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Original Research

Preventive intramuscular phenylephrine in elective cesarean section under spinal anesthesia: A randomized controlled trial

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ABSTRACT

Background: Phenylephrine is the first-line vasoactive drug in the cesarean section under spinal anesthesia. The rate of hypotension remains high after intravenous preventive use of phenylephrine. However, few studies have investigated the effect of preventive intramuscular phenylephrine via a longer period of usage on fetal and maternal outcomes.
Methods: A total of 99 healthy parturients undergoing elective cesarean delivery were randomly allocated into three groups: M group (preventive intramuscular use of 5 mg phenylephrine), V group (preventive intravenous use of 100 μg phenylephrine), and P group (0.9% normal saline placebo). Rescue phenylephrine, ephedrine and atropine were used intraoperatively to adjust blood pressure and heart rate. The primary outcome was umbilical artery pH.
Results: Significant differences in umbilical artery pH (M group: 7.32 ± 0.05 versus V group: 7.25 ± 0.04 versus P group: 7.21 ± 0.03, $P < 0.05$), fetal acidosis (M group: 3% [n = 33] versus V group: 15% [n = 33] versus P group: 30% [n = 33], $P = 0.01$) and maternal intraoperative hypotension (M group: 12% [33] versus V group: 39% [33] versus P group: 73% [33], $P < 0.0001$) were identified among the groups. Multiple linear regression analysis demonstrated that treating arms, neonatal birthweight and the interval from the end of anesthesia to baby delivery were associated with umbilical artery pH.
Conclusion: Compared with the preventive intravenous use of phenylephrine and placebo, preventive intramuscular phenylephrine exhibited a better neonatal acid-base status and more stable maternal hemodynamics in elective cesarean under spinal anesthesia.

1. Introduction

In cesarean section, spinal anesthesia is the most widely used anesthesia method for elective cesarean section with the exception of general anesthesia for laboring mothers and serious fetal distress [1]. The blockade of sympathetic nerves in spinal anesthesia leads to decreased peripheral vascular resistance with relatively insufficient blood volume, causing a high incidence of hypotension [2]. Placental hypoperfusion occurs if hypotension is not corrected in a timely manner, damaging the fetal acid-base balance [3]. Different measures are applied to correct hypotension: appropriate anesthetic dosage, change of surgical position, fluid prehydration or cohydration, and the utilization of vasoactive drugs [4–6].

Currently, phenylephrine is recommended as the first-line vasopressor to correct hypotension in cesarean section under spinal anesthesia [7–9]. Compared with ephedrine, the previous first-line drug, phenylephrine exhibits reduced fetal metabolism stimulation due to reduced permeation through the placenta, thereby increasing the pH and base excess in the umbilical cord blood [10]. Current trials of phenylephrine mainly focused on its intravenous use to prevent or treat hypotension [8,11]. In a randomized controlled trial (RCT) by Nazir Iqra [12], the application of prophylactic intravenous bolus dose of 100 μg phenylephrine to prevent hypotension in cesarean delivery under spinal anesthesia still exhibited a high incidence of hypotension (70%). Phenylephrine, a α1-adrenergic agonist, exhibits a 10- to 15-min effect time after single intravenous injection and 1-h effect time after single intramuscular injection. Currently, numerous studies focused on the intravenous use of phenylephrine instead of its intramuscular use given that this approach offers a longer effect time and milder effect to improve blood pressure [12,13]. Therefore, we hypothesized that

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preventive intramuscular injection of phenylephrine may ameliorate the neonatal acid-base status with more stable maternal hemodynamics.

Our purpose of this RCT was to compare a preventive single intramuscular injection of 5 mg phenylephrine, preventive single intravenous injection of 100 μg phenylephrine and preventive placebo (0.9% normal saline) injection in elective cesarean section under spinal anesthesia. Outcomes included fetal acid-base status and maternal hemodynamics. The primary outcome of this RCT was umbilical artery (UA) pH.

2. Materials and methods

This RCT was approved by the ethics committee of Affiliated Hospital of *** Medical University and the study number was XYFY2018-KL010-01. We registered this RCT on clinicaltrials.gov, an international prospective registration website (protocol ID: NCT03507387). The first study subject was enrolled after obtaining the ethical endorsement and registration information. This study was performed from April 2018 to August 2018 at the Affiliated Hospital of *** Medical University. Every participant provided written informed consent before entering the trial. The results are reported in a manner consistent with the CONSORT statement [14].

2.1. Participants

Parturients scheduled for elective cesarean section under spinal anesthesia were continuously assessed for inclusion from April 2018 to August 2018. The following inclusion criteria were employed: 1) singleton pregnancy at term via elective cesarean section; 2) age from 18 to 40 years, height from 150 cm to 180 cm, American Society of Anesthesiologists (ASA) grade from I to II grade, and BMI less than 40 kg/m^2.

The following exclusion criteria were employed: 1) multiple pregnancy; 2) contraindications for spinal anesthesia; 3) parturients with comorbidities: gestational or nongestational hyptertension, diabetes, eclampsia, etc.; 4) preoperative history of bradycardia (heart rate (HR) less than 60 bpm); 5) fetal complications: fetal macrosomia, fetal malformation, fetal distress in uterus, etc.; 6) participants refused to sign informed consent.

2.2. Randomization, blinding and allocation concealment

Random sequence was generated by Stata 12.0, and each individual was randomly assigned to the intramuscular injection of phenylephrine group (M group), intravenous injection of phenylephrine group (V group) or 0.9% normal saline placebo group (P group) in a 1:1:1 ratio. Researchers, patients and statistical analyst were blind to the group arrangements. Allocation concealment was conducted by placing a random sequence in opaque, sealed envelopes that were opened after each participant entered the operating room to determine the group assignments.

2.3. Intervention

All the parturients accepted fasting for 8 h before surgery and received no food and drink before anesthesia. When the participants entered the operation theater, each parturient was assigned to a specific group after another researcher opened the envelope in a sequential fashion. This researcher prepared syringes with a blank label in advance (syringe 1: 1 ml, 10 mg phenylephrine + 1 ml 0.9% normal saline; syringe 2: 2 ml, 200 μg phenylephrine; syringe 3: 2 ml 0.9% normal saline) and gave these syringes to the anesthetist involved in the surgery. To successfully implement blinding to reduce bias, every parturient received intramuscular injection and intravenous injection. In group M, 1 ml (5 mg) phenylephrine was intramuscularly injected into the gluteus maximus 5 min before anesthesia, and 1 ml placebo (0.9% normal saline) was intravenously injected upon completion of the subarachnoid injection. In group V, 1 ml placebo (0.9% normal saline) was intramuscularly administered, and 1 ml phenylephrine (100 μg) was intravenously administered. In group P, 1 ml placebo (0.9% normal saline) was used both intramuscularly and intravenously.

After parturients quietly rested on the operation table in the supine position with 15° left lateral tilt for 5 min, noninvasive blood pressure (BP) and heart rate (HR) were continuously measured every 2 min. Baseline systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were defined as the arithmetic average of three continuous measurements with variation within 10%. Noninvasive BP and HR were measured every 1 min from the end of anesthesia to the delivery of the baby and every 2 min after the delivery of the baby. Conventional 2 L/min oxygen inhalation via nasal tube was administered to all the parturients. An intravenous line was established in one forearm, and 10 ml/kg Ringer's lactate solution was intravenously infused over 10 min as prehydration before anesthesia. Spinal anesthesia was administered in the left lateral position at L3-4 vertebral interspace. When the cerebrospinal fluid flowed out, 10 mg of hyperbaric 0.75% bupivacaine was injected into the subarachnoid space. After the anesthesia procedure was complete, the parturient was arranged in the supine position with 15° left lateral tilt, and the operation table was adjusted to make the block level between T4 and T6. The spinal sensory level was tested by a pinprick to achieve the block level for surgery. If hypotension (decrease in SBP > 20% baseline SBP) occurred without bradycardia (HR < 60 bpm) during surgery, 40 μg phenylephrine was intravenously (i.v.) injected to treat hypotension. If bradycardia occurred without hypotension, a bolus of 0.3 mg atropine i.v. was administered. If hypotension and bradycardia appeared simultaneously, a bolus of 6 mg ephedrine i.v. was administered. Before the first breath of the newborn, two vessel forceps were used to clamp the umbilical cord. Two heparinized syringes were separately applied to collect umbilical artery (UA) and umbilical vein (UV) blood, which was immediately tested by the Roche cobas b 123 POC blood gas analyzer (Roche Group, Basel, Switzerland).

2.4. Study outcomes

2.4.1. Primary outcome: UA pH

Secondary outcomes: neonatal outcomes: 1) other UA and UV blood gas analysis values: pH, base excess (BE), lactate, PaO2, PaCO2; 2) the incidence of fetal acidosis (UA pH < 7.20); 3) Apgar scores (1 min and 5 min after birth); 4) incidence of neonatal ICU (NICU) admission. Maternal outcomes: 1) intraoperative SBP, DBP and HR; 2) the incidence of hypotension, hypertension (the increase of SBP > 20% baseline SBP), bradycardia, nausea and vomiting; 3) time to first use of rescue phenylephrine after anesthesia (completion of the subarachnoid injection was defined as 0 time point); 4) the number of times rescue phenylephrine was used during surgery; 5) the number of times rescue ephedrine and atropine were used.

2.5. Statistical analysis

The calculation of sample size was conducted according to the primary outcome (UA pH) with PASS 11.0 (NCSS, LLC, Kaysville, USA). Due to the lack of sufficient prior research data, the sample size was calculated based on the following pre-experiment results: the mean UA pH of M group was 7.30 and the standard deviation (SD) was 0.08; the mean for V group was 7.26 and SD was 0.08; the mean for P group was 7.23 and SD was 0.07. A total of 95 patients were required to achieve 90% power with an α of 0.05 based on the module of analysis of variance (ANOVA) in PASS [15]. Accounting for a 4% dropout rate, each group needed 33 patients in this trial.

For continuous data, Shapiro-Wilk test was used to assess the normality. Normally distributed continuous data were presented as the means (SD), and nonnormal data were presented as medians (interquartile range). Binary data were presented as number (percentage). ANOVA and Kruskal-Wallis H test were used for normally and nonnormally distributed continuous data followed by LSD test and Mann-Whitney *U* test for post hoc multiple comparisons. For repeatedly measured outcomes, repeated-measures analysis of variance was used. Binary outcomes were compared using $\chi 2$ tests or Fisher exact tests between groups. Kaplan-Meier curves were generated to demonstrate the time to first use of rescue phenylephrine after anesthesia in three groups, and log-rank tests and post hoc analyses were applied to compare the first rescue time in the three groups. Multiple linear regression analyses were applied to for the primary outcome (UA pH). Treating arm was viewed as an independent variable, and maternal age, gestational week, neonatal weight, and interval between the end of anesthesia and baby delivery were also included in the univariate linear regression. Univariate linear regression identified factors with $P < 0.10$ that were included in the subsequent multivariate linear regression. A *P*-value less than 0.05 was considered statistically significant. For post hoc multiple comparisons, a *P*-value less than 0.017 was considered statistically significant after Bonferroni correction. All statistical was analyses were conducted using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

A total of 162 parturients scheduled for elective cesarean section were sequentially screened for inclusion between April, 2018 and August, 2018. In total, 45 participants were excluded according to inclusion and exclusion criteria, and written informed consent was not obtained for 18 participants. Finally, 99 parturients were randomly allocated to the intramuscular injection of phenylephrine group (M group), intravenous injection of phenylephrine group (V group) and 0.9% normal saline placebo group (P group) in a 1:1:1 ratio. No participant was lost to follow-up in this trial, and 33 participants in each group were included in the final analysis. The specific flow diagram of patient selection is presented in Fig. 1.

3.1. Baseline characteristics

No significant differences in maternal demographics, baseline hemodynamics, neonatal weight and some characteristics of anesthesia and surgery were noted among the 3 groups (Table 1).

3.2. Neonatal outcomes

Neonatal outcomes are presented in Table 2. Significant differences in the primary outcome (UA pH) were noted among the three groups (M group: 7.32 ± 0.05 versus V group: 7.25 ± 0.04 versus P group: 7.21 ± 0.03, $P < 0.05$). According to the post hoc multiple comparisons, the M group exhibited an increased UA pH compared with the V group ($P < 0.05$), and the V group exhibited an increased UA pH compared with the P group ($P < 0.05$). Similarly, the M group exhibited an increased UV pH compared with the V group ($P < 0.05$), and the V group exhibited an increased UV pH compared with the P group ($P < 0.05$). No significant differences in other UA and UV outcomes were noted: BE ($P > 0.05$), Lac ($P > 0.05$), PaO_2 ($P > 0.05$) and $PaCO_2$ ($P > 0.05$). The incidence of fetal acidosis (UA pH < 7.20) differed in three groups (M group: 3% [n = 33] versus V group: 15% [n = 33] versus P group: 30% [n = 33], $P = 0.01$). Post hoc analysis demonstrated that the M group exhibited a reduced fetal acidosis rate compared with the V group ($P < 0.017$), and the V group exhibited a reduced fetal acidosis rate compared with the P group ($P < 0.017$). No significant differences in Apgar scores (1 min and 5 min after birth) and the incidence of admission to the NICU were noted among the three groups.

Multiple linear regression analysis was used for UA pH (Table 3). The univariate linear regression analysis demonstrated that treating arms, neonatal weight, parturient age and the interval between the end of anesthesia and delivery were associated with UA pH ($P < 0.10$). Subsequently, multivariate linear regression analysis revealed that only treating arms, neonatal weight and the interval between the end of anesthesia and delivery were associated with UA pH ($P < 0.0001$).

3.3. Maternal outcomes

Maternal outcomes are presented in Table 4. Significant differences in the incidence of postanesthesia hypotension were observed (M group: 12% [33] versus V group: 39% [33] versus P group: 73% [33], $P < 0.0001$). Post hoc analysis also revealed significant differences between each comparison ($P < 0.017$). Significant differences in the number of times i.v. rescue phenylephrine and the incidence of nausea were noted among groups. Similar results regarding the number of times i.v. rescue atropine and ephedrine, the incidence of hypertension, bradycardia and vomiting were noted among the groups. Fig. 2 depicts the change in SBP over time after anesthesia. Baseline SBP was similar among the three groups (M group: 120.5 ± 10.4 versus V group: 119.4 ± 9.5 versus P group: 118.5 ± 8.7, $P = 0.70$). With the

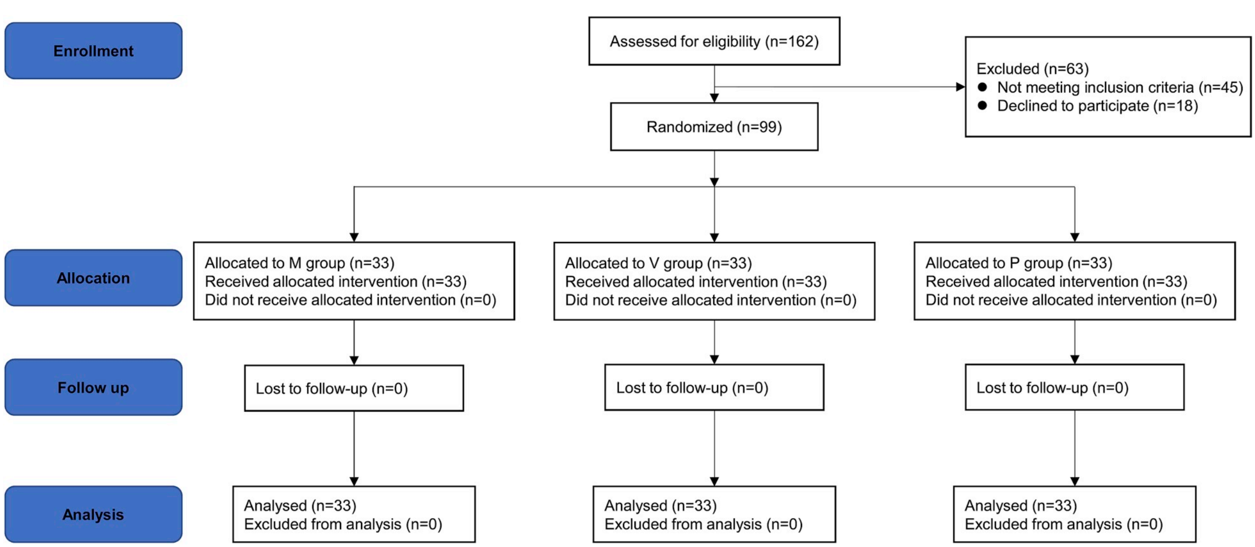

Fig. 1. Flow diagram based on Consolidated Standards of Reporting Trials (CONSORT) statement.

Table 1
Baseline characteristics of parturients.

	M group (n = 33)	V group (n = 33)	P group (n = 33)	*P*
Age (y)	30 (26,31)	28 (25,31)	30 (27,33)	0.26
Gestational week (wk)	38 (37,39)	38 (37,39)	38 (38,39)	0.52
Height (cm)	163 (160,166)	163 (160,168)	162 (158,165)	0.40
Weight (kg)	75.1 ± 10.0	72.6 ± 8.8	73.1 ± 11.7	0.59
BMI (kg/m^2)	28.1 ± 3.6	27.1 ± 2.6	27.9 ± 4.3	0.43
ASA grade (I/II)	25/8	26/7	25/8	0.95
Number of previous delivery	1 (0,1)	1 (0,1)	1 (0,1)	0.12
Baseline SBP (mmHg)	120.5 ± 10.4	119.4 ± 9.5	118.5 ± 8.7	0.70
Baselin DBP (mmHg)	71.1 ± 6.0	72.6 ± 7.7	73.3 ± 7.9	0.50
Baseline HR (bpm)	77.2 ± 5.7	77.7 ± 6.9	76.4 ± 6.6	0.69
Neonatal weight (g)	3370.3 ± 497.0	3264.6 ± 469.8	3403.9 ± 432.8	0.45
Anesthesia time (min)	10 (9,11)	10 (9,11)	10 (9,11)	0.54
Time from end of anesthesia to delivery (min)	8 (8,9)	8 (8,9)	9 (8,10)	0.19
Intraoperative fluid volume (ml)	1653.5 ± 126.6	1697.0 ± 175.9	1700.6 ± 51.2	0.26
Intraoperative blood loss (ml)	424.6 ± 25.9	422.1 ± 19.9	432 ± 19.8	0.34
Intraoperative urine volume (ml)	370.0 ± 15.0	367.9 ± 20.1	373.6 ± 17.3	0.40

Data are mean (SD) or median (interquartile range). ASA = American Society of Anesthesiologists, SBP= Systolic Blood Pressure, DBP = Diastolic Blood Pressure, HR= Heart Rate.

Table 2
Neonatal outcomes.

	M group (n = 33)	V group (n = 33)	P group (n = 33)	*P* value
Umbilical artery				
pH	7.32 ± 0.05	7.25 ± 0.04	7.21 ± 0.03	< 0.05
BE	−2.28 ± 0.12	−2.25 ± 0.07	−42.27 ± 0.14	0.63
Lac	2.27 ± 0.07	2.28 ± 0.08	2.29 ± 0.07	0.56
PaO2	15.76 ± 3.44	15.21 ± 3.77	15.52 ± 4.30	0.85
PaCO2	50.30 ± 6.44	50.12 ± 6.45	51.67 ± 8.15	0.63
Umbilical vein				
pH	7.35 ± 0.04	7.31 ± 0.04	7.26 ± 0.03	< 0.05
BE	−3.51 ± 0.22	−3.51 ± 0.29	−3.49 ± 0.33	0.94
Lac	2.35 ± 0.08	2.38 ± 0.08	2.38 ± 0.09	0.42
PaO2	29.94 ± 5.68	30.82 ± 7.22	30.30 ± 6.03	0.85
PaCO2	42.55 ± 5.74	41.76 ± 6.53	42.09 ± 5.46	0.86
Fetal acidosis	1 (3)	5 (15)	10 (30)	0.01
Apgar score				
1min	8 (8,9)	8 (8,9)	8 (8,9)	0.96
5min	9 (8,10)	9 (8,10)	9 (8,10)	0.80
Admission to NICU	0 (0)	0 (0)	1 (3)	1.00

Data are mean (SD) and number (percentage). NICU=Neonatal Intensive Care Unit.

Table 3
Univariate and multivariate linear regression for UA pH.

	Univariate		Multivariate	
	Stanardized Coefficients	*P* value	Stanardized Coefficients	*P* value
Treating arms	−0.736	< 0.0001	−0.700	< 0.0001
M group (reference)				
V group	−0.567	< 0.0001	−0.616	< 0.0001
P group	−0.850	< 0.0001	−0.806	< 0.0001
Gestational week (wk)	−0.147	0.148	–	–
Neonatal weight (g)	−0.596	< 0.0001	−0.589	< 0.0001
Age (y)	−0.258	0.01	0.009	0.761
Time from end of anesthesia to delivery (min)	−0.290	0.004	−0.115	< 0.0001

Factors of $P < 0.10$ in the univariate analysis were included in the multivariate analysis. M group was regarded as the reference in the factor of treating arms.

Table 4
Maternal outcomes.

	M group (n = 33)	V group (n = 33)	P group (n = 33)	*P* value
Hypotension (n)	4 (12)	13 (39)	24 (73)	< 0.0001
Number of rescue iv phenylephrine (n)				< 0.0001
0	29 (88)	20 (61)	9 (27)	
1	4 (12)	9 (27)	14 (42)	
2	0 (0)	4 (12)	6 (18)	
3	0 (0)	0 (0)	4 (12)	
Number of iv rescue atropine (n)	1 (3)	1 (3)	2 (6)	0.78
Number of iv rescue ephedrine (n)	1 (3)	2 (6)	2 (6)	0.80
Hypertension (n)	2 (6)	2 (6)	2 (6)	1.00
Bradycardia (n)	2 (6)	3 (9)	4 (12)	0.69
Nausea (n)	2 (6)	7 (21)	14 (42)	0.002
Vomiting (n)	1 (3)	2 (6)	2 (6)	0.80

Data are mean (SD) and number (percentage).

exception of 7, 9 and 10 min after anesthesia, SBP values in the M group were higher compared with the V group and P group at other time points. Fig. 3 presents the probability of not receiving first i.v. rescue phenylephrine after anesthesia over time in the three groups. The probability of not using rescue phenylephrine decreased over time in all three groups. The log-rank tests demonstrated that less parturients received rescue phenylephrine in the M group compared with the V group ($P < 0.017$) and in the V group compared with the P group ($P < 0.017$).

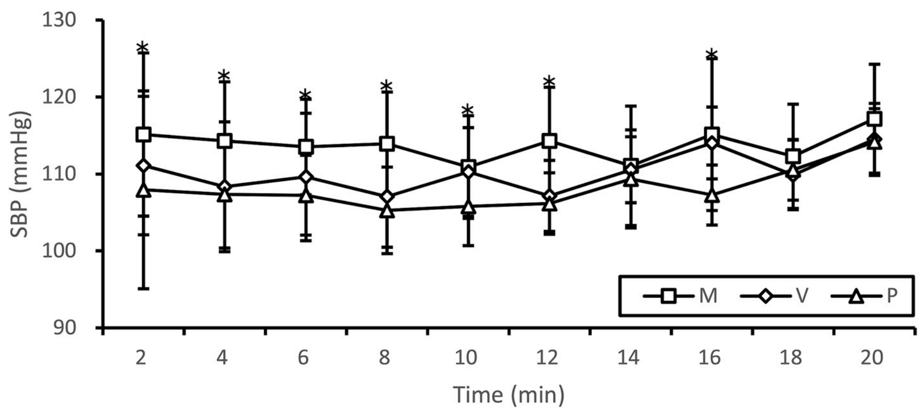

Fig. 2. Systolic blood pressure of three groups over 20 min after anesthesia. (M group, n = 33; V group, n = 33; P group, n = 33). * in the figure represented a difference between the three groups at this time.

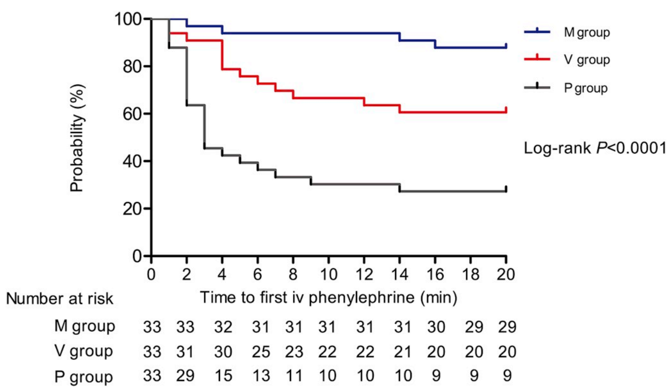

Fig. 3. Kaplan-Meier curves for time to first intravenous rescue use of phenylephrine after anesthesia in three groups.

4. Discussion

Compared with preventive intravenous use of phenylephrine and normal saline placebo, preventive intramuscular use of phenylephrine exhibited a better acid-base equilibrium status (increased UA pH and reduced fetal acidosis rate) and lower intraoperative hypotension rate. Multiple linear regression analysis for the primary outcome (UA pH) also demonstrated that treating arms, neonatal weight and the interval between the end of anesthesia and delivery were associated with UA pH.

pH, BE and lactate values in the umbilical cord blood are objective indicators reflecting the fetal acid-base state. Many studies defined UA pH value less than 7.20 as fetal acidosis [16–18]. Umbilical cord blood pH is a sensitive and feasible index of fetal acid-base equilibrium status that contains both respiratory and metabolic elements, whereas BE and lactate only reflect metabolic aspects [19,20]. Therefore, pH was chosen as the primary outcome based on a logarithmic calculation of the fetal acid-base status. In this RCT, significant differences in UA pH were noted among the three groups (M group: 7.32 ± 0.05 versus V group: 7.25 ± 0.04 versus P group: 7.21 ± 0.03, $P < 0.05$). The median time from the end of anesthesia to baby delivery was 8–9 min, and SBP was increased in the M group compared with the V group and P group during this time. Thus, better uteroplacental blood perfusion in the M group may lead to higher UA pH. In the same manner, the fetal acidosis rate differed among the three groups (M group: 3% [n = 33] versus V group: 15% [n = 33] versus P group: 30% [n = 33], $P = 0.01$). Although differences in the umbilical cord blood gas values were noted, the clinical outcomes of the fetuses (1-min and 5-min Apgar scores) were similar between groups.

Ituk US et al. conducted a retrospective study including 146 parturients with pre-eclampsia undergoing cesarean section under spinal anesthesia [21]. Ituk US's research employed multiple linear regression analyses of UA pH and found that only nonreassuring fetal heart trace was associated with reduced UA pH. In contrast to Ituk US's study, our study only included healthy parturients undergoing elective cesarean section without any fetal abnormalities. Similar to Itus US's study, age and gestational week were not risk factors of UA pH. In our trial, treating arms, the interval between the end of anesthesia and baby delivery and neonatal weight were statistically significant after multivariate regression analyses. As mentioned above, different treating arms accounted for the diverse SBP and uteroplacental perfusion levels, influencing the fetal acid-base status. A longer interval between the end of anesthesia and delivery caused the parturients more exposed to hypotension induced by the sympathetic inhibition effect of anesthetics. Heavier neonatal birthweight increased the uterine volume, causing greater uterine compression on the inferior vena cava and increasing the incidence of supine hypotensive syndrome [22,23]. In addition, heavier birthweight increased the operation difficulty, and the time between the end of anesthesia and baby delivery was prolonged.

Our study revealed that the intraoperative hypotension rate and time to first rescue via intravenous use of phenylephrine differed among groups. The intramuscular group exhibited a more stable hemodynamic status due to considerably longer maintenance time compared with a single incident of intravenous use of phenylephrine (1 h versus several minutes). Although the intraoperative vomiting rate was similar among groups, the incidence of nausea differed among the three groups (M group: 6% [n = 33] versus V group: 21% [n = 33] versus P group: 42% [n = 33], $P = 0.002$). The sympathetic block effect of spinal anesthesia could lead to nausea and vomiting via gastrointestinal hyperactivity due to the subsequently increased parasympathetic activity [24]. Intraoperative nausea and vomiting were also induced by the hypotension event. Reduced nausea rates in the M group may be attributed to the relatively increased blood pressure in this group.

The peak effect of intramuscular use of phenylephrine was 10–15 min after administration. Phenylephrine was intramuscularly injected into the gluteus maximus 5 min before anesthesia, and the median anesthesia time was 10 min. Thus, intramuscular phenylephrine works before the sympathetic inhibition of spinal anesthesia. However, what if the lumbar puncture procedure failed and caused hypertension in parturients? All 99 parturients completed the spinal anesthesia procedure in 10 min based on the following reasons. First, the adhesions of subarachnoid space were not serious given that the majority of included parturients were primiparas or experienced at most one cesarean section, improving the success rate of anesthesia. Second, we excluded extremely overweight parturients, and the greatest BMI was less than 40 kg/m^2, which may be associated with an increased anesthesia success rate. Third, recent research demonstrated that ultrasound-guided lumbar puncture increased the first-time success rate of spinal anesthesia with increased comprehension of the anatomical structure [25,26]. In this RCT, ultrasound was used in parturients with puncture difficulty, and the success rate was also improved.

The measurement of blood pressure in the study was noninvasive, which was less sensitive and accurate compared with invasive blood pressure measurements. However, studies demonstrated that intermittent noninvasive blood pressure measurement represents a valid method of arterial pressure undergoing elective cesarean section and is widely recognized as the conventional method measurement for healthy parturients undergoing elective cesarean section [27,28].

Limitations existed in our study. First, the participants included in this RCT were nonlaboring healthy parturients accepting elective cesarean delivery without fetal abnormality and the results may not be extrapolated to laboring parturients and parturients with pregnancy complications or fetal abnormalities. Second, the calculation of sample size was based on UA pH, which may be underpowered to detect differences in maternal outcomes, and the subsequent research should recruit more participants to achieve increased testing power.

5. Conclusion

Compared with preventive intravenous use of phenylephrine and placebo, preventive intramuscular use of phenylephrine exhibited a longer action time, gentler effect, better neonatal acid-base status and more stable maternal hemodynamics in healthy parturients undergoing elective cesarean section. Our trial demonstrated that heavier neonatal birthweight and longer interval from the end of anesthesia to baby delivery were associated lower umbilical artery pH. More trials should be conducted to investigate the effect of intramuscular preventive use of phenylephrine on parturients with pregnancy complications or fetal abnormalities.

Ethical approval

This trial was approved by the ethics committee of Affiliated Hospital of Xuzhou Medical University (Jiangsu, China) as study number XYFY2018-KL010-01.

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None.

Author contribution

Chao Xu and Dongchen Qian: study design, data collections, data analysis and writing.

Aohua Liu, Su Liu and Yajie Chen: data collections and data analysis.

Chang Liu and DunYi Qi: Study design, data analysis and writing.

Conflicts of interest

None.

Registration unique identifying number (UIN)

This trial was registered on ClinicalTrials. Registration Number: NCT03507387.

Guarantor

DunYi Qi.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Chao Xu: Conceptualization, Investigation, Methodology, Project administration, Writing - original draft. **Su Liu:** Investigation, Methodology, Project administration, Writing - review & editing. **Dongchen Qian:** Project administration, Resources, Software. **Aohua Liu:** Project administration, Resources, Software. **Chang Liu:** Investigation, Methodology, Project administration. **Yajie Chen:** Investigation, Methodology, Project administration. **Dunyi Qi:** Conceptualization, Data curation, Project administration, Supervision, Validation, Visualization, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2018.12.014.

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