

Effects of continuous infusion of phenylephrine vs. norepinephrine on parturients and fetuses under LiDCOrapid monitoring: A randomized, double-blind, placebo-controlled study

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Abstract

Background: Hypotension following spinal anesthesia (SA) during cesarean delivery (CD) occurs commonly and is related with maternal and fetal complications. Norepinephrine infusion is increasingly used for prevention of post-SA hypotension; however, its effects as compared to the traditional phenylephrine infusion remain unclear. This study aimed to compare the effects of phenylephrine and norepinephrine administered as continuous infusion during elective CD on maternal hemodynamic parameters and maternal and fetal outcomes.

Methods: This prospective, single-center, randomized, controlled study included 238 consecutive in-term parturients who underwent CD from February 2019 to October 2019. They were randomized to receive continuous infusion of 0.25 µg/kg/min phenylephrine, 0.05 µg/kg/min norepinephrine, or placebo. Hemodynamic monitoring was performed at 10 time points using LiDCOrapid. We analyzed umbilical vein (UV), umbilical artery (UA), and peripheral vein (PV) blood gas indexes and recorded intraoperative complications.

Results: In phenylephrine group, the systolic blood pressure (SBP) maintain stable during the whole operation. Compared to the control group, phenylephrine, but not norepinephrine, significantly increased the systemic vascular resistance (SVR) to counteract the SA-induced vasodilatation T4: 957.4 ± 590.3 vs 590.1 ± 273.7 ($P < 0.000001$); T5: 1104 ± 468.0 vs 789.4 ± 376.2 ($P = 0.000002$). T6: 1084 ± 524.8 vs 825.2 ± 428.6 ($P = 0.000188$). Parturient in the phenylephrine group had significantly lower UV (1.91 ± 0.43) ($P = 0.0003$) and UA (2.05 ± 0.61) ($P = 0.0038$) lactate level compared to controls. Moreover, the UV pH value was higher in the phenylephrine than in the control group 7.37 ± 0.03 ($P = 0.0013$).

Conclusions: Continuous phenylephrine and norepinephrine infusion reduced the incidence of SA-induced maternal hypotension while decreasing overall complications. Phenylephrine infusions are considered the better choice during CD because of the significant benefit to the fetus.

Background

Spinal anesthesia (SA) is the standard and preferred mode of care for elective cesarean delivery (CD).¹ Although it is considered to be advantageous over general anesthesia, SA can still negatively affect the parturient or the fetus by reducing the placental perfusion.² SA-induced maternal hemodynamic fluctuations during CD can invoke nausea and vomiting, cardiovascular collapse, massive hemorrhage, unconsciousness with resulting pulmonary aspiration, or, in extreme cases, cardiorespiratory arrest.^{3,4} According to recent studies, SA-induced hypotension occurs in 80% of all parturients and nearly 60% of in-term parturients during CD without prophylactic use of vasopressors due to sympathetic blockade by the anesthesia.^{5,6} Thus, obstetric anesthetists increasingly opt for prophylactic vasopressor use for routine prevention of post-SA hypotension during CD.⁷ In recent years, SA takes priority over general and epidural anesthesia because of its unique advantages—it is a simple technique, offers rapid onset of anesthesia, causes a dense sensory block with less tissue trauma and lower risk of spinal-epidural

hematoma, and is easily used in the setting of acute fetal compromise. However, the optimization of hemodynamics, particularly post-SA hypotension during CD, remains the critical management challenge for anesthesiologists.

Phenylephrine, an α -adrenergic agonist and a vasopressor of choice in obstetric anesthesia, is sometimes associated with maternal cardiac depression or reflex bradycardia. This cardiac depressant effect limits its use in parturients with cardiac comorbidities. Norepinephrine, a potent α -adrenergic agonist with weak β -adrenergic agonistic activity, is associated with a lower incidence of maternal bradycardia. Thus, recently, norepinephrine is considered a potential vasopressor of choice during CD at a maintenance dose of 0.05 $\mu\text{g}/\text{kg}/\text{min}$.⁸ However, new evidence points to post-SA hypotension reversal by phenylephrine without significant maternal bradycardia.⁹ In addition, prophylactic use of phenylephrine at 0.25 $\mu\text{g}/\text{kg}/\text{min}$ results in better neonatal outcomes and reduced maternal mortality.¹⁰ These pharmacologic properties make norepinephrine and phenylephrine attractive choices as vasopressors in CD. Nonetheless, comparative studies of these two drugs are limited, and evidence on the optimum vasopressor choice is lacking.

Therefore, this study aimed to compare the effects of phenylephrine and norepinephrine administered as continuous infusion during elective CD on 1) maternal hemodynamic parameters using noninvasive LiDCOrapid™; and 2) maternal and fetal outcomes based on umbilical vein (UV), umbilical artery (UA), and maternal peripheral vein (PV) blood gas indexes.

Methods

Ethical considerations

This study was approved by the Capital Medical University Institutional Review Board on January 23, 2019 (IRB # 2019-058). Written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov (<http://clinicaltrials.gov>; NCT-03833895) on February 1, 2019. Participant recruitment was performed from February 2019 to October 2019. Our methodology followed the international guidelines for randomized clinical studies according CONSORT Guidelines.

Study design and participants

This was a prospective, single-center, randomized, controlled clinical study conducted from February 2019 to October 2019 in the Xuanwu Hospital, Beijing, China. Parturient meeting the following inclusion criteria were recruited: 1) healthy singleton pregnancy; 2) scheduled elective CD under combined spinal-epidural anesthesia (CSEA); 3) American Society of Anesthesiologists physical status I/II; and 4) age between 20 and 45 years. The exclusion criteria were as follows: 1) history of mental disorder, epilepsy, or other central nervous system disease; 2) tricyclic or imipramine antidepressant use; 3) preexisting or pregnancy-induced hypertension; 4) lumbar injury; 5) severe hypovolemia; 6) allergy or history of hypersensitivity to vasopressors; 7) body mass index $>40 \text{ kg}/\text{m}^2$; and 8) infection at the puncture site.

Randomization and blinding

Randomization was performed using computer-generated randomized numbers and allocation concealment was ensured using sequentially numbered opaque sealed envelopes. An anesthesiologist not involved in parturient care was responsible for opening the envelopes and preparing the study medicine.

The study medicine and sealed wrapping instructions were delivered to the operating room before the time of CD. The study medicine was prepared in 50 mL syringes containing phenylephrine, norepinephrine, or placebo, marked with a randomization number. The dose of each medicine was calculated according to the participant's standard weight, defined as the actual height minus 110 cm, and then the medicine was diluted to 50 mL at different concentrations. The three groups were infused in the same speed at 20ml/h. Anesthesiologists involved in infusion of the medicine or parturient care were blinded to the group allocation. Randomization codes were not revealed to the blinded anesthesiologists until all measurements and calculations had been entered into the database and statistical methods had been specified.

Anesthesia protocol

On arrival in the operating room, standard monitoring was initiated, including noninvasive blood pressure (BP) measurement, heart rate (HR) measurement, pulse oximetry, and electrocardiography. Patients were asked to rest still for 5 min. Subsequently, hemodynamic parameters were measured thrice at 2-min intervals, and the mean value was considered the baseline. Next, venous access was established using a 16-gauge intravenous (IV) cannula and 10 mL/kg lactated Ringer's solution (LR) was infused in all groups before CSEA.

CSEA was performed with the patient in the right lateral position using 0.5% bupivacaine (7.5 mg, 1.5 mL, isobaric, 1.0 mL/10 s) injected into the subarachnoid space at the L2–L3 interspace. An epidural catheter was inserted cephalad for a rescue SA. Immediately after anesthesia induction, patients were placed in the supine position with 15° left lateral tilt. The sensory block level before surgical incision was T4.

Intraoperatively, maintenance LR (3 ml/kg/h) was provided for all groups according to the parturients' standard weight. Additionally, parturients received a continuous infusion of the study drug according to the group allocation. After delivery of the fetus, a bolus of 5 IU oxytocin was administered IV followed by a slow infusion of another 5 IU over the remainder of the operation in all three groups.

Interventions

In the phenylephrine group, parturients received a continuous infusion of phenylephrine at the rate of 0.25 µg/kg/min according to their standard weight.¹¹ In the norepinephrine group, parturients received a continuous infusion of norepinephrine at the rate of 0.05 µg/kg/min according to their standard weight.⁸ In the control group, parturients received a continuous infusion of LR as the same speed.

Hypotension was defined if the systolic BP (SBP) reduced by 30% relative to the baseline value or an absolute SBP value of <100 mm Hg. The time interval for BP measurement was set at 3 min. The shortest interval for vasopressor administration was every 1 min. In case of severe hypotension (SBP reduced by more than 30% relative to the baseline value), additional bolus of vasopressor was given; 25 µg of phenylephrine in the phenylephrine group or 4 µg of norepinephrine in the norepinephrine group. In the control group, additional bolus of 4 µg norepinephrine was administered in case of hypotension combined with a HR >60 bpm and additional bolus of 25 µg phenylephrine was administered in case of hypotension combined with a HR <60 bpm. In this study, 0.5mg atropine was administered continually for 3 min only in case of simple bradycardia (HR <50 bpm). The vasopressor infusion was stopped if the SBP increased to >150 mm Hg for over 3 min.

Outcome measurement

LiDCOrapid Pulse Contour Analysis System (LiDCO Ltd., London, UK) was used in all three groups to measure the hemodynamic parameters at each time point. The hemodynamic parameters included stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and HR. All parameters were measured at baseline (T1), at the time of spinal injection (T2), at placement in supine position (T3), 3 min following norepinephrine/phenylephrine/LR administration (T4), 5 min following norepinephrine/phenylephrine/LR administration (T5), at the time of incision (T6), immediately after fetus delivery (T7), at the time of placental expulsion (T8), 5 min after placental expulsion (T9), and at discharge to the postoperative unit (T10).

Blood samples were taken from the UA, UV, and PV for analysis by the blood gas analyzer (Radiometer ABL800 FLEX analyzer, Radiometer A/S, Copenhagen, Denmark) immediately after delivery. The measured parameters included oxygen partial pressure (PO₂), oxygen saturation (SO₂), carbon dioxide partial pressure (PCO₂), glucose and lactate levels, base excess (BE), pH, and anion gap (AG). Intraoperative fluid input and output were recorded. The postoperative incidence of maternal complications, such as hypotension, tachycardia, bradycardia, nausea and vomiting, breathing difficulty, and dizziness was also recorded.

The primary outcome of the study was the SBP as important one of hemodynamic parameters in each group at different time point. The secondary outcomes included hemodynamic parameters (DBP, MAP, HR, SV, CO, SVR), the blood gas indices (PO₂, SO₂, PCO₂, BE, pH, AG) in UV, UA, and PV blood samples, and the incidence of complications.

Sample size calculation

In our pilot study (n=20), the increase of systolic blood pressure (SBP) in the norepinephrine and phenylephrine compare with control groups were Δ31 mmHg and Δ20 mmHg respectively. Using PASS 15.0, a sample size of 71 in the phenylephrine group and 70 in the norepinephrine group was required for

α (Type I error) of 0.05 and β (Type II error) of 0.2. Considering a 10% withdrawal rate, the sample size was calculated at 79 per group.

Statistical analysis

Statistical analyses were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). Categorical data were expressed as number of episodes/participants counts and compared among the three groups by the Chi-squared test. Intergroup comparisons of the mean values of parameters and the mean variations using the Tukey Kramer multiple comparison test. In the time-series data in each group was determined using one-way repeated measures ANOVA during the whole operation. All data were analyzed by the Shapiro-Wilk test for normality of distribution. Normally distributed quantitative variables were presented as means \pm standard deviation. A *P* value of <0.05 was considered statistically significant.

Results

Demographic data

Of the 266 recruited parturients, 28 were excluded, 238 were included in the study, and 235 successfully completed the study (Fig. 1). The parturient's demographics (age, weight, height, BMI) and baseline of the parameter (SBP, DBP, MAP, HR, CO, SV, SVR) were similar in all three groups (Table 1). There was no significant difference among the three groups. The median sensory block height at skin incision reached T4 in all three groups. The urine output, amount of blood loss, and the total volume of infusion were also similar in all groups. There was no significant difference in the duration of delivery, anesthesia, and operation, and the APGAR score among the three groups (Table 2).

Hemodynamic parameters

SBP in Phenylephrine Group were significantly higher than control group at T4,5 timepoints. T4: 109.8 ± 19.09 vs 91.63 ± 19.30 ($P=0.002697$); T5: 121.6 ± 17.88 vs 106.0 ± 15.66 ($P=0.016501$). SBP in Norepinephrine were also significantly higher than control group at T4,5 timepoints: T4: 120.3 ± 16.60 vs 91.63 ± 19.30 ($P < 0.000001$); T5: 115.4 ± 14.33 vs 106.0 ± 15.66 ($P=0.002804$). DBP in Phenylephrine Group were significantly higher than control group at T3, 4,5,6 timepoints. T3: 71.23 ± 14.86 vs 63.21 ± 15.44 ($P=0.002474$); T4: 67.30 ± 14.72 vs 47.18 ± 13.98 ($P < 0.000001$); T5: 73.01 ± 13.69 vs 65.26 ± 12.91 ($P=0.003311$); T6: 71.39 ± 11.99 vs 64.87 ± 12.19 ($P=0.020635$). DBP in Norepinephrine significantly were higher than control group at T3,4 timepoints: T3: 71.80 ± 14.86 vs 63.21 ± 15.44 ($P=0.001132$); T4: 70.00 ± 14.72 vs 47.1 ± 13.98 ($P < 0.000001$). MAP in Phenylephrine Group were significantly higher than control group at T4, 5 timepoints. T4: 78.52 ± 15.61 vs 64.96 ± 18.44 ($P < 0.000001$); T5: 81.75 ± 11.94 vs 73.01 ± 14.02 ($P=0.001162$). MAP in Norepinephrine Group were also significantly higher than control group at T4, 5 timepoints. T4: 86.39 ± 15.97 vs 64.96 ± 18.44 ($P < 0.000001$); T5: 87.95 ± 15.78 vs 73.01 ± 14.02 ($P < 0.000001$). MAP in Phenylephrine Group was significantly higher than Norepinephrine group at T4 timepoints: T4: $78.52 \pm$ vs 86.39 ± 15.97 ($P=0.009866$). HR in Phenylephrine Group were significantly lower than control group at T3,4, 5,6,7,8 timepoints. T3: 85.27 ± 16.87 vs 94.13 ± 17.43

($P=0.001804$); T4: 79.31 ± 19.55 vs 88.59 ± 15.98 ($P=0.001077$); T5: 73.14 ± 14.47 vs 85.12 ± 14.46 ($P=0.000009$); T6: 70.41 ± 14.74 vs 87.37 ± 16.63 ($P<0.000001$). T7: 71.72 ± 13.93 vs 88.67 ± 15.56 ($P<0.000001$); T8: 79.08 ± 15.88 vs 86.72 ± 15.60 ($P=0.007320$); T9: 77.79 ± 14.61 vs 86.34 ± 13.74 ($P=0.002531$); HR in Phenylephrine Group were significantly lower than Norepinephrine group at T5,6,7,8,9 timepoints. T5: 73.14 ± 14.47 vs 81.54 ± 14.91 ($P=0.002737$); T6: 70.41 ± 14.74 vs 80.65 ± 12.33 ($P=0.000177$); T7: 71.72 ± 13.93 vs 86.73 ± 14.32 ($P<0.000001$); T8: 79.08 ± 15.88 vs 87.72 ± 13.84 ($P=0.002530$); T9: 77.79 ± 14.61 vs 86.41 ± 13.94 ($P=0.002530$). (Fig. 2A). SVR in Phenylephrine Group significantly were higher than Control group at T4,5,6 timepoints. T4: 957.4 ± 590.3 vs 590.1 ± 273.7 ($P<0.000001$); T5: 1104 ± 468.0 vs 789.4 ± 376.2 ($P=0.000002$). T6: 1084 ± 524.8 vs 825.2 ± 428.6 ($P=0.000188$); SVR in Norepinephrine Group was significantly higher than Control group at T4 timepoints. T4: 865.0 ± 360.1 vs 590.1 ± 273.7 ($P=0.000043$) (Fig. 2B).

In control group, compare with T1 (122.5 ± 13.63), the SBP was significantly decreased at T3, 110.4 ± 20.67 ($P<0.0001$), T4, 92.33 ± 19.30 ($P<0.0001$), T5, 106.9 ± 15.66 ($P<0.0001$), T6, 105.9 ± 15.30 ($P<0.0001$), T7, 113.7 ± 13.33 ($P=0.0050$). In norepinephrine group, compare with T1, 120.6 ± 12.38 , the SBP was slightly decreased at T6, 110.4 ± 19.57 ($P=0.0014$). In control group, compare with T1 (68.49 ± 13.05), the DBP was significantly decreased at T4, 47.18 ± 13.98 ($P<0.0001$), In norepinephrine group, compare with T1 (69.54 ± 11.98), the DBP was significantly decreased T10, 60.42 ± 16.50 ($P=0.0011$). In phenylephrine group, compare with T1, 87.41 ± 11.57 , the HR was slightly decreased at T5, 73.14 ± 14.47 ($P<0.0001$). T6, 70.41 ± 14.74 ($P<0.0001$), T7, 71.72 ± 13.93 ($P<0.0001$), T8, 79.08 ± 15.88 , ($P=0.0084$); T9, 77.79 ± 14.61 , ($P=0.0013$); T10, 78.34 ± 14.35 , ($P=0.0030$). In norepinephrine group, compare with T1, 91.16 ± 10.54 , the HR was slightly decreased at T4, 83.19 ± 15.07 ($P=0.0034$). T5, 81.54 ± 14.91 ($P=0.0002$), T6, 80.65 ± 12.33 ($P<0.0001$). In control group, compare with T1 (81.34 ± 16.03), the MAP was significantly decreased at T4, 64.96 ± 18.44 ($P<0.0001$), T5, 73.01 ± 14.02 ($P=0.0029$). In norepinephrine group, compare with T1, 81.59 ± 18.59 , the MAP was slightly decreased at T10, 72.15 ± 14.79 ($P=0.0016$) (Fig. 2A). In control group, compare with T1 (8.381 ± 2.451), the CO was significantly increased at T9, 10.03 ± 2.849 ($P=0.0033$). In phenylephrine group, compare with T1 (7.868 ± 2.578), the CO was significantly increased at T8, 10.52 ± 4.104 ($P<0.0001$), T9, 9.965 ± 2.742 ($P=0.0003$). In control group, compare with T1 95.41 ± 25.33 , the SV was significantly increased at T7, 110.3 ± 31.56 , ($P=0.0026$), T8, 104.9 ± 30.35 , ($P=0.0010$). In control group, compare with T1 970.8 ± 344.9 , the SVR was significantly increased at T3, 738.2 ± 358.3 , ($P=0.0003$), T4: 590.1 ± 273.7 ($P<0.0001$); T7, 735.3 ± 350.0 , ($P=0.0002$); T8, 696.5 ± 348.3 , ($P<0.0001$); T9, 654.9 ± 289.7 , ($P<0.0001$); T10, 766.5 ± 286.6 , ($P=0.0022$) (Fig. 2B).

Blood gas indices

The UV PO_2 in Phenylephrine, 30.50 ± 6.24 ($P=0.0143$) and norepinephrine, 30.62 ± 6.91 ($P=0.0093$) significantly higher and SO_2 values in Phenylephrine, 64.68 ± 13.79 ($P=0.0109$) and norepinephrine, 64.49 ± 15.76 ($P=0.0123$) than those in the control group, 27.44 ± 7.54 ; 57.26 ± 17.92 . However, the UV lactate level, 1.91 ± 0.43 in the phenylephrine group was significantly lower than those in the control, 2.30 ± 0.84 ($P=0.0003$) and norepinephrine groups 2.25 ± 0.66 ($P=0.0106$). The UV BE value showed no significant difference among the three groups. The phenylephrine group had a relatively higher UV pH

value 7.37 ± 0.03 ($P=0.0113$) than those in the control 7.36 ± 0.04 , but the mean pH value in all three groups was within the normal clinical range. The UA AG value was significantly lower in the phenylephrine group 0.02 ± 2.73 than those in the control 1.49 ± 2.96 ($P=0.0005$) and norepinephrine groups 1.84 ± 1.72 ($P=0.0001$) (Fig. 3A).

Regarding the UA parameters, there was no significant difference in the PO_2 , SO_2 , PCO_2 , pH, AG, and glucose values among the three groups. The UA lactate level in the phenylephrine group 2.05 ± 0.61 ($P=0.0038$) was significantly lower than that in the control group 2.53 ± 1.01 . Only the norepinephrine group showed a positive UA BE value 0.24 ± 1.86 when compared with the other two groups -0.53 ± 1.84 , -0.38 ± 1.53 ($P=0.0039$) ($P=0.0056$) (Fig. 3B).

Regarding the maternal PV parameters, there were no significant differences in any of the parameters among the three groups (Fig. 3C).

Comparison of adverse reactions among the three groups

In the phenylephrine group, bradycardia occurred in two cases, but there was no significant difference compared with the other two groups. Administering prophylactic norepinephrine and phenylephrine infusion significantly reduced the incidence of tachycardia, intra-operative hypotension, and nausea during CD as compared with the control group. Control group has higher intraoperative hypotension (phenylephrine vs. control group, χ^2 value=21.04, df=1, $P < 0.0001$; norepinephrine vs. control group, χ^2 value=24.44, df=1, $P < 0.0001$). The phenylephrine group has lower Nausea incidence (phenylephrine vs. control group, χ^2 value=8.088, df=1, $P = 0.0045$). Control group has relatively higher Tachycardia (phenylephrine vs. control group, χ^2 value=7.695, df=1, $P = 0.0055$; norepinephrine vs. control group, χ^2 value=8.011, df=1, $P = 0.0046$). When compare each group, after Bonferroni adjust, the P value < 0.0167 indicated the significant different. There was no significant difference in the incidence of vomiting, dizziness, difficulty breathing among the three groups (Table 3).

Discussion

In this study, we compared the effects of phenylephrine and norepinephrine administered as continuous infusion during elective CD on the maternal hemodynamic parameters and the maternal and fetal outcomes. We determined that phenylephrine and norepinephrine have similar efficacy for the prevention of SA-induced hypotension, with no difference in the incidence of maternal bradycardia. However, phenylephrine better preserved the SVR by maintaining appropriate cardiac afterload and provided better neonatal outcomes base on blood gas parameter.

In phenylephrine group, the SBP maintain stable no significant decrease compare with the baseline during the whole operation. In T4, T5 timepoint, decreases both the SBP, DBP and MAP in control group, but significant decrease observed in phenylephrine and norepinephrine groups.

In this study, we successfully employed the LiDCOrapid system for noninvasive assessment of the macro-hemodynamic parameters (CO, SV, and SVR) during phenylephrine or norepinephrine infusion in CD. The LiDCOrapid system was previously validated for use in non-pregnant and pregnant populations.¹²⁻¹⁴ This system enables continuous assessment of the SV based on noninvasive pulse contour analysis under spontaneous breathing, which provides a reliable hemodynamic trend.^{15,16} SVR, a precise dynamic marker of preload responsiveness, describes the degree of hemodynamic fluctuation during surgery. The typical hemodynamic response to SA in parturients adversely affects the SVR and requires a compensatory antagonist.¹⁷ Phenylephrine increases the SVR to counteract the SA-induced vasodilatation. In our study, the SVR in the phenylephrine group was significantly higher than that in the other two groups at T4, T5, and T6 time points.

Based on our results, both 0.25 µg/kg/min phenylephrine and 0.05 µg/kg/min norepinephrine infusions maintain sufficient CO. Unlike norepinephrine, which has a weak β-agonistic action, phenylephrine has no β-agonistic action and is expected to cause a greater decrease in HR. The decrease in HR caused by phenylephrine may affect the maternal CO.¹⁸ In our result, the HR of phenylephrine group decreased compare with the baseline, and slightly lower than control group, but also in the clinical normal range. Even though, the CO maintain stable during the whole operation. The physiologic principal due to the SVR in phenylephrine relatively compensate the HR decrease, then maintain the CO level. Furthermore, a positive correlation has been suggested between the maternal CO and the uteroplacental blood flow in a previous study. The use of combined phenylephrine: norepinephrine at 5:1 concentration is associated with higher uteroplacental blood flow and oxygen delivery to the fetus. In Nagankee's study, the higher dose of phenylephrine (0.5 µg/kg/min) caused lower CO.¹⁹ Phenylephrine negatively affects the CO in a dose-independent manner,²⁰ and a low CO may adversely affect uteroplacental perfusion.²¹ However, in this study, there was no significant decrease in the CO in the phenylephrine group, likely due to the appropriate dosage in our research chosen. The maternal SV also remained constant during phenylephrine infusion throughout the study period.

In the present study, phenylephrine and norepinephrine significantly increased the PO₂ and SO₂ values in the UV. These parameters are known to correlate with fetal oxygenation. Stewart et al. emphasized that even with fetal compromise, there is a need to maintain fetal oxygen delivery.²² The increase in the UV PO₂ and SO₂ values indicates that phenylephrine and norepinephrine enable greater oxygen delivery to the fetus. The changes in the UV glucose levels noted in this study during the vasopressor infusions reflected the changes in the maternal blood glucose levels due to stress reaction. However, the norepinephrine infusion could also have exhibited the stress hormone effect, increasing the placental transfer and UV glucose levels.²³ In the present study, neither the UV nor the UA glucose levels varied among the three groups, which indicates that, at the appropriate dosage, both phenylephrine and norepinephrine can maintain the parturient and the fetus in a low-stress condition. Serum lactate level is the best surrogate indicator of metabolic changes in the fetus. The main finding of our study is that both phenylephrine and norepinephrine tended to decrease the UV lactate levels. The UV lactate level was the lowest in the phenylephrine group, suggesting that phenylephrine could improve the umbilical blood flow

and thereby decrease the metabolic products level, further improving the fetal circulation and oxygen supply. Phenylephrine has the propensity to increase the afterload owing to its α -antagonist action. Catecholamines do not readily cross the placental barrier²⁴; hence, the UA blood gases cannot be affected by phenylephrine or norepinephrine. Changes in the UA blood gases are more likely the result of the fetal stress and fetal catecholamine level. Such changes affect the UA pH value. In this study, the UA pH value was better in the phenylephrine group than in the norepinephrine and control groups. Thus, infusion of low-dose phenylephrine allows for better UA pH. In contrast, norepinephrine induces β -agonist-mediated stimulation of the fetal metabolism and placental transfer, leading to slight reduction in the pH value. Ngan Kee et al. reported no difference in the UA pH value when comparing phenylephrine with norepinephrine, which is consistent with our results. BE is a widely used indicator of fetal distress because previous studies have shown that higher BE values indicate better fetal acid-base status with reduced incidence of fetus acidosis. We observed higher BE values with the use of phenylephrine than those in the control or norepinephrine groups. The lower number of episodes of maternal/fetal acidosis in the phenylephrine group may reflect the positive effects of phenylephrine on the fetus.

In our study, the incidence of maternal adverse events was reduced both in the norepinephrine and phenylephrine groups compared to that in the control group. Prophylactic norepinephrine or phenylephrine infusion effectively reduce tachycardia during CD. Nausea, occur secondary to cerebral hypoperfusion due to hypotension.^{25,26} Numerous studies have reported reduced incidence of hypotension, intraoperative nausea, vomiting, and dizziness with prophylactic bolus of phenylephrine or norepinephrine at various doses.²⁷⁻²⁹ The incidence of nausea and tachycardia in the present study significantly reduced in the norepinephrine and phenylephrine groups compared to that in the control group, whereas dizziness did not occur in the phenylephrine group. Allen et al. reported a rate of hypotension of 15% with 50 $\mu\text{g}/\text{min}$ of phenylephrine, which is similar to our results.

A few study limitations need to be considered. We did not analyze the placental transfer or the metabolic effect of the vasopressors. Thus, although the administration of phenylephrine for prophylaxis of post-SA hypotension has shown promising results, further research is required to explore the placental transfer and metabolic effect of these doses of phenylephrine.

Conclusion

In summary, Phenylephrine, in particular, better preserves the SVR by maintaining appropriate cardiac afterload. However, the neonatal outcomes are better with phenylephrine than with norepinephrine infusion, as evaluated by the decrease in the UV lactate and AG values and the increase in the UV pH value. Therefore, continuous infusion of phenylephrine at 0.25 $\mu\text{g}/\text{kg}/\text{min}$ may improve the outcomes of parturients. These results suggested that the use of low-dose phenylephrine (0.25 $\mu\text{g}/\text{kg}/\text{min}$) does not decrease the CO, thereby providing a better SVR and better perfusion of the fetus.

Abbreviations

SA:spinal anesthesia; CD:cesarean delivery; UV:umbilical vein; UA:umbilical artery; PV:peripheral vein; SBP:systolic blood pressure; SVR:systemic vascular resistance; CSEA:combined spinal-epidural anesthesia; BP:blood pressure; HR:heart rate; IV:intravenous; ASA:American Society of Anesthesiologists; LR:Ringer's solution; SV:stroke volume; CO:cardiac output; DBP:diastolic blood pressure; MAP:mean arterial pressure; PO2:oxygen partial pressure; SO2:oxygen saturation; PCO2:carbon dioxide partial pressure; BE:base excess; AG:anion gap.

Declarations

Ethics approval and consent to participate: This study was approved by the Capital Medical University Institutional Review Board on January 23, 2019 (IRB # 2019-058). Written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov (<http://clinicaltrials.gov>; NCT-03833895) on February 1, 2019. Participant recruitment was performed from February 2019 to October 2019. Our methodology followed the international guidelines for randomized clinical studies according CONSORT Guidelines.

Consent for publication: Not applicable.

Availability of data and materials: The raw data of this study are available from the corresponding author on reasonable request.

Competing interests: None.

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Authors' contributions: KF; Contribution: contributed to study conduction and drafting the manuscript. XW; Contribution: contributed to data analysis and interpretation and reviewing the manuscript. XF; Contribution: contributed to anesthesia performance and record, collection the data. JZ; Contribution: contributed to blood sample collection, blood gas analysis. WX; Contribution: contributed to trial conduction and helped evaluate the patients' responses and was blinded to the medicine concentrations. FW; Contribution: contributed to trial conduction and performing the operation. QZ; Contribution: contributed to performing the operation, substantively revised the manuscript. TW; Contribution: contributed to the study design, funding, and agreed to be accountable for all aspects of this work. All authors read and approved the final manuscript version.

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Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

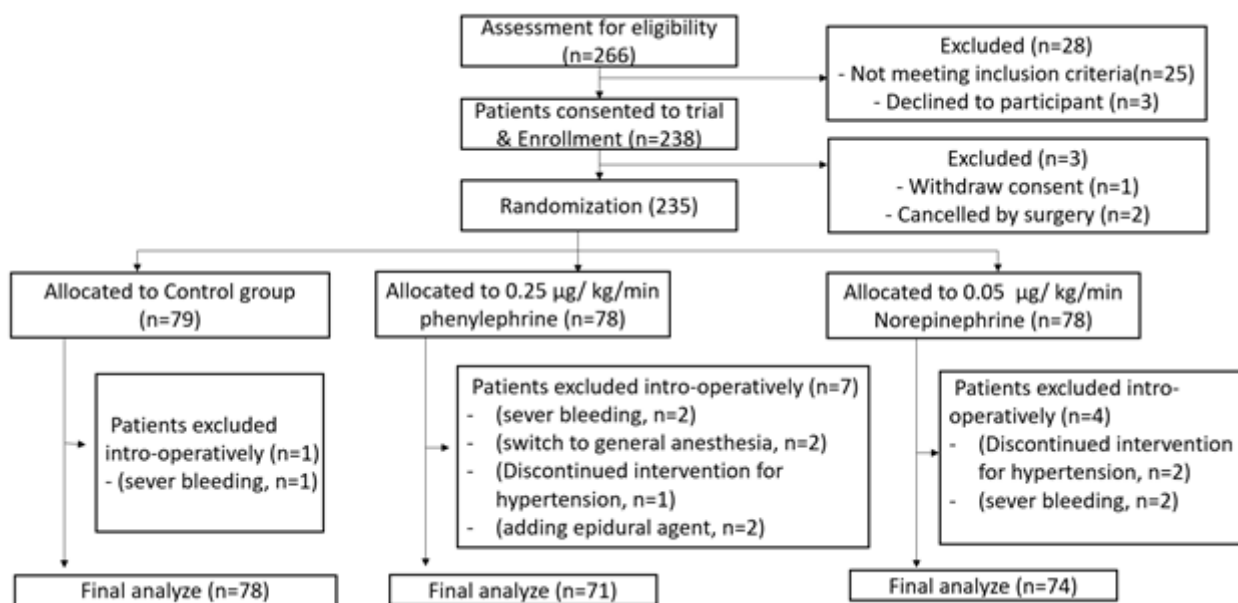


Figure 1

Participant flowchart.

Fig 2B Hemodynamic parameters include SV, SVR and CO in three groups.

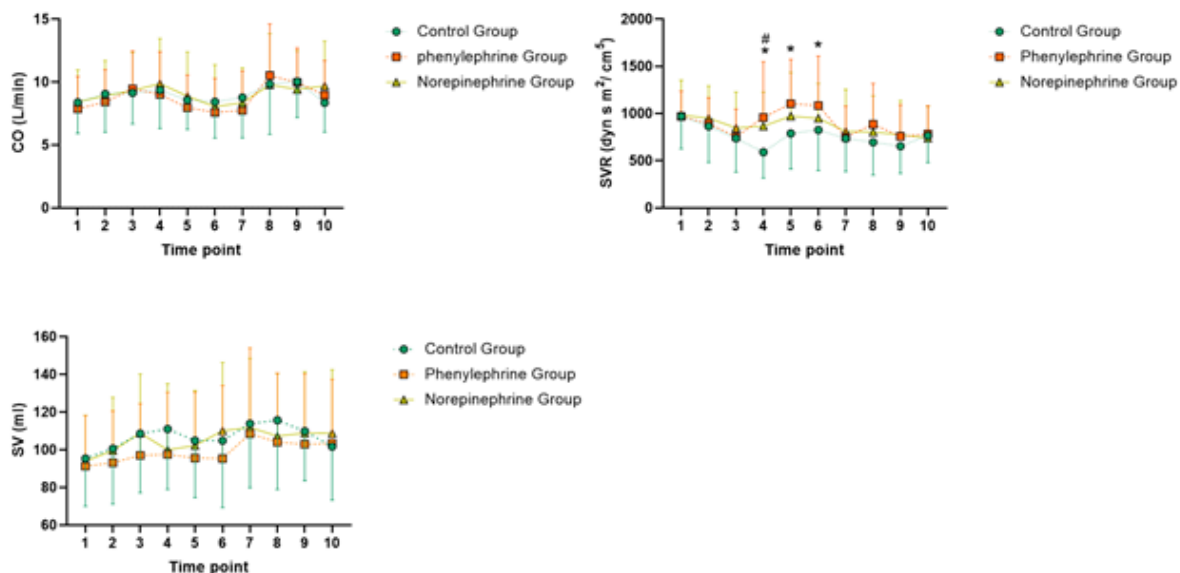


Fig 2A Hemodynamic parameters include SBP, DBP, MAP and HR in three groups.

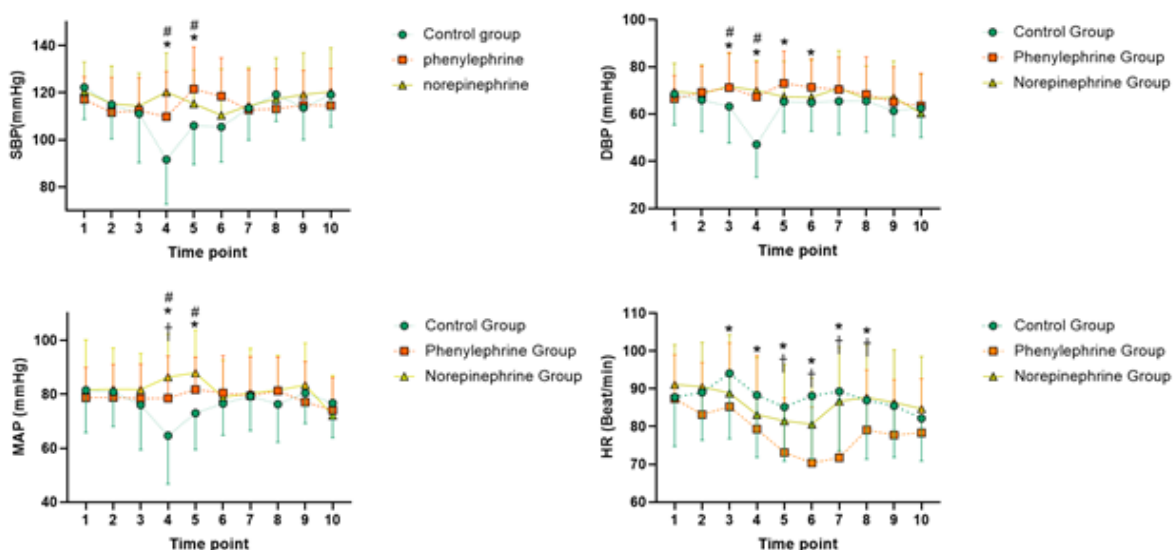


Figure 2

Hemodynamic parameters. (A) Stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) by LiDICOrapid monitoring at the 10 time points. Post hoc Bonferroni correction was performed for within- versus between-subject comparisons. Data are expressed as mean \pm standard deviation. *0.25 $\mu\text{g}/\text{kg}/\text{min}$ phenylephrine vs. control group, $P < 0.05$; #0.05 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine vs. control group, $P < 0.05$; †0.25 $\mu\text{g}/\text{kg}/\text{min}$ phenylephrine vs. 0.05 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine group, $P < 0.05$. (B)

Fluctuations in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) during operation at 10 time points. Markers are means, and error bars are standard deviation. *statistical significance between the 0.25 $\mu\text{g}/\text{kg}/\text{min}$ phenylephrine and control groups; #statistical significance between 0.05 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine group and control groups; †statistical significance between 0.25 $\mu\text{g}/\text{kg}/\text{min}$ phenylephrine and 0.05 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine groups. Post hoc Bonferroni correction was performed for within- versus between-subject comparisons.

Fig. 3 A umbilical vein blood analysis results of three groups.

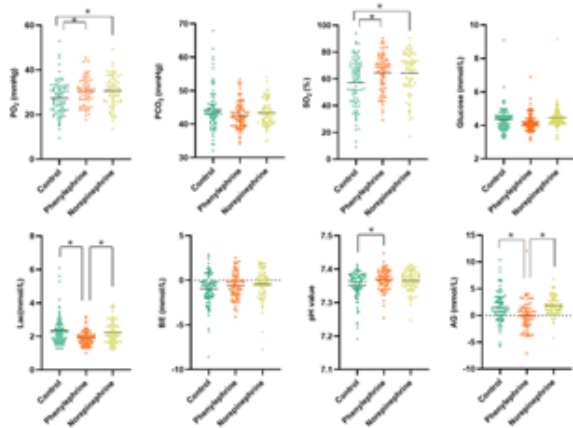


Fig. 3 B umbilical artery blood analysis results of three groups.

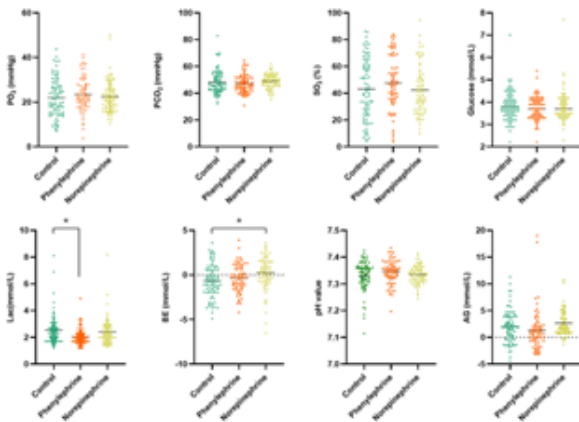


Fig. 3 C maternal peripheral vein blood sample of three groups.

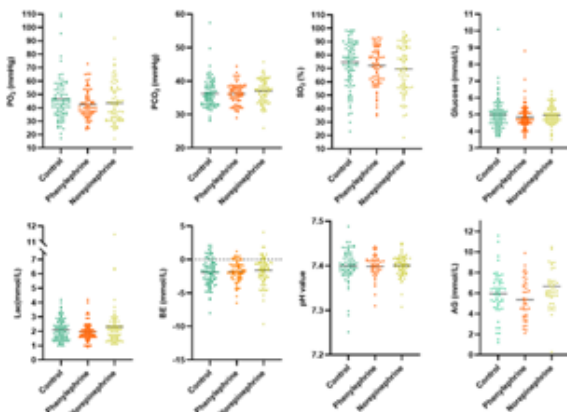


Figure 3

Blood gas analyses. PO₂, PCO₂, SO₂, glucose, lactate (Lac), base excess (BE), pH value, and anion gap (AG) of the (A) umbilical vein, (B) umbilical artery, (C) maternal peripheral vein blood sample of the three groups. * P<0.05

Supplementary Files

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