14] Briefly, standardized SBP and HR were first obtained by calculating the average area under the SBP and HR curves. Then, derived values were compared using standard intergroup analysis with either a *t* test or Mann-Whitney *U* test.

3. Results

Figure 1 shows the detailed flow chart of parturients enrollment, allocation, follow-up, and analysis. A total of 142 eligible women consented to participate in the trial, with 48 and 49 parturients finally subject to statistical analysis in groups N and E, respectively. As presented in Table 1, demographic variables, surgical times, and drug consumption were similar in both groups.

Maternal hemodynamic variables are shown in Table 2. In groups N versus E, respectively, baseline SBP was 116 ± 8.8 versus 118 ± 7.1 mm Hg, $P = .34$; and baseline HR was 84.8 ± 7.8 versus 83.1 ± 8.4 bpm, $P = .31$. Although neither SBP nor HR between groups had statistical difference at each time point, standardized SBP over time was lower in group N compared with group E (87.2 ± 9.6 vs 91.4 ± 9.5 mm Hg, $P = .04$), with a difference of 4.1 ± 1.9 mm Hg (95% confidence interval [CI] = 0.27–8.0). Further, standardized HR over time was lower in group N compared with group E (70.3 ± 11 vs 75 ± 11 bpm, $P = .04$), with a difference of 4.7 ± 2.2 mm Hg (95% CI = 0.24–9.1). Furthermore, either the lowest or the highest HR was lower in group N compared to group E (both $P < .05$). The incidence of tachycardia, defined as HR >100 bpm was consistently lower in group N compared with group E (4.2% vs 30.6%, $P = .002$, odds ratio = 0.11, 95% CI = 0.02–0.47). As for hemodynamic stability, the bias for HR to be above baseline increased with an MDPE of HR lower in group N compared with group E (1.3 ± 9.6 vs 8.4 ± 13.5 mm Hg, $P = .003$), with a difference of 3.1 ± 1.8 mm Hg (95% CI = −0.6–6.7). Other hemodynamic variables had no statistically significant intergroup differences, including the incidence of bradycardia, hypertension, hypotension, severe hypotension, the number of vasopressor episodes, and the number of rescue top-ups. The bias for SBP to be above baseline, that is an MDPE of SBP, as well as the median extent of deviations of SBP or HR above or below baseline, that is an MDAPE of SBP and HR were comparable between groups.

Although the incidence of hypotension was as high as 43.8% and 30.6% after norepinephrine and ephedrine prophylactic infusion, the incidence of severe hypotension was only 14.6% and 10.2%, that is, 7 and 5 cases in groups N and E, respectively. Nearly all women experiencing hypotension had only one episode of hypotension [1(1–1) vs 1(1–1), $P > .99$] with a required number of rescue top-ups [1(1–1.5) vs 1(1–2), $P = .24$], collectively suggesting the efficacy of prophylactic infusion of both types of vasopressors. Figure 2A and B present the SBP and HR trajectory for the first 10 minutes postspinal anesthesia, a time point when data are available for most parturients.

Maternal side effects were presented in Table 3, with no intergroup differences observed. Neonatal Apgar score, as well as UA blood gas and pH, is shown in Table 4. Due to equipment failure, insufficient blood sample volume, or inadequate anticoagulation, UA blood gas was not performed in 4 subjects for each group, respectively. As presented, no neonate experienced an Apgar score <7 at 1 minute or an Apgar score <9 at 5 minutes in groups N and E, respectively. Meanwhile, no neonate experienced neonatal acidosis, defined as an UA pH <7.20. However, we observed a higher base

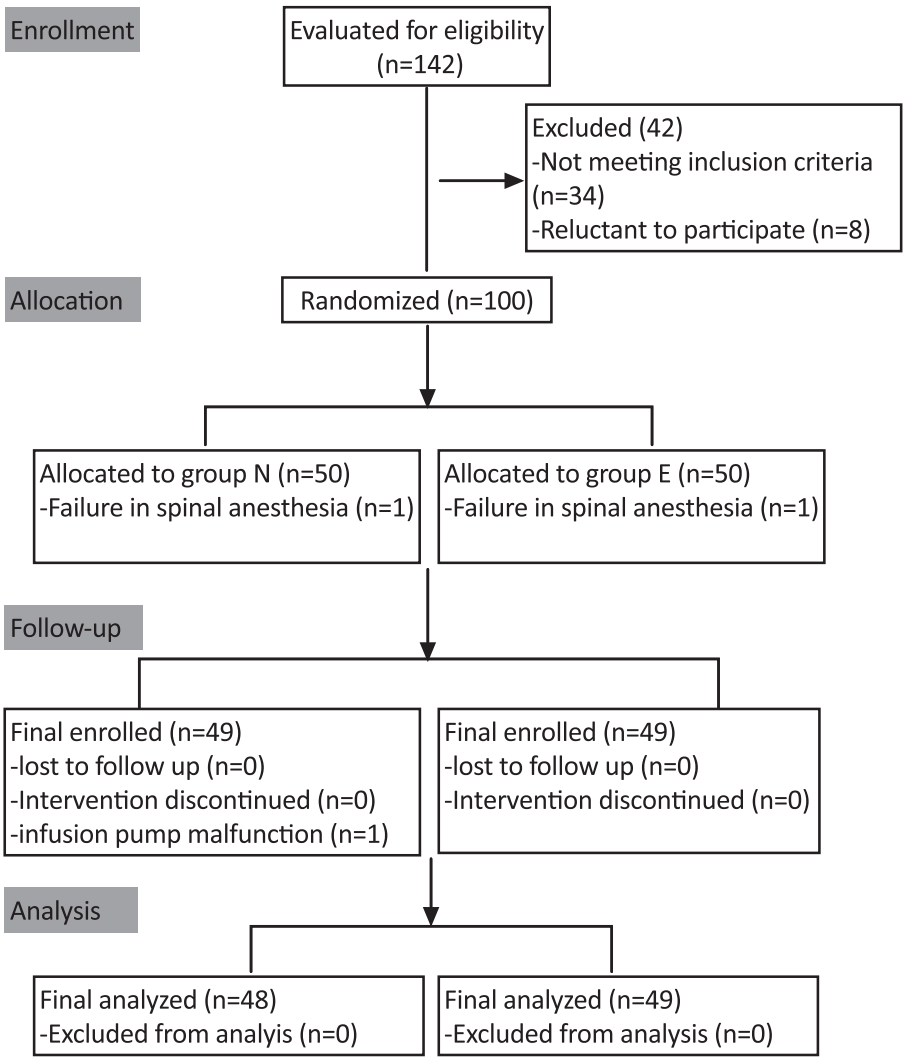

Figure 1. Flow chart of parturients enrollment, allocation, follow-up, and analysis.

Table 1

Demographic characteristics and surgical times.

Demographic characteristics	Group N (n = 48)	Group E (n = 49)	*P*
Age, y	32 ± 4.2	32 ± 4.6	.71
Height, cm	162 ± 5.1	162 ± 4.0	.98
Weight, kg*	77 ± 7.7	75 ± 5.1	.07
Gestational age, wk	40 ± 2	40 ± 2	.48
Repeated cesarean delivery	23 (48%)	25 (51%)	.84
Block dermatome (at 5 min)	T5 (T5–T6)	T5 (T5–T6)	.52
Block dermatome (at 15 min)	T4 (T4–T5)	T4 (T4–T4)	.25
Fasting time, h	11 ± 3.7	11 ± 3.2	.66
Volume of cohydration, mL	764 ± 93	772 ± 95	.19
Estimated blood loss, mL	475 ± 155	486 ± 156	.74
Time intervals			
Induction to delivery, min	8.9 ± 2.2	9.4 ± 2.0	.20
Uterine incision to delivery, s	57 ± 38	59 ± 34	.82
Drug consumption			
Norepinephrine, μg	25 (20–30.5)	0 (0–8)	
Ephedrine, mg		22.5 (20–25)	
Volume of vasopressor, mL	6.6 ± 0.35	6.7 ± 0.26	.89
Birth weight, g	3397 ± 424	3493 ± 457	.29

Values are expressed as mean ± SD, number (percentage), or median (IQR). IQR = interquartile range, SD = standard deviation.

* Patient weight at the day of surgery.

excess (BE) and a lower lactate level in group N compared with group E (both $P < .001$).

4. Discussion

In this study, we observed that norepinephrine infusion was associated with fewer cases of tachycardia, less fluctuation of HR, and a less stressed fetal status than ephedrine to maintain maternal BP in parturients undergoing elective cesarean section with spinal anesthesia; meanwhile, norepinephrine was related to a lower standardized SBP compared with ephedrine.

The use of norepinephrine for the treatment of maternal hypotension during cesarean section is a recent advance, and our review and meta-analysis suggest it is a promising alternative to phenylephrine.[15,16] However, this conclusion was obtained from less than 10 available reports, this finding is therefore too under powered to draw a definite conclusion. Although ephedrine is not the main vasopressor in obstetric anesthesia; it is still favored by many due to its efficacy, safety, availability, and its ease of preparation. Thus, in this study, we compared norepinephrine with ephedrine, aiming to deepen our knowledge

Table 2

Maternal hemodynamic variables.

Hemodynamic variables	Group N (n = 48)	Group E (n = 49)	*P*	Mean difference (95% CI)	Odds ratio (95% CI)
Baseline SBP, mm Hg	116 ± 8.8	118 ± 7.1	.34		
Baseline HR, bpm	84.8 ± 7.8	83.1 ± 8.4	.31		
Standardized SBP over time, mm Hg	87.2 ± 9.6	91.4 ± 9.5	.04	4.1 ± 1.9 (0.27–8.0)	
Standardized HR over time, bpm	70.3 ± 11	75 ± 11	.04	4.7 ± 2.2 (0.24–9.1)	
Lowest SBP in percentage of baseline values, %	80.6 ± 2.4	83.6 ± 1.9	.30		
Highest SBP in percentage of baseline values, %	101.5 ± 1.6	104.7 ± 1.3	.12		
Lowest HR in percentage of baseline values, %	89.9 ± 1.5	96 ± 1.9	.01	6.1 ± 2.4 (1.3–10.9)	
Highest HR in percentage of baseline values, %	115.7 ± 2.4	124.8 ± 2.5	.009	9.1 ± 3.4 (2.3–15.9)	
Tachycardia	2 (4.2%)	15 (30.6%)	.002		0.11 (0.02–0.47)
Bradycardia	5 (10.4%)	4 (8.2%)	.74		
Hypertension	3 (6.25%)	3 (6.1%)	>.99		
Hypotension	21 (43.8%)	15 (30.6%)	.21		
Severe hypotension	7 (14.6%)	5 (10.2%)	.55		
Number of hypotensive episodes	1 (1–1)	1 (1–1)	>.99		
Number of rescue top-ups	1 (1–1.5)	1 (1–2)	.24		
MDPE of SBP, %	−8.3 ± 10.4	−6.5 ± 9.6	.38		
MDPE of HR, %	1.3 ± 9.6	8.4 ± 13.5	.003	3.1 ± 1.8 (−0.6–6.7)	
MDAPE of SBP, %	11.1 ± 8.7	10.6 ± 6.2	.71		
MDAPE of HR, %	10.7 ± 6.9	13.7 ± 10.8	.10		

Values are expressed as the mean ± SD, number (percentage), or median (IQR). CI = confidence interval, HR = heart rate, IQR = interquartile range, MDAPE = median absolute performance error, MDPE = median performance error, SBP = systolic blood pressure, SD = standard deviation.

of the efficacy and safety of the clinical application of norepinephrine in spinal hypotensive parturients.

Prophylactic titrated infusions of norepinephrine and ephedrine were used, starting at a dose of 4 μg/minute and 4 mg/minute, respectively. Prophylactic infusion is a highly recommended paradigm for the treatment of spinal hypotension,[17] resulting in minimal hemodynamic fluctuation and the least maternal side effects. Previous literature suggested that a norepinephrine infusion range of 0 to 5 μg/minute with manual titration[18] or a fixed dose of 0.05 μg/kg/minute[19] are optimal doses to maintain BP near baseline but not jeopardize neonatal safety, with a higher dose leading to more hypertension cases. Considering the mean body weight of 70 to 80 kg for women in our institute, a starting dose of 4 μg/minute was determined for

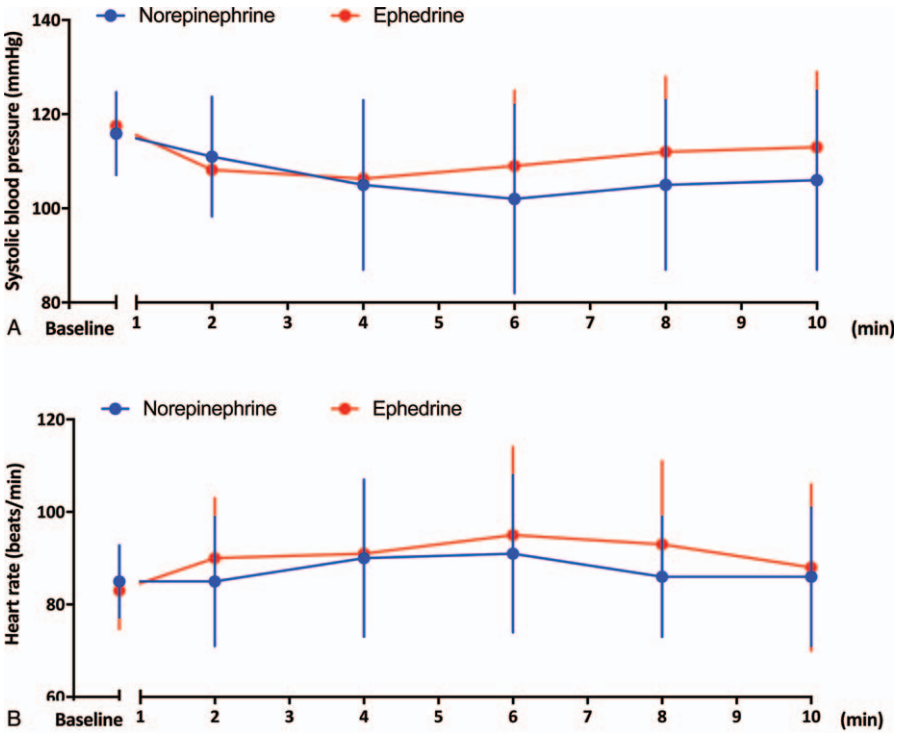

Figure 2. Serial changes in systolic blood pressure (A) and heart rate (B). Serial values for the first 10 minutes when data are available for most parturients. Data are shown as mean ± standard deviation (SD).

Table 3

Maternal side effects.

	Group N (n = 48)	Group E (n = 49)	*P*
Headache	2	1	.62
Nausea	7	8	>.99
Vomiting	0	3	.23
Dizziness	0	0	>.99
Chest pain	5	7	.76
Shortness of breath	0	4	.12
Shivering	12	10	.63

Values are expressed as number.

norepinephrine. In addition, the relative potency of norepinephrine versus ephedrine was indirectly speculated. Based on a comparative dose–response analysis, the potency of norepinephrine versus phenylephrine was estimated to be nearly 13:1[12]; while phenylephrine versus ephedrine is 80:1 to prevent hypotension after spinal anesthesia for cesarean section.[20] Thus, a potency ratio of approximately 1000:1 was indirectly obtained for norepinephrine versus ephedrine. Accordingly, a starting infusion dose of ephedrine at 4 mg/minute was used in this study. Although some anesthesiologists prefer to inject ephedrine by rescue bolus; such a technique is related to a higher incidence of hypertension and fetal acidemia.[21] Thus, an on/off titrating infusion of both vasopressors was used, a simple technique to perform.

As shown in Figure 2, both norepinephrine and ephedrine infusion are effective at maintaining maternal SBP at the desired range of 80% to 120% of baseline. However, the incidence of hypotension was as high as 43.8% and 30.6% after norepinephrine and ephedrine infusion, respectively. However, we also note that all women experiencing hypotension had only one episode of hypotension [1(1–1) vs 1(1–1), $P > .99$] and required less rescue top-ups [1(1–1.5) vs 1 (1–2), $P = .24$], collectively suggesting the efficacy of prophylactic infusion of both vasopressors with the determined doses.

Hemodynamic stability is another consideration for vasopressors in our study. We found an increased bias for HR to be maintained above baseline after ephedrine infusion but a similar bias for SBP or inaccuracy of HR and SBP control. These findings are in line with ephedrine having direct chronotropic effect, making HR increase compared to norepinephrine, which is only a weak β-adrenergic agonist. Consistently, ephedrine infusion was associated with tachycardia [15 (30.6%) vs 2(4.2%), $P = .002$] and a high maintenance for HR, as suggested by the higher lowest or highest HR compared with baseline values. In a previous study comparing a varying proportion of phenylephrine and ephedrine infusion to maintain SBP near baseline, as the ratio of ephedrine increased, either MDPE or MDAPE for SBP increased, indicating a reduced hemodynamic stability.[13] The authors attributed the greater hemodynamic fluctuation to ephedrine's slow onset and long duration of action, rendering a precise titration difficult when compared with short-acting drugs, for example, phenylephrine. As a supplement, we also showed a greater HR fluctuation with ephedrine, collectively suggesting norepinephrine rather than ephedrine might be a suitable alternative for women with tachycardia.

Maternal side effects were observed including headache, nausea, vomiting, dizziness, chest pain, shortness of breath, and shivering. No difference was observed between groups. Other than maternal safety, neonatal outcomes were generally favorable for both vasopressors. There was no difference in Apgar score, an indicator of neonatal well-being in the initial minutes after birth, or UA pH, which is useful to assess fetal condition immediately before delivery. No neonate had a 1 minute Apgar <7, 5 minutes Apgar <9, or UA pH value <7.2, the commonly accepted lower limit of normal.[22] In a multivariate analysis of factors relating to UA pH and BE after cesarean section with spinal anesthesia, the use of ephedrine and uterine incision-to-delivery interval is closely related to fetal acidosis.[4] The cumulative dose of ephedrine, 22.5 (20–25) mg, although smaller than that in other reports,[23,24] has reached the threshold 15 mg that might compromise fetal status[4] and thus should be used with caution.

Notably, in women receiving norepinephrine, we observed a higher BE and lower lactate levels, which are signs of fetal acid-base status and metabolic markers. We assume such high fetal lactate from ephedrine might be a result of its greater placental transfer and a stronger fetal metabolism stimulation effect.[25] We are still uncertain of the clinical significance of such differences in lactate levels; however, there is evidence that fetal lactate is better than pH to predict severe neonatal morbidity.[26] Therefore, a possible interpretation of these results is that we should be more prudent in the use of ephedrine in potential fetal compromise or uteroplacental insufficiency, such as emergency cases or cases with preeclampsia.

One previous study has shown that phenylephrine was related to a lower UA or umbilical venous PO_2 when compared to ephedrine,

Table 4

Neonatal outcomes.

	Group N (n = 48)	Group E (n = 49)	*P*	Mean difference (95% CI)
Apgar scores (0–10)				
1-min	8 (7–9)	8 (7–9)	.76	
5-min	10 (9–10)	10 (9–10)	.26	
1-min Apgar <7 (n)	0	0	>.99	
5-min Apgar <9 (n)	0	0	>.99	
UA blood gas analysis	(n = 44)	(n = 45)		
pH	7.33 ± 0.02	7.32 ± 0.03	.15	
pH <7.2	0	0		
PO_2, mm Hg	14.7 ± 6.0	16.7 ± 7.3	.15	
PCO_2, mm Hg	50.6 ± 4.1	48.5 ± 7.2	.09	
BE	0.36 ± 1.6	−1.5 ± 3.0	<.001	−1.8 ± 0.5 (−2.8 to −0.8)
Glucose, mmol/L	3.4 ± 0.67	3.4 ± 0.93	.76	
Lactate, mmol/L	1.3 ± 0.3	1.8 ± 0.5	<.001	0.5 ± 0.09 (0.4 to 0.7)

Values are expressed as mean ± SD, number (percentage), or median (IQR). BE = base excess, CI = confidence interval, IQR = interquartile range, SD = standard deviation, UA = umbilical artery.

possibly attributable to its greater vasoconstriction properties, resulting in a reduction of uteroplacental perfusion and an increase in oxygen extraction.[27] Norepinephrine decreased peripheral vascular resistance less than phenylephrine.[8] Minzter et al[28] reported that norepinephrine had no effect on fetal arterial perfusion pressure, and fetoplacental microcirculation was not compromised. In our study, UA PO_2 was slightly lower in group N compared to group E; however, no statistical significance was observed, suggesting that norepinephrine might not compromise fetal oxygen supply with the present dose used.

We acknowledge that there are several limitations to our study. Firstly, norepinephrine used in our study is in the form of norepinephrine bitartrate, which having a potency as 2-fold standard norepinephrine dose. Thus, norepinephrine and ephedrine are not equipotent, with the former 2-fold less than expected, which might partially explain the observed lower SBP and more frequent hypotension episodes for norepinephrine in this study. Secondly, we did not measure uterine arterial blood flow to directly observe the effect of vasopressors on uteroplacental perfusion. Thirdly, norepinephrine was used in group E as a rescue bolus, reducing the confidence in our experimental results from the comparison of the 2 drug treatments. Therefore, norepinephrine is a promising vasopressor to treat maternal hypotension in obstetric anesthesia; however, a more in-depth study is required to fully validate this new treatment.

5. Conclusion

Norepinephrine infusion at 4 μg/minute presented fewer cases of tachycardia, less fluctuation, and a lower HR compared to baseline values, as well as a less stressed fetal status compared to ephedrine infusion at 4 mg/minute. Furthermore, norepinephrine infusion presented a lower standardized SBP compared to ephedrine.

Author contributions

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