

Comparison of two vasopressor protocols for preventing hypotension post-spinal anesthesia during cesarean section: a randomized controlled trial

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Abstract

Background: Norepinephrine infusion decreases hypotension after spinal anesthesia during cesarean section. This study aimed to compare the efficacy of norepinephrine infusion and ephedrine bolus against post-spinal hypotension in parturients.

Methods: In this double-blinded, randomized controlled clinical trial, parturients scheduled for elective cesarean section were randomly allocated to receive norepinephrine infusion ($0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) just before spinal anesthesia continuing for 30 min or ephedrine bolus (0.15 mg/kg) just before spinal anesthesia. A rescue bolus (5 μg norepinephrine for the norepinephrine group, and 5 mg ephedrine for the ephedrine group) was administered whenever hypotension occurred. Our primary outcome was the incidence of hypotension within 30 min of spinal anesthesia administration. Secondary outcomes included maternal and neonatal outcomes 30 min after spinal block, and neonatal cerebral oxygenation 10 min after birth.

Results: In total, 190 patients were enrolled; of these patients, 177 were included in the final analysis. Fewer patients suffered hypotension in the norepinephrine group than in the ephedrine group (29.5% vs. 44.9%, odds ratio [OR]: 0.51, 95% confidence interval [CI]: 0.28–0.95, $P=0.034$). Moreover, the tachycardia frequency was lower in the norepinephrine group than in the ephedrine group (OR: 0.22, 95% CI: 0.11–0.44, $P<0.001$), and patients suffered less nausea and vomiting (OR: 0.28, 95% CI: 0.11–0.70, $P=0.004$). There was no difference in Apgar scores and umbilical arterial blood gas analysis between the two groups. However, neonatal cerebral regional saturations were significantly higher after birth in the norepinephrine group than in the ephedrine group (mean difference: 2.0%, 95% CI: 0.55%–3.45%, $P=0.008$).

Conclusion: In patients undergoing elective cesarean section with spinal anesthesia, norepinephrine infusion compared to ephedrine bolus resulted in less hypotension and tachycardia, and exhibited potential neonatal benefits.

Trial Registration: ClinicalTrials.gov, NCT02542748; <https://clinicaltrials.gov/ct2/show/record/NCT02542748>

Keywords: Hypotension; Spinal anesthesia; Norepinephrine; Ephedrine; Cesarean section

Introduction

Spinal anesthesia is the technical choice for patients undergoing cesarean section. Post-spinal anesthesia hypotension is one of the most common complications during cesarean delivery, and the hypotension rate without pharmacological prophylaxis can be as high as 70% to 80%.^[1] This may induce complications including nausea, vomiting, and fetal compromise. Fluid preload, lateral tilt, and vasoactive agents are effective prophylactic mea-

asures.^[2] Among vasoactive drugs, ephedrine and phenylephrine are commonly used. However, ephedrine is associated with a slow onset of action and prolonged duration, making accurate blood pressure titration difficult, whereas phenylephrine is associated with a high incidence of bradycardia.^[3] Ephedrine easily passes through the placenta, and fetal tachycardia may appear unexpectedly, increasing the risk of fetal acidosis.^[4] Even in healthy parturients with no fetal compromise, the fetal acid-base status has been shown to be less favorable after

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ephedrine administration than after phenylephrine administration.^[5]

Norepinephrine, a potent α -adrenergic receptor agonist with a mild effect on the β -adrenergic receptor, was recently introduced for the prevention of post-spinal hypotension. Therefore, using norepinephrine to maintain parturients' blood pressure during cesarean section may be a better choice because it has fewer negative effects on the heart rate (HR).^[6] Although ephedrine is considered as one of the most widely used vasopressors for preventing post-spinal hypotension,^[3] comparative studies on norepinephrine with ephedrine remain limited. One study demonstrated that using norepinephrine bolus to maintain parturients' blood pressure during cesarean section provided better hemodynamic stability than using ephedrine bolus,^[7] and the fast onset and short duration of action made norepinephrine more suitable for infusion.^[8] Therefore, it is important to investigate whether norepinephrine infusion is advantageous over ephedrine for preventing spinal hypotension.

The main objective of this study was to compare two commonly used protocols of hypotension prevention (continuous infusion of norepinephrine *vs.* ephedrine bolus) against post-spinal hypotension in parturients.

Methods

Ethical approval

This study was approved by the Institutional Review Board of Xijing Hospital (No. KY20151214-2). The study was registered at www.clinicaltrials.com (NCT 02542748) and conducted from October 2015 to June 2016. Written informed consent was obtained from all participants.

Patients

This was a single-center, randomized, double-blinded clinical study. Patients scheduled for elective cesarean sections were screened. Inclusion criteria were as follows: age ≥ 18 years, American Society of Anesthesiologists physical status class 1 and 2, full-term pregnancy, singleton pregnancy, and scheduled elective cesarean section under spinal anesthesia. Patients were excluded if they met any of the following criteria: cardiovascular disease, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes requiring insulin, body mass index >40 kg/m², suspicion of fetal distress, and suspicion of abnormal placentation. Patients were dropped out of the study if the dermatomal level of the spinal block exceeded the fourth thoracic level or was lower than the tenth thoracic level, or failed spinal anesthesia.

Randomization, intervention, and blinding

Patients were simply randomized into the norepinephrine group or ephedrine group using a computer-generated sequence at a 1:1 ratio. Randomization results were sealed in sequentially numbered envelopes and were not revealed until patients arrived at the operating room. An investigator who was not involved in anesthesia and outcome assessment

executed the randomization and prepared the drugs. For norepinephrine group, norepinephrine (0.03 mg/kg) was diluted to 50 mL with normal saline (NS) for infusion. Two bolus syringes were prepared; one contained 5 mL of NS and another contained 5 mL of norepinephrine (5 μ g/mL). For ephedrine group, one syringe contained 50 mL of NS was prepared for infusion. Two bolus syringes were prepared; in one syringe, 0.75 mg/kg ephedrine was diluted to 5 mL with NS (0.15 mg·kg⁻¹·mL⁻¹), an additional 5 mL of ephedrine (5 mg/mL) was prepared for rescue bolus. All syringes were labeled with randomization codes of patients. The patients, anesthetists, surgeons, and staff performing outcome measurements were unaware of the group allocation.

Norepinephrine group: norepinephrine infused at 5 mL/h (0.05 μ g·kg⁻¹·min⁻¹) was initiated immediately before spinal injection and persisted for 30 min, and an NS bolus of 1 mL was administered just after spinal anesthesia. If hypotension occurred, 1 mL of norepinephrine (5 μ g) was administered for rescue.

Ephedrine group: 50 mL NS infused at 5 mL/h was initiated immediately before spinal injection and persisted for 30 min, and an ephedrine bolus of 1 mL (0.15 mg/kg) was administered just after spinal anesthesia. If hypotension occurred, 1 mL of ephedrine (5 mg) was administered for rescue.

Procedures

Baseline HR and non-invasive systolic blood pressure (SBP) (measured at upper left limb), expressed as the average of three consecutive measurements, were taken 5 min apart before anesthesia administration. Before spinal injection, 10 mL/kg of lactated Ringer's solution was preloaded through an intravenous catheter previously placed in the upper extremity, after that the infusion rate was slowed to a maintenance rate. Spinal anesthesia was performed by skilled anesthetists in the right lateral position. After skin sterilization and regional infiltration with 3 mL 2% lidocaine, a 25-gauge pencil-point needle (Tuoren Medical Instruments Inc., Xinxiang, Henan, China) was inserted at the L3–4 vertebral interspace, where 1.4 mL 0.75% hyperbaric bupivacaine 10.5 mg combined with 0.2 mL 50% glucose injection was injected. Administration of the medication in our study was initiated at the time of spinal injection. Following spinal anesthesia, patients were positioned supine with 15° left lateral table tilt. Dermatomal levels of analgesia were assessed bilaterally with a pinprick test and the sixth thoracic dermatomal level was the minimum acceptable level prior to surgical incision. SBP and HR were recorded every 2 min immediately after spinal injection for 30 min. Umbilical arterial blood was drawn and evaluated using a bed-side GEM® Premier™ 4000 blood-gas analyzer (Instrumentation Laboratory, Bedford, MA, USA) immediately after the umbilical cord was clamped. 20 IU of oxytocin was injected intramuscularly to promote uterine contraction and an additional 250 μ g carboprost tromethamine was intramuscularly injected in patients with poor uterine contraction. Neonates were immediately transferred to an infant radiant warmer (Infa Warmer, Atom Medical Corporation, Japan). Cerebral regional saturation

of oxygen (crSO_2) was monitored every 2 s for 10 min using a non-invasive infrared regional saturation (NIRS) device (FORE-SIGHT, CASMED, Branford, CT, USA). Mean values of pulse oxygen saturation (SpO_2) and crSO_2 , and fractional tissue oxygen extraction ($[\text{FTOE}] = [\text{SpO}_2 - \text{crSO}_2]/\text{SpO}_2$) for each minute were calculated in each neonate.^[9] The mean values of crSO_2 at each minute were compared with the 10th percentile of published reference ranges in full-term and late-preterm neonates.^[9,10]

Outcomes

The primary outcome was the incidence of post-spinal hypotension. Hypotension was defined as two successive measurements of SBP lower than 90 mmHg or a 20% decrease in SBP from the baseline value. A rescue bolus (5 μg norepinephrine for the norepinephrine group, and 5 mg ephedrine for the ephedrine group) was administered by the anesthetist whenever hypotension occurred.

Secondary outcomes included maternal and neonatal consequences. Maternal outcomes included incidence of severe hypotension (mean arterial pressure <70% baseline or SBP <80 mmHg), frequency of extra bolus, incidence of tachycardia and bradycardia, hypertension (SBP >120% baseline), dizziness, dyspnea, chest tightness, and score of nausea and vomiting 30 min after spinal injection. Neonatal index included Apgar scores at 1 and 5 min after birth, umbilical blood gas analysis results, crSO_2 values within 10 min after birth and the incidence of neonates transferring to intensive care unit.

Sample size calculation

The primary outcome was the incidence of post-spinal hypotension. A pilot study showed that the incidence of post-spinal hypotension in parturients receiving ephedrine was 58.8%. At an alpha error of 0.05, we estimated that a sample size of 164 patients (82 patients per group) would provide the trial with 90% power to detect a reduction in the frequency of post-spinal hypotension from 58.8% in the ephedrine group to 33.8% in the norepinephrine group, calculated using PASS 15 (NCSS, Kaysville, UT, USA). To account for potential dropouts, 190 patients were scheduled to be enrolled.

Statistical analysis

All analyses were performed in a modified intention-to-treat population that included all patients who had undergone randomization and interventions. All patients were followed during the study period, except for those who withdrew consent. In the latter case, data were censored at the time of consent withdrawal. Because there were no missing data for the primary outcome and less than 5% missing for all secondary outcomes, no data imputation was performed.

Data analysis was performed using SPSS version 24.0 (IBM, Armonk NY, USA). Continuous data were tested for normality using Shapiro-Wilk test and presented as either mean (standard deviation) or median (interquartile range) as appropriate. Continuous data were analyzed using

either Student's *t* test for normal distribution data or the Mann-Whitney *U* test for skewed data. The difference (and 95% confidence interval [CI]) between two medians was calculated with the Hodges-Lehmann estimator. Repeated measurement data (hemodynamic parameters, crSO_2 , and fractional cerebral tissue oxygen extraction [FTOE]) were compared between intervention and control groups using generalized linear model. Model covariates were unadjusted. Categorical data were expressed as frequency (%) and analyzed with Chi-square test or Fisher exact test as appropriate. The odds ratio (OR) and 95% CI were used to describe the differences of dichotomous outcomes. Two-tailed tests were used in all statistical analyses, and *P* value ≤ 0.05 was considered statistically significant.

Results

One hundred and ninety patients consented to and were enrolled in the study. Six patients were omitted for meeting the exclusion criteria, 184 patients underwent randomization, and 7 patients did not receive the intervention because of failed spinal puncture. One hundred and seventy-seven patients completed the study and had data available for final analysis [Figure 1]. Overall, the two groups were well matched for demographic data and baseline characteristics [Table 1].

Primary outcome

Twenty-six patients (29.5%) in the norepinephrine group suffered hypotension following spinal anesthesia, which was less than the 40 patients (44.9%) in the ephedrine group (OR: 0.51, 95% CI: 0.28–0.95, *P* = 0.034) [Table 2].

Secondary outcomes

Changes in SBP and HR over time were shown in Figure 2; SBP was similar between groups (mean difference: -0.62 , 95% CI: -1.60 to 0.37 , *P* = 0.222), whereas HR was greater in the ephedrine group compared with that in the norepinephrine group (mean difference: -9.60 , 95% CI: -10.77 to -8.43 , *P* < 0.001).

Compared with the ephedrine group, patients in the norepinephrine group had lower maximum percentage of decrease in SBP (mean difference: -3.43% , 95% CI: -6.73 to -0.14 , *P* = 0.041) and lower frequency of tachycardia (OR: 0.22, 95% CI: 0.11–0.44, *P* < 0.001). The frequencies of severe hypotension, extra bolus, hypertension, and bradycardia were comparable between the two groups [Table 2].

Compared with the ephedrine group, patients in the norepinephrine group had fewer frequency of nausea (OR: 0.28, 95% CI: 0.11–0.70, *P* = 0.004) and lower score of nausea and vomiting (median difference: 0, 95% CI: -1 to 0 , *P* = 0.005). The frequencies of dizziness, chest tightness, and dyspnea were comparable between the two groups. There was no difference in the volume of fluid infusion and uterine tonic administration between the two groups.

Neonatal baseline characteristics and outcomes including Apgar scores at 1 and 5 min and umbilical arterial blood gas analysis were comparable between groups [Tables 1 and 2]. Changes in crSO_2 and FTOE over time shown in

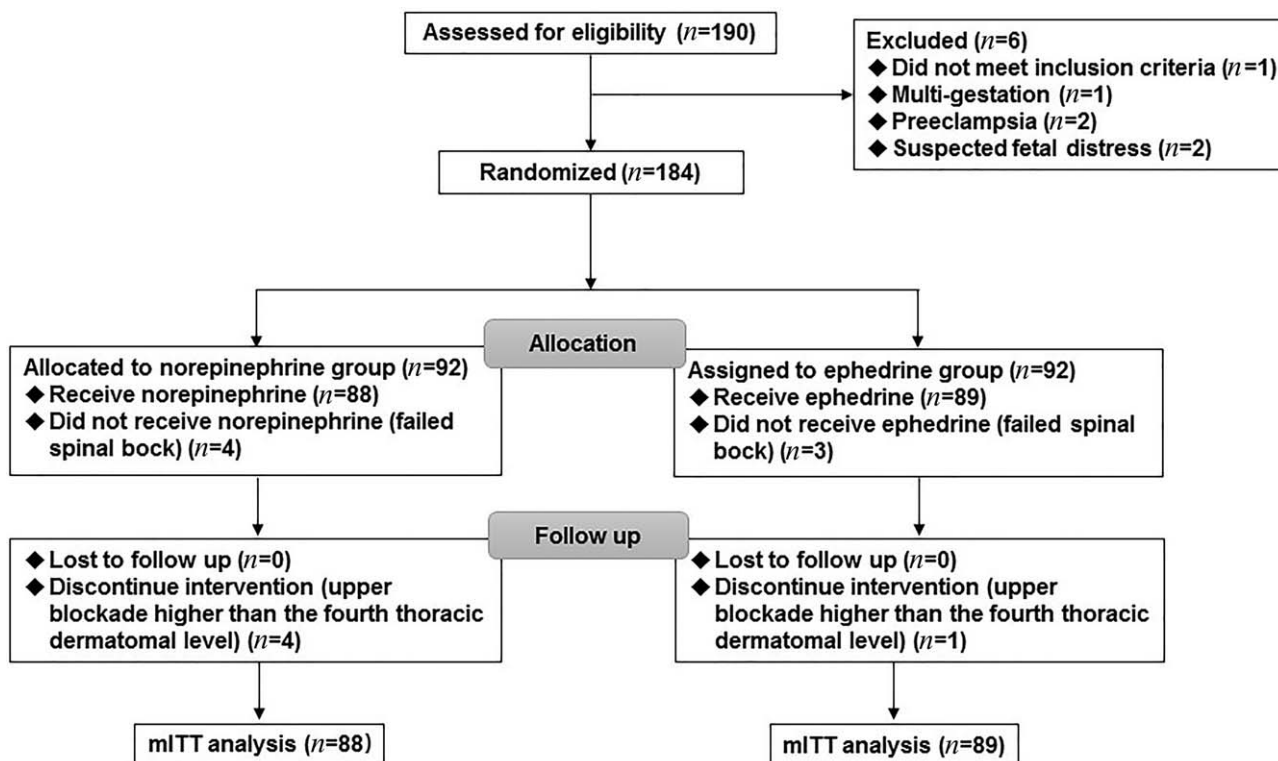


Figure 1: Consolidated standards of reporting trials chart showing patient recruitment. mITT: Modified intention-to-treat.

Table 1: Demographic and surgical outcomes of the parturients in norepinephrine and ephedrine groups.

Characteristics	Norepinephrine group (n = 88)	Ephedrine group (n = 89)	P value
Age (years)	31.2 ± 4.5	30.3 ± 4.4	0.198
Body mass index (kg/m ²)	28.0 ± 3.6	28.5 ± 3.3	0.340
Height (cm)	162.1 ± 4.5	161.8 ± 4.5	0.627
Weight (kg)	73.7 ± 10.8	74.6 ± 9.5	0.542
Gravidity	2 (1, 3)	2 (1, 3)	0.192
Type of parturient			0.064
Primipara	24 (27.3)	36 (40.4)	
Pluripara	64 (72.7)	53 (59.6)	
Gestation (weeks)	39.3 ± 1.1	39.5 ± 1.1	0.274
Upper blockade	T6 (T6, T7)	T6 (T6, T7)	0.458
Duration from SA to umbilical cord clamp (min)	21.5 ± 7.6	21.4 ± 7.4	0.910
Uterine tonic			0.647
Only oxytocin	65 (73.9)	63 (70.8)	
Oxytocin + carboprost tromethamine	23 (26.1)	26 (29.2)	
Duration of surgery (min)	48.6 ± 13.6	49.3 ± 15.8	0.786
Volume of lactated Ringer solution (mL)	1293.4 ± 277.1	1224.8 ± 216.8	0.062
Estimated blood loss (mL)	222.0 ± 41.6	231.0 ± 55.6	0.230

Data are shown as mean ± standard deviation, n (%) or median (interquartile range). Data were compared by Student’s *t* test or Mann-Whitney *U* test. *P* < 0.05 statistically significant. SA: Spinal anesthesia.

Figure 3. crSO₂ monitoring was initiated 2 min after birth. Figure 3A showed the course of crSO₂ during the first 10 min. Means of crSO₂ during the first 10 min after birth were higher than the 10th percentile of published reference ranges in both groups [Figure 3A]. Mean crSO₂ was significantly higher in the norepinephrine group compared with that of the ephedrine group (mean difference: 2.0%, 95% CI: 0.55%–3.45%, *P* = 0.008) [Figure 3A]. Mean

F_{TOE} was higher in the ephedrine group than in the norepinephrine group (mean difference: –2.51%, 95% CI: –3.96%–1.06%, *P* = 0.001) [Figure 3B].

Discussion

Our results show that norepinephrine infusion reduced post-spinal hypotension, tachycardia, and nausea com-

Table 2: Maternal and fetal outcomes in the norepinephrine and ephedrine groups.

Items	Norepinephrine group (n = 88)	Ephedrine group (n = 89)	OR or difference (95% CI)	P
Maternal outcomes				
Incidence of hypotension	26 (29.5)	40 (44.9)	OR = 0.51 (0.28–0.95)	0.034
Incidence of severe hypotension	15 (17.0)	23 (25.8)	OR = 0.59 (0.28–1.22)	0.154
Lowest SBP (mmHg)	94.3 ± 12.4	90.8 ± 14.9	D = 3.49 (–0.59 to 7.57)	0.093
Maximal SBP decrease	19.9 ± 10.5	23.4 ± 11.6	D = –3.43 (–6.73 to –0.14)	0.041
Incidence of hypertension	10 (11.4)	12 (13.5)	OR = 0.82 (0.33–2.02)	0.669
Frequency of extra bolus	1 (0, 1)	1 (0, 1)	D = 0 (0 to 0)	0.079
Incidence of bradycardia	10 (11.4)	5 (5.6)	OR = 2.15 (0.71–6.58)	0.170
Incidence of tachycardia	46 (52.3)	74 (83.1)	OR = 0.22 (0.11–0.44)	<0.001
Incidence of nausea and vomiting	7 (8.0)	21 (23.6)	OR = 0.28 (0.11–0.70)	0.004
Nausea and vomiting score	2 (0, 2)	2 (1, 2)	D = 0 (–1 to 0)	0.005
Incidence of dizziness	4 (4.5)	6 (6.7)	OR = 0.66 (0.18–2.42)	0.747
Incidence of chest tightness	3 (3.4)	5 (5.6)	OR = 0.59 (0.14–2.56)	0.720
Incidence of dyspnea	5 (5.7)	6 (6.7)	OR = 0.83 (0.24–2.84)	0.770
Fetal outcomes				
Male/female	47/41	45/44	-	0.705
Birth weight	3435.9 ± 533.9	3481.8 ± 489.4	D = –45.9 (–244.0 to 142.1)	0.647
Apgar score at 1 min	9 (8, 10)	9 (8, 10)	D = 0 (0–0)	0.947
Apgar score at 5 min	10 (9, 10)	10 (9, 10)	D = 0 (0–0)	0.964
Umbilical arterial pH value	7.34 ± 0.04	7.34 ± 0.04	D = 0.007 (–0.005 to 0.018)	0.272
Umbilical arterial pH value <7.2	1 (1.1)	1 (1.1)	OR = 1.01 (0.06–16.43)	1.000
Umbilical arterial lactate (mmol/L)	1.71 ± 0.54	1.77 ± 0.47	D = –0.06 (–0.22 to 0.09)	0.434
Umbilical arterial base excess (mmol/L)	(–3.2) ± 1.7	(–3.3) ± 1.5	D = –0.04 (–0.31 to 0.58)	0.909
Umbilical arterial PO ₂ (mmHg)	27.8 ± 7.0	28.6 ± 6.9	D = –0.81 (–3.45 to 1.83)	0.545
Umbilical arterial PCO ₂ (mmHg)	42.0 (39.0, 45.0)	41.0 (39.0, 45.0)	D = 0 (–2 to 2)	0.822
Admission to the neonatal ICU	1 (1.1)	0	-	0.497

Data are shown as n (%), mean ± standard deviation, or median (interquartile range). Data were compared by independent samples *t* test, Mann-Whitney *U* test, Chi-square test, or Fisher exact test. *P* < 0.05 statistically significant. D: Difference; OR: Odds ratio.

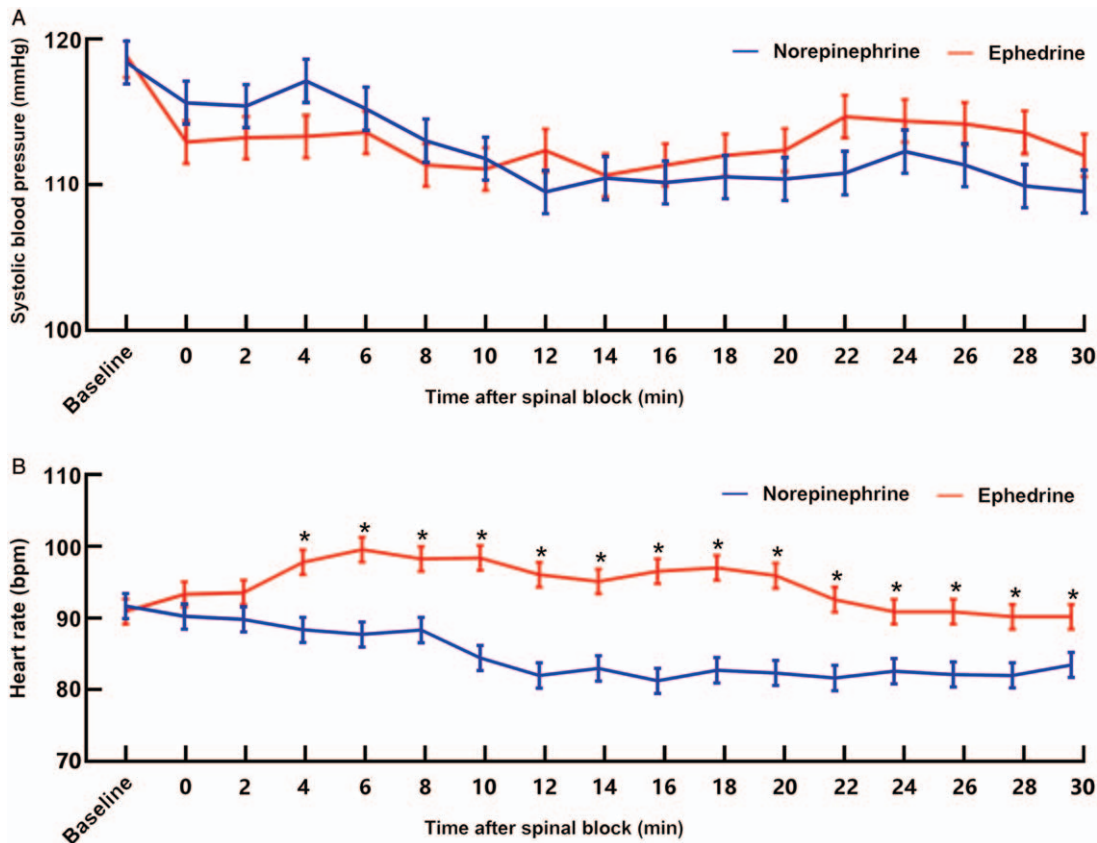


Figure 2: (A) Systolic blood pressure (B) and heart rate at 2-min intervals, 30 min after spinal block. Markers indicate means, and error bars indicate standard errors. *Statistical significance between groups. bpm: Beats per minute.

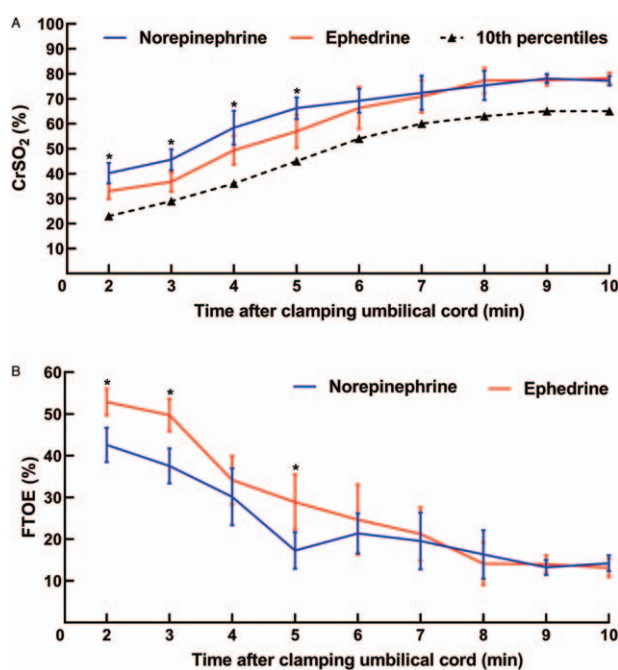


Figure 3: (A) crSO₂ and (B) fractional tissue oxygen extraction during the first 10 min after birth. Line with hollow square (A): the 10th percentile of crSO₂ in full and late preterm neonates. *Significance differences between groups. crSO₂: Cerebral regional saturation of oxygen.

pared with ephedrine bolus during cesarean section. Although no marked difference was noted for the fetal acid-base status between groups, norepinephrine may have an advantage in early neonatal cerebral oxygenation.

Our results were in accordance with recently published studies comparing norepinephrine and ephedrine,^[7,11] however, norepinephrine infusion was used in our study, whereas norepinephrine bolus was used in previous studies.^[7,11] Norepinephrine has a faster onset and shorter duration than ephedrine. In addition, norepinephrine or phenylephrine infusion may be a better approach^[12,13] because in both normal and obese parturients, phenylephrine infusion provided tighter blood pressure control as well as decreased hypotension related nausea, vomiting, and fetal acidosis, compared with bolus.^[14-16] Ngan *et al*^[13] found that titrated norepinephrine infusion (0–5 µg/min) resulted in reduced post-spinal hypotension compared with norepinephrine bolus (5 µg) (17% *vs.* 66%) during cesarean section. In another study, Ngan *et al*^[6] tested computer-controlled approaches for norepinephrine infusion. Considering maternal blood pressure, neonatal outcomes, and possible tissue injury from norepinephrine extravasation and local vasoconstriction, a fixed-rate infusion of 0.05 µg·kg⁻¹·min⁻¹ was used for norepinephrine in our study. In recent studies on post-spinal hypotension during cesarean section, this rate was proved to be as effective as 0.1 µg·kg⁻¹·min⁻¹ phenylephrine,^[17] more effective than 0.025 µg·kg⁻¹·min⁻¹ norepinephrine and as effective as 0.075 µg·kg⁻¹·min⁻¹ norepinephrine.^[18] Previous studies have demonstrated that when used to rescue spinal hypotension, the potency of phenylephrine versus ephedrine is estimated to be 80:1,^[19] and the estimated dose equivalent to phenyleph-

rine 100 µg is norepinephrine 8 µg.^[6] Thus, a potency ratio of 1000:1 was obtained for norepinephrine versus ephedrine. Accordingly, an ephedrine bolus of 0.15 mg/kg was used in this study because it was equivalent to norepinephrine infusion at 0.05 µg·kg⁻¹·min⁻¹ for 30 min.

Fluid infusion, uterine tonic administration, and maternal positioning during surgery are confounders that may influence the evaluation of vasoactive agents for spinal hypotension and HR. To minimize the effects of these factors, the regimens of fluid infusion, uterine tonic administration, and maternal position during surgery were standardized in this study. The results showed that there were no differences with respect to the volume of fluid infusion and the use of uterine tonic between the two groups [Tables 1 and 2]. These findings indicate that the women we included in the present study showed similar in terms of the characteristics that might interact with the interventions and outcomes.

Our results showed that norepinephrine induced a reduction in tachycardia compared with ephedrine. The advantage of norepinephrine in terms of HR is likely related to its weak β-agonist activity, whereas ephedrine has a direct chronotropic effect.^[20] A previous study comparing the efficacy of ephedrine to norepinephrine for spinal hypotension^[20] also showed that although there was no difference in efficacy between norepinephrine and ephedrine for BP maintenance, a greater HR fluctuation was observed with ephedrine, indicating norepinephrine may be superior to ephedrine for preserving maternal HR.

The incidence of maternal nausea and vomiting was reduced from 21% to 7% in the norepinephrine infusion group, and the severity indicated by the nausea and vomiting scores was also alleviated. Intra-operative nausea and vomiting during cesarean section under regional anesthesia are very common and have multiple etiologies, including demography, operative procedures, intra-operative hypotension, and uterotonic agents.^[21] Intra-operative hypotension may result in cerebral and gut hypoperfusion, which can stimulate the release of serotonin from the vomiting center in the brainstem.^[22,23] Tight intra-operative blood pressure control, that is, within 100% of the baseline, reduces nausea, and vomiting.^[24] Uterine exteriorization is also associated with a higher risk of nausea and vomiting compared with *in situ* cesarean section.^[25] However, these details and their possible impacts on nausea and vomiting were not explored in the present study and should be considered in future study designs.

In this study, we did not detect any difference in fetal umbilical artery blood gas analysis between the norepinephrine and ephedrine groups. These results were in agreement with the study of Ali *et al*^[7] The use of ephedrine is generally thought to be associated with lower fetal pH values and base excess than those with the use of phenylephrine.^[26] The underlying mechanisms may be related to the ability of ephedrine to readily cross the placenta and stimulate fetal metabolism, as evidenced by considerably greater values for umbilical venous/maternal arterial and umbilical arterial/umbilical venous plasma

concentration ratios in the ephedrine group.^[27] However, only one patient in each group suffered fetal acidosis (defined as pH <7.20) in our study. The umbilical arterial pH value was 7.34 ± 0.04 in the ephedrine group. Both pH value and incidence of fetal acidosis were not clinically significant between the two groups ($P = 0.272$ and 1.000 , respectively). Norepinephrine was reported to have the same fetal effect as phenylephrine,^[6,17] indicating that norepinephrine had no adverse effect on fetal acid-base status.

Although there was no difference in fetal acid-base status, a higher crSO₂ was observed in the norepinephrine group than in the ephedrine group in the first minutes after birth, indicating that a stable maternal BP would benefit the neonate. The effect of maternal vasopressors on neonatal crSO₂ has not been studied in previous studies. Evidences have showed that in adult patients, patients received dopamine or ephedrine have a higher crSO₂ compared with patients received phenylephrine and may be associated with changes in cardiac output (CO).^[28,29] However, there is no study comparing the effect of ephedrine and norepinephrine on neonates' crSO₂ and need further discussed. In full term neonates, crSO₂ achieved the plateau earlier (after 7–8 min) than SpO₂.^[30,31] Fractional tissue oxygen extraction displayed a similar time course as cerebral oxygen saturation. The brain is extremely sensitive to hypoxia-ischemia during neonatal transition. Measuring crSO₂ based on NIRS is one of the approaches used to continually measure cerebral oxygenation. Two observational studies described the adverse cerebral outcomes of lower crSO₂ values, such as an increased rate of intraventricular hemorrhage and an increased burden of cerebral hypoxia.^[32,33] A previous study demonstrated that crSO₂ monitoring to guide oxygen delivery for neonatal transition and resuscitation could reduce cerebral hypoxia burden in preterm neonates.^[9] In our study, we compared crSO₂ with the 10th percentile of a published reference range.^[10] In a recently published observational study, preterm neonates with crSO₂ lower than the 10th percentile of published reference ranges in the first 15 min after birth were at an increased risk of intraventricular hemorrhage,^[32] although, there was no difference in SpO₂ and HR. In our study, during the first minutes after birth, the values of crSO₂ were all higher than the 10th percentile. The clinical significance of higher crSO₂ in the norepinephrine group requires further research. Prospective and randomized studies are needed to address whether routine use of vasopressors might be beneficial to reduce neonate neurocognitive complications. Studies are again needed to demonstrate whether the administration of norepinephrine rather than ephedrine relates to a better neonate outcome.

One limitation of this study is that we failed to compare CO. Previous studies have compared the effect of norepinephrine on CO. Conventional methods for measuring CO are invasive and thus are difficult to accept by otherwise healthy parturients. Non-invasive methods include transthoracic echocardiography and a non-invasive hemodynamic monitoring system (Nexfin). Results regarding the accuracy of non-invasive devices compared with invasive devices are variable.^[34,35] Another limitation is that crSO₂ values could not be stably achieved in the first

2 min after birth because during this period some other procedures were being performed with the neonate, such as withdrawing an umbilical arterial blood sample and transiting the neonate to the warmer. However, we do not have missing data on crSO₂ during 2 to 10 min, a period during which crSO₂ changes rapidly.^[30,31] Moreover, the duration of hypotension was not measured and compared in this study. Sustained spinal hypotension has been reported to have adverse effects on neonatal outcomes.^[36] However, blood pressure was measured at a 2 min interval in our study and vasopressors were given immediately in the event of spinal hypotension, which greatly reduced the incidence of sustained hypotension.

In conclusion, norepinephrine fixed-rate infusion is more effective than ephedrine bolus for preventing post-spinal hypotension with potential neonate benefits. Further research is required to optimize the regimen for determining and maximizing norepinephrine's neonatal benefits.

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Conflicts of interests

None.

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