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Neonatal Umbilical Artery pH Following Position-Specific Metaraminol Infusion During Elective Caesarean Delivery: A Randomised Noninferiority Trial

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ABSTRACT

The standard 15° left tilt during cesarean delivery has long been recommended, but its actual clinical benefit has been questioned in recent studies. We investigated whether starting metaraminol at a higher dose in the supine position could maintain neonatal umbilical arterial pH as effectively as the conventional left tilt approach. A total of 124 healthy women scheduled for elective cesarean delivery were randomly assigned to either a supine position (n = 62) or 15° left tilt (n = 62) following spinal anesthesia with 0.5% bupivacaine (9 mg). Metaraminol infusion began at 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the supine group and 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the tilt group. Infusion rates were adjusted using a standardized protocol to maintain maternal systolic blood pressure. The primary outcome was umbilical arterial pH, with secondary outcomes including base excess, maternal blood pressure, and incidence of hypotension or reactive hypertension.

Umbilical arterial pH and base excess in the supine group were comparable to the tilt group (pH: 7.325 [7.29–7.35] vs 7.33 [7.30–7.35], P = 0.76; base excess: −0.92 ± 2.77 mM vs −0.98 ± 2.59 mM, P = 0.9). Maternal systolic blood pressure and hypotension rates were similar between groups, whereas reactive hypertension was more frequent in the supine group (P < 0.001). For healthy parturients (BMI < 35 kg/m^2), a higher starting dose of metaraminol in the supine position provides neonatal acid–base outcomes equivalent to the 15° left tilt, suggesting the tilt may not be necessary when blood pressure is actively managed.

Keywords: Cesarean section, Maternal positioning, Supine position, Left tilt, Metaraminol, Neonatal pH

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Introduction

During cesarean delivery, the gravid uterus can compress the inferior vena cava, and following spinal anesthesia, the resulting reduction in systemic vascular resistance often precipitates significant maternal hypotension, which may compromise fetal acid–base homeostasis [1]. In 1972, Crawford *et al*. reported that tilting the surgical table 15° to the left improved umbilical artery pH (UA-pH) compared with the supine position (15° tilt: 7.31 ± 0.04 vs supine: 7.27 ± 0.09, P < 0.001) in women under general anesthesia [2]. Notably, many patients were tilted to the right due to surgical convenience. Subsequent studies have generally supported left tilt positioning, which remains a recommended practice [2–4].

However, practical limitations exist. For instance, most anesthesiologists achieve smaller tilt angles without specialized devices, with over 90% using less than the recommended 15° [5]. Visual estimation yielded an average tilt of 10.8 ± 2.1°, tolerated by only 3% of surgeons, while 48% requested reduction to below 8° due to operative interference [6]. Moreover, studies in healthy volunteers have shown that modest left tilts (5°–12.5°) during cesarean delivery after spinal anesthesia do not significantly enhance maternal hemodynamics or umbilical blood flow [7, 8], and up to 76% of parturients report discomfort in a tilted position [6]. The use of wedges or tilts may also increase the risk of sciatic nerve compression [9, 10]. These factors have prompted debate regarding the routine need for left tilt in contemporary obstetric practice.

Lee *et al*. re-evaluated supine versus left tilt positioning under modern anesthetic protocols, including spinal anesthesia with fluid preloading and phenylephrine infusion titrated to baseline blood pressure [11]. While the 15° tilt did not improve fetal acid–base status, it was associated with increased maternal systolic blood pressure (SBP) and cardiac output. Shayegan *et al*. suggested maintaining the tilt for potential maternal hemodynamic benefits [12].

In the supine position, inferior vena cava compression is more pronounced, requiring higher doses of vasoactive agents to maintain blood pressure compared with tilted positions [13, 14]. Previous studies determined the 90% effective dose (ED90) of weight-adjusted metaraminol infusion for hypotension prevention as 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the supine position and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with a 15° tilt [13, 14].

Metaraminol has recently gained attention as a preferable alternative to phenylephrine due to its mild β1 agonist activity, which counteracts reflex bradycardia, and less reduction in cardiac output caused by strong α receptor stimulation [15]. Network meta-analyses suggest metaraminol is superior to phenylephrine in maintaining maternal blood pressure and optimizing fetal acid–base balance [16, 17]. However, ED90 values for metaraminol in both supine and tilted positions have yet to be compared directly in clinical trials.

We hypothesize that initiating a higher metaraminol infusion rate in the supine position (2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ supine vs. 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ tilt) will yield umbilical artery pH outcomes that are non-inferior to those achieved with the conventional 15° left tilt.

Materials and Methods

This trial was approved by the Ethics Committee of Peking University People's Hospital (protocol ID: 2021PHB455-001), and all participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT05084599) prior to enrollment. Reporting adhered to the CONSORT guidelines [18].

Study participants

Inclusion criteria included: singleton pregnancies at term scheduled for elective cesarean delivery, maternal height between 150–180 cm, ASA physical status II–III, and BMI < 35 kg/m^2. Exclusion criteria comprised transverse fetal presentation or macrosomia, uterine anomalies, polyhydramnios, ruptured membranes or oligohydramnios, intrauterine growth restriction, maternal hypertensive or metabolic disorders, autonomic neuropathies, renal failure, contraindications to combined spinal-epidural anesthesia, or refusal to participate.

Randomization and blinding

A total of 124 participants were randomly assigned using a random number table from http://tools.medsci.cn/rand, with allocation concealed in opaque envelopes. The trial was open-label for clinical staff, but blood gas measurements and statistical analyses were performed by blinded personnel. The clinician scoring Apgar outcomes was not blinded [2].

Surgical procedures

Participants fasted 6–8 hours but could ingest clear fluids up to 2 hours before surgery. Peripheral venous access was established, and standard monitoring included ECG, non-invasive blood pressure, and pulse oximetry, with supplemental oxygen (5 L/min) via nasal cannula. Baseline SBP was measured after 5 minutes in the operating room in both supine and 15° left tilt positions. Three consecutive measurements were taken at 2-minute intervals, and if any value differed from the mean by >10%, measurements were repeated after 2 minutes. This procedure ensured SBP stabilization before intervention. Differences in SBP between the two positions were considered acceptable due to expected vena cava compression in the supine position.

Intraoperative procedures

Combined spinal-epidural anesthesia (CSEA) was administered by a single anesthesiologist in the left lateral position using a needle-through-needle approach. A 16-G epidural needle was inserted, with entry into the epidural space confirmed by loss-of-resistance to air. Subsequently, a 25-G pencil-point spinal needle was advanced through the epidural needle until cerebrospinal fluid (CSF) was observed, after which 9 mg of 0.5% isobaric bupivacaine was injected at the estimated L3-L4 interspace. The spinal needle was removed, and an epidural

catheter was advanced 3–5 cm into the epidural space before removing the epidural needle. The moment of spinal injection was defined as time zero.

Sensory blockade was assessed using pinprick testing, with exclusion if T6 sensory level was not achieved within 10 minutes [19]. If patients experienced pain before delivery, 5 mL of 2% lidocaine was administered via the epidural catheter. A researcher opened the randomization envelope during neuraxial block placement to determine the assigned group.

Immediately after the spinal injection, patients were positioned either supine or with a 15° left tilt, and metaraminol infusion was started at 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the supine group and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the tilt group, based on preoperative weight measurements. Non-invasive blood pressure (NIBP) readings were recorded every minute until delivery. Infusion adjustments were made according to SBP relative to baseline: infusion was halved if SBP was 110%–120% for three consecutive minutes and stopped if SBP remained above baseline. Reactive hypertension, defined as SBP ≥120% of baseline, was managed by pausing the infusion until SBP returned to baseline.

For patients with baseline SBP <90 mmHg, the target was to maintain SBP ≥90 mmHg. If SBP dropped to 80%–90% of baseline for three minutes, infusion was increased to 150% of the initial rate, and to double the initial rate if SBP remained low. Persistent hypotension (>20% drop from baseline or SBP <90 mmHg) for 3 minutes allowed additional interventions, including phenylephrine, ephedrine, IV fluids, position adjustments, or epinephrine at the discretion of the anesthesiologist. Bradycardia (HR ≤50 bpm without hypotension) was treated with 0.5 mg atropine. Total metaraminol consumption before delivery was recorded.

The 15° tilt angle was confirmed using a phone-based gradienter (Simple Gradienter 5.5.6, Longjie Network Technology, Shanghai, China). Rapid infusion of Ringer's solution (10 mL/kg) was administered within 10–15 minutes to stabilize SBP before switching to a slow maintenance infusion [13, 20, 21].

Immediately after delivery, umbilical artery (UA) and vein (UV) blood were collected from a double-clamped segment of the cord and analyzed within 30 seconds using a GEM Premier 4000 blood gas analyzer by personnel blinded to group allocation. Apgar scores were assessed at 1 and 5 minutes.

Statistical analysis

The primary endpoint was UA pH, while secondary outcomes included UA and UV blood gas parameters, incidence of maternal hypotension (SBP ≤80% of baseline or <90 mmHg), nausea, vomiting (≥10 mL or solid emesis), and bradycardia (HR ≤50 bpm) before delivery [22]. Exploratory outcomes included reactive hypertension (SBP ≥120% baseline), Apgar scores, SBP within 20 minutes post-spinal anesthesia, metaraminol usage, and duration of hypotension. SBP was recorded up to 20 minutes to reflect the interval from spinal anesthesia to delivery at the study center. Analyses followed an intention-to-treat approach [22].

Data were analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL). Continuous variables were tested for normality with the Kolmogorov–Smirnov test. Normally distributed data are reported as mean ± SD and compared with unpaired t-tests, while non-normal data are reported as median (IQR) and compared using the Mann–Whitney U test, with the Hodges–Lehmann estimator used for median differences. Repeated measures were analyzed with generalized linear mixed models. Categorical data are expressed as proportions. A P-value ≤0.05 was considered statistically significant.

Sample size calculation

The trial's primary outcome was UA pH [2, 23]. Based on prior research, a UA pH difference of 0.03 was considered clinically relevant for fetal outcomes [2, 24, 25]. Crawford *et al*. demonstrated that a 15° tilt changed UA pH by 0.039, supporting the clinical use of this angle [2]. A non-inferiority margin of 0.021 (70% of 0.03) was applied. Assuming an SD of 0.03, with one-sided $\alpha = 0.025$ and $\beta = 0.1$, 88 patients were required.

Secondary outcome UA base excess (UA-BE) was considered, with a clinically relevant difference of 2 mmol/L and a non-inferiority margin of 1 mmol/L based on Lee *et al*. [11]. Assuming SD = 1.5 mmol/L, 98 patients were needed. Accounting for potential dropouts and type II errors, 62 patients were recruited per group.

Results and Discussion

Of 274 screened women, 124 met inclusion criteria and were randomized equally to supine (n = 62) or 15° tilt (n = 62) groups. The CONSORT flow diagram is shown in **Figure 1**. Data from all 124 patients were included in the analyses, although UA samples were missing for two patients in each group.

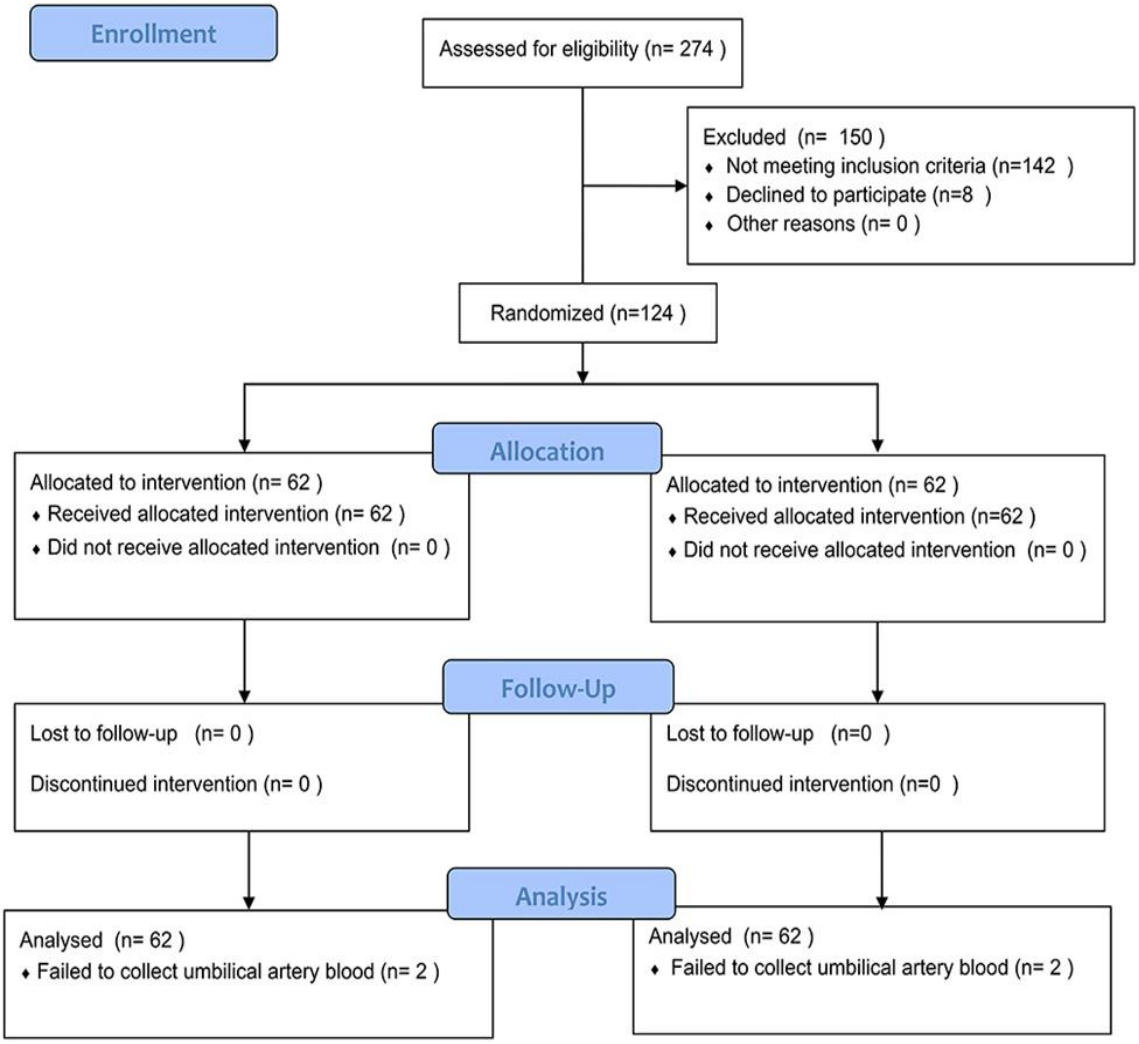

Figure 1. CONSORT flow diagram.

Baseline data

There was no clinically significant difference between the baseline data of the two groups of patients **(Table 1)**.

Table 1. Maternal Baseline Data

	Supine Group (n = 62)	**Tilt Group (n =62)**	**P Value**
Age (yr)	33 (31, 36)	33 (30, 36)	0.83
Height (cm)	162 (159, 165)	162 (160, 165)	0.96
Weight (kg)	71 (65.3, 75)	70.5 (67, 75)	0.61
BMI (kg/m^2)	26.9 (2.5)	27.2 (2.8)	0.53
Gestational age (dy)	39.3 (38.9, 39.8)	39.3 (38.9, 39.7)	0.62
Neonatal weight (kg)	3.4 (0.4)	3.4 (0.3)	0.96
Sensory block level	T6 (T4, T6)	T6 (T4, T6)	0.22
Intraoperative fluid volume (mL)	1000 (900, 1200)	1000 (900, 1300)	0.85
Intraoperative blood loss (mL)	300 (288, 400)	300 (200, 400)	0.36

Intraoperative urine volume (mL)	200 (150, 300)	200 (148, 313)	0.33
Baseline SBP (mmHg)	113 (108, 119)	116 (111, 121)	0.14
Baseline HR (times per minute)	84 (11)	84 (9)	0.86
Time from end of anesthesia to delivery (min)	22 (19, 27)	22 (19, 26)	0.69

Notes: For quantitative data, normally distributed data are represented by mean ± SD; nonnormally distributed data are represented by median (interquartile range). Count data are expressed by n (percentage).
Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; BMI, Body Mass Index.

Neonatal outcomes

Umbilical artery (UA) samples were missing for two neonates in each group, while umbilical vein (UV) samples were unavailable for five neonates in both the supine and tilt groups. There was no significant difference in UA pH between groups (tilt: 7.33 [7.30, 7.35] vs supine: 7.325 [7.29, 7.35], P = 0.76), with mean ± SD values of 7.319 ± 0.05 for the tilt group and 7.316 ± 0.05 for the supine group. The estimated median difference in UA pH (95% CI) was 0 (−0.02 to 0.01). The lower bound of the two-sided 95% CI (−0.02) exceeded the predefined non-inferiority margin of −0.021, confirming that the supine position is non-inferior to the 15° left tilt. **Figure 2** presents a box plot showing the distribution of UA pH by group.

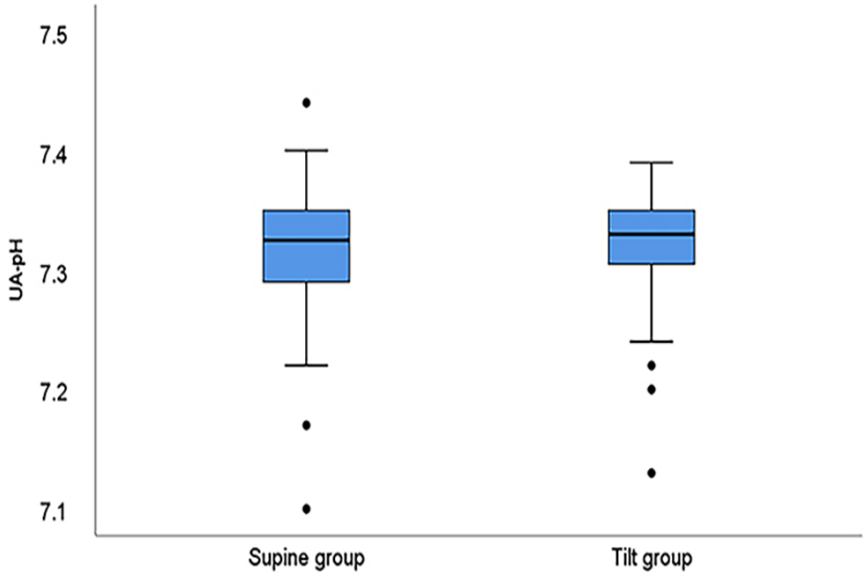

Figure 2. Box plot of the distribution of the pH of the umbilical artery by group. The line outlier median, box outlier interquartile range, whisker outlier 2.5th percentile and 97.5th percentile and dots represent outlier values.

Neonatal acid–base and apgar outcomes

The umbilical artery base excess (UA-BE) did not differ significantly between the groups (tilt: −0.98 [2.59] mM vs supine: −0.92 [2.77] mM, P = 0.9; mean difference = −0.62). The estimated median difference (95% CI) in UA-BE was −0.62 (−0.91 to 1.03). The lower bound of the two-sided 95% CI (−0.91) remained above the pre-specified non-inferiority margin of −1, indicating that the supine position was non-inferior to the 15° left tilt.
No significant differences were observed in umbilical vein pH (UV-pH) or base excess (UV-BE) between groups. All neonates had normal Apgar scores at 1 and 5 minutes, with no significant differences between the supine and tilt groups **(Table 2)**.

Table 2. Neonatal Acid–Base Status and Apgar Scores

	Supine Group	**Tilt Group**	**P Value**
UA blood gases	(n=60)	(n=60)	
pH	7.325 (7.29, 7.35)	7.33 (7.3, 7.35)	0.76
BE (mmol/L)	−0.92 (2.77)	−0.98 (2.59)	0.9

$P0_2$ (mmHg)*	22 (18.3, 25.8)	24 (20, 29)	0.13
PCO_2 (mmHg)	51 (45.3, 54.8)	48 (44, 52.8)	0.38
Lac (mmol/L)	1.8 (1.6, 2.3)	1.7 (1.5, 2.1)	0.33
HCO_3 (mmol/L)	25.2 (2.8)	25 (2.6)	0.55
UV blood gases	(n=57)	(n=57)	
pH	7.35 (7.33, 7.38)	7.36 (7.33, 7.37)	0.45
BE (mmol/L)	−2 (−3.3, 0.9)	−2.2 (−3.2, −1.2)	0.93
$P0_2$ (mmHg)*	34.3 (6.3)	32.5 (7.4)	0.16
PCO_2 (mmHg)	41 (39, 44.5)	42 (39, 46)	0.51
Lac (mmol/L)	1.7 (1.5, 1.9)	1.7 (1.4, 1.975)	0.71
HCO_3 (mmol/L)	23.2 (22.1, 24.7)	23.2 (22.3, 24.2)	0.98
Apgar score	(n=62)	(n=62)	
<7 at 1 min	0 (0)	0 (0)	–
<7 at 5 min	0 (0)	0 (0)	–

Notes: Normally distributed data are represented by mean ± SD and compared by unpaired *t* test. Nonnormally distributed data are represented by median (interquartile range) and compared by Mann–Whitney *U*-test. Number (percentage) and were compared using$\chi 2$ tests. *PO_2 values less than 10 mmHg are reported as "less than 10 mmHg" and were treated as 10 mmHg for this analysis.
Abbreviations: UA, umbilical artery; UV, umbilical vein.

Neonatal acid–base and apgar outcomes

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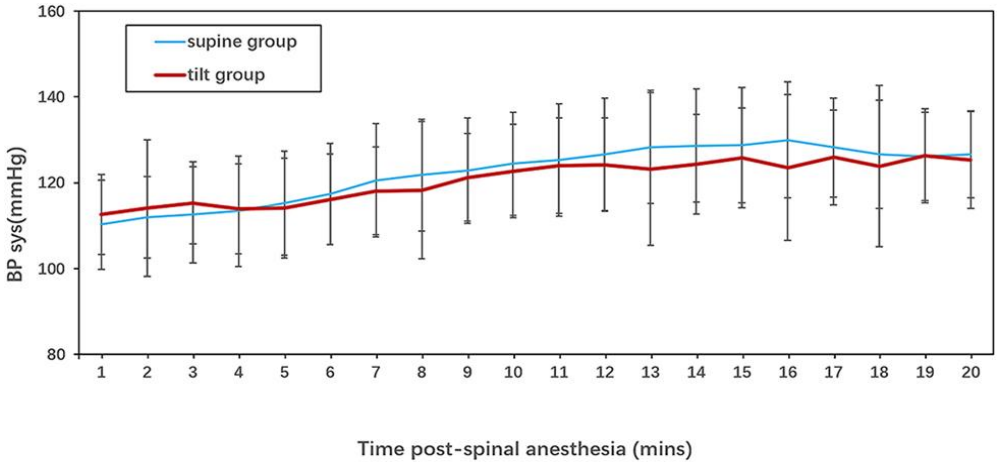

Figure 3. Differences in the SBP within 20 minutes after spinal anaesthesia between the two groups. The whiskers represent the standard deviation. All patients were followed up until delivery or 20 minutes after spinal anaesthesia. P value of time × group interaction = 0.31, P value of group = 0.16

Neonatal acid–base and apgar outcomes

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No significant differences were observed in umbilical vein pH (UV-pH) or base excess (UV-BE) between groups. All neonates had normal Apgar scores at 1 and 5 minutes, with no significant differences between the supine and tilt groups **(Table 2)**.

Table 3. Other Outcome Measures

	Supine Group (n=62)	**Tilt Group (n=62)**	***P* Value**
Metaraminol requirement before delivery (μg)	2880 (2268, 3878)	2662 (1958, 3275)	0.11
Duration of hypotension (minute)	0 (0,0)	0 (0,0)	0.82
Incidence of hypotension (n)	6 (9.6)	5 (8)	0.75
Incidence of hypertension (n) *	32 (52)	13 (21)	< 0.001
Incidence of bradycardia (n)	8 (13)	4 (6)	0.22
Incidence of nausea and vomiting (n)	0 (0)	0 (0)	–

Notes: Data are median (interquartile range) and number (percentage) and were compared using Mann–Whitney *U*-test and $\chi 2$ tests. *There are statistical differences between two groups of data.

Maternal hemodynamic outcomes

The frequency of maternal hypotension was comparable between the two groups, with 6 patients affected in the supine group and 5 in the tilt group (P = 0.75). Conversely, episodes of hypertension were more frequent in the supine group (52%) than in the tilt group (21%) (P < 0.001). The average duration of hypotensive episodes did not differ notably: supine patients experienced roughly 1 minute, while the tilt group averaged 1.8 minutes, with variations ranging from 1 to 3 minutes. The occurrence of bradycardia was 13% in the supine group versus 6% in the tilt group, a difference that was not statistically significant (P = 0.22). No cases of maternal nausea or vomiting were observed in either group before delivery **(Table 3)**.

Our study indicates that initiating metaraminol at a higher infusion rate in mothers positioned supine can maintain fetal acid–base balance and does not increase maternal hypotension compared with the conventional 15° left-tilt position. Umbilical artery pH (P = 0.76) and base excess (P = 0.9) were similar between the two groups, and there were no meaningful differences in the incidence or duration of hypotension (P = 0.75 and P = 0.82, respectively) or in maternal SBP within the first 20 minutes after spinal anesthesia (P = 0.16). These results suggest that for otherwise healthy women with BMI <35 kg/m² undergoing elective cesarean delivery, the tilt position may be unnecessary if an appropriate vasopressor dose is used.

Although the 15° left tilt has been standard practice for decades, modern strategies—including prophylactic vasopressor infusion and fluid co-loading—have reduced its necessity to maintain maternal blood pressure, while highlighting practical limitations such as surgeon discomfort and maternal inconvenience [5, 6, 9, 10]. Prior research by Lee *et al*. demonstrated that while fetal acid–base status is preserved in the supine position with vasopressors, maternal SBP and cardiac output may be lower, necessitating higher doses to maintain hemodynamic stability [11, 12].

Using weight-adjusted ED90 doses of vasopressors has been shown to prevent hypotension effectively while maintaining fetal well-being [13, 14]. In line with this, our study employed ED90 metaraminol infusions of 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for supine patients and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for tilt patients, producing similar hypotension rates (9.6% vs 8%). The brief and limited nature of hypotensive episodes likely explains the comparable neonatal acid–base outcomes and suggests that minimal intervention was needed by anesthesiologists.

However, reactive hypertension was observed more frequently in the supine group (52% vs 21%), requiring more frequent reductions in infusion rate, though total metaraminol consumption did not differ significantly (P = 0.11). Slightly higher maternal SBP in the tilt group during the first few minutes post-spinal anesthesia may reflect the initial drop in systemic vascular resistance [26, 27]. These findings suggest that while the tilt may provide modest hemodynamic stability, in healthy patients without complications, the inconvenience of maintaining this position outweighs its limited benefit. Therefore, the supine position with weight-adjusted metaraminol infusion is a reasonable and practical approach for elective cesarean deliveries in this population.

Limitations

This study was restricted to healthy, singleton pregnancies, excluding patients with complications such as preeclampsia. Consequently, caution should be exercised when extrapolating these findings to higher-risk

populations. Additionally, all participants had a BMI below 35 kg/m², and responses to spinal anesthesia or vasoactive agents may differ in obese patients. Women with larger uteri, including cases of macrosomia, polyhydramnios, or multiple gestations, were not included; these patients are at greater risk of significant aortocaval compression, limiting the generalizability of our results.

Only the ED90 of metaraminol was evaluated in both supine and tilted positions, which guided our selection of this agent over other commonly used vasoactive drugs. Previous studies indicate that weight-adjusted ED90 infusions of phenylephrine, norepinephrine, and metaraminol can achieve comparable outcomes in maternal hemodynamics and fetal acid–base status [28]. Future investigations should establish the ED90 for other vasoactive agents in the supine position to inform clinical practice.

Our spinal anesthesia protocol used 9 mg of bupivacaine rather than the 12–14 mg more commonly reported, following institutional practice and prior research (e.g., Fei *et al*., 10 mg) [13]. This difference may limit applicability to patients receiving higher intrathecal doses. Intrathecal opioids were also omitted, consistent with prior ED90 studies of metaraminol in the supine position [14], though nearly all patients achieved adequate T4–T6 sensory levels, and hypotension incidence remained low (~10%), supporting the clinical relevance of our findings. Finally, patient-reported comfort or satisfaction with the supine versus tilt position was not assessed, which may have limited the evaluation of positional acceptability.

Summary statement

Administering metaraminol at a higher weight-adjusted initial rate in the supine position maintained fetal acid–base balance and did not increase the occurrence of maternal hypotension compared with the conventional 15° left-tilt position.

Conclusion

In healthy women with BMI <35 kg/m² undergoing elective cesarean delivery under spinal anesthesia, maintenance of maternal blood pressure using a higher dose of metaraminol renders the left-tilted position unnecessary. This approach provides a practical alternative that preserves fetal well-being without compromising maternal hemodynamics.

Acknowledgments: The trial was registered in clinical trials (registration number: NCT05084599).

URL:
https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000BCSL&selectaction=Edit&uid=U00044ZX&ts=138&cx=p7q59w.

Conflict of Interest: None

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Ethics Statement: This study was approved by the Ethics Committee of Peking University People's Hospital (protocol ID: 2021PHB455-001), and written informed consent was obtained from all subjects participating in the trial. This study complies with the Declaration of Helsinki.

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