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Effect of Position-Based Dosing Strategy for Metaraminol on Neonatal Acid–Base Status During Elective Caesarean Delivery: A Noninferiority Randomised Controlled Trial

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Background: The 15° left tilt position during caesarean delivery has been recommended by guidelines for many years, but recent studies have questioned the clinical benefit of left tilt position. We hypothesize that using a higher starting dose of metaraminol in the supine position will result in a non-inferior umbilical arterial pH, compared to the 15° left tilt position.

Methods: Healthy women undergoing elective caesarean delivery were randomized to the supine position (n = 62) or 15° left tilt position (n = 62) after spinal anaesthesia (0.5% bupivacaine 9 mg). Different starting doses of metaraminol infusion were initiated at 2.7 μg kg^{-1} min^{-1} for the supine position group and 2.0 μg kg^{-1} min^{-1} for the tilt position group. The infusion rates were then adjusted using a fixed algorithm to maintain systolic blood pressure. The primary outcome was the pH of the umbilical artery.

Results: Compared with tilt group, pH (supine group: 7.325 (7.29, 7.35) vs tilt group: 7.33 (7.3, 7.35), P = 0.76) and base excess (tilt group: −0.98 (2.59) mM vs supine group: −0.92 (2.77) mM, P = 0.9) of the umbilical artery are non-inferior. There was no difference in SBP (P = 0.16) or incidence of hypotension (P = 0.75) between the two groups. The incidence of reactive hypertension was greater in the supine position group (P < 0.001).

Conclusion: If maternal blood pressure is maintained using the higher starting dose of metaraminol, the left tilted position may not be necessary among healthy patients (BMI less than 35 kg/m^2) undergoing elective caesarean delivery with spinal anaesthesia.

Keywords: Caesarean delivery, supine position, tilt position, metaraminol, noninferiority trial

Introduction

Due to compression of the inferior vena cava by the enlarged uterus, a decrease in systemic vascular resistance after spinal anaesthesia often leads to severe hypotension and impairment of the fetal acid–base balance.[1]

In 1972, Crawford et al reported that a 15° tilt of the surgical bed can significantly improve the pH of the umbilical artery (UA-pH) (15° group: 7.31 ± 0.04 versus supine group: 7.27 ± 0.09, P < 0.001).[2] Notably, patients were under general anaesthesia, and a large proportion was tilted to the right because of the surgeons' inconvenience with the left tilt position. The results of several studies have supported the left tilt recommendation, which is currently used.[2–4]

As in the study of Crawford et al, the 15° left tilt position is not always acceptable.[2] According to reports, more than 90% of anaesthesiologists perform measurements at smaller tilt angles without devices.[5] Seventy-five percent of anaesthesiologists performed a tilt of 10.8 ± 2.1° based on vision; only 3% of surgeons could tolerate this position, and 48% of surgeons requested a reduction in tilt angle to below 8° on the grounds of impaired surgical conditions.[6] However, a small left-sided tilt among healthy prospective volunteers (5°–12.5°) during caesarean delivery after spinal

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anaesthesia has been demonstrated to not significantly improve material haemodynamics or umbilical arterial blood flow.[7,8] In addition, 76% of mothers feel uncomfortable when in a tilted position.[6] The use of tilt and wedges for caesarean section may increase the risk of sciatic nerve compression.[9,10] These limitations have led anaesthesiologists to question whether the left tilt position should still be maintained in contemporary clinical practice.

Lee et al reperformed a comparison of the tilt and supine positions with modern anaesthesia practice (spinal anaesthesia, fluids and a phenylephrine infusion titrated to baseline blood pressure).[11] Notably, in this study, both groups of patients received the same infusion rate of phenylephrine. Although the 15° left tilt position did not improve fetal acid–base balance, it could increase maternal systolic blood pressure (SBP) and cardiac output. Shayegan et al therefore suggested that the left tilt position should not be abandoned.[12]

In the supine position, the inferior vena cava receives more pressure from the gravid uterus, so patients should receive higher doses of vasoactive drugs than patients in the tilt position to increase blood pressure.[13,14] Two trials were conducted to determine the 90% effective dose (ED90) of weight-adjusted infusions of metaraminol for preventing hypotension during caesarean delivery in the supine (2.7 μg kg^{-1} min^{-1}) and 15° tilt positions (2 μg kg^{-1} min^{-1}).[13,14]

Metaraminol has recently been considered a better alternative to phenylephrine because it has mild β1 adrenergic receptor agonism, can combat reflex bradycardia and can decrease cardiac output caused by its strong α receptor agonism.[15] Two network meta-analyses found that metaraminol is a better choice than phenylephrine in preventing hypotension and improving foetal acid-base balance.[16,17] Furthermore, only the ED90s of metaraminol (but not phenylephrine or norepinephrine) were determined in both the supine and tilted positions, which still needs to be compared in clinical trials.

We hypothesize that using a higher starting dose of metaraminol in the supine position (2.7 μg kg^{-1} min^{-1} for supine position and 2 μg kg^{-1} min^{-1} for tilt position) will result in a non-inferior umbilical arterial pH, compared to the 15° left tilt position.

Methods

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. The trial was registered prior to patient enrolment at clinicaltrials.gov tration number: NCT05084599. The articles were written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[18]

Study Participants

The inclusion criteria were as follows: (1) singleton pregnancy at term scheduled to be delivered via elective caesarean delivery, (2) height 150 cm-180 cm, (3) American Society of Anaesthesiologists (ASA) grade II–III, and (4) body mass index (BMI) less than 35 kg/m^2.

The exclusion criteria were as follows: (1) transverse presentation or fetus macrosomia, (2) uterine abnormalities (eg, large fibroids or bicornuate uterus), (3) polyhydramnios, (4) ruptured membranes or oligohydramnios, (5) intrauterine growth restriction, (6) gestational or nongestational hypertension, diabetes, or eclampsia, (7) hypertensive disorders or any condition associated with autonomic neuropathy (such as diabetes mellitus for more than 10 years) or renal failure, (8) contraindications for combined spinal-epidural anesthesia, or (9) refusal to sign informed consent forms.

Randomization and Blinding

Subjects were randomized by use of a random number table (n = 124) provided by the randomization website http://tools.medsci.cn/rand, and the allocation was hidden using an opaque envelope. The clinical conduct of the trial was not blinded, but the blood gas assessments for individuals who were performing them and all data analyses for statisticians were conducted in a blinded fashion; the groups were labelled 1 and 2. The clinician who assessed the Apgar scores was not blinded to group allocation.[2]

Surgical Procedures

Patients fasted for 6–8 hours but were allowed clear fluids for up to 2 hours prior to surgery. There was no premedication.

In the operating room, peripheral venous access was obtained in the left upper arm. Patients were monitored via electrocardiography, noninvasive blood pressure and pulse oximetry; 5 L/minute of oxygen was supplied via a nasal cannula. After the pregnant woman had been in the operating room for 5 minutes, baseline SBP was measured in both the supine and 15° left tilt positions. In each position, three consecutive SBP measurements were taken at 2-minute intervals. The average of the three measurements in each position was calculated. If any of the three measurements deviated from the mean by more than 10%, the patient was allowed to rest for an additional 2 minutes before repeating the set of three measurements. This process was repeated until all three consecutive measurements differed from the mean by no more than 10%, indicating that the mother's SBP had stabilized. A difference in SBP between the supine and left tilt positions was acceptable, regardless of its magnitude, due to the expected inferior vena cava compression in the supine position.

Intraoperative Procedures

Combined spinal-epidural anesthesia was performed by a single anaesthesiologist. Combined spinal-epidural anaesthesia was performed in the left lateral position using a needle-through-needle technique with a 16-G epidural needle, with the loss of resistance to air used to confirm entry into the epidural space. A 25-G pencil-point spinal needle was advanced through the epidural needle, and the flow of CSF was demonstrated; 9 mg of 0.5% isobaric bupivacaine was injected at the estimated L3-L4 vertebral interspace. The spinal needle was removed, an epidural catheter was advanced 3–5 cm into the epidural space, and the epidural needle was removed. The end of the spinal injection was at time zero.

The sensory block level was measured by assessing the loss of painful pinprick sensation. Patients were excluded if the block did not reach T6 by 10 minutes after injection.[19] If the patient experienced pain prior to delivery, 5 mL of 2% lidocaine was given via the epidural catheter.

During placement of the neuraxial blockade, a researcher opened the envelope to determine the group assignment of the patients.

Immediately after spinal injection, patients were placed in the 15° left-tilt position or supine position, and the infusions were initiated with 2 μg kg^{-1} min^{-1} metaraminol (tilt group) or 2.7 μg kg^{-1} min^{-1} metaraminol (supine group) at the initial rate according to the grouping (weight collection from the day of surgery).

The NIBP was cycled every minute until delivery. When the SBP was maintained at 90%–110% of the baseline, metaraminol was administered at the initial rate.

When the SBP was 110%–120% of the baseline value for 3 consecutive minutes, the percentage of patients receiving metaraminol was halved. If the SBP remained at 110%–120% of baseline for 3 consecutive minutes after halving, the infusion of metaraminol was stopped until the SBP fell below baseline. Reactive hypertension was defined as an increase in SBP to ≥120% of the baseline value and was managed by stopping the metaraminol infusion until the SBP fell below baseline.

If the patient's baseline SBP was less than 90 mmHg, the target was to maintain an SBP at or above 90 mmHg. When the SBP was 80%–90% of the baseline for 3 consecutive minutes, 150% of the initial rate was metaraminol. If the SBP remained at 80%–90% of the baseline for 3 consecutive minutes, metaraminol was administered at double the initial rate until the SBP was greater than the baseline. Maternal hypotension (SBP reduction > 20% of the baseline value or SBP < 90 mmHg) was treated with intervention drugs administered at double the initial rate until the SBP was greater than the baseline value. If hypotension (SBP reduction > 20% of the baseline value or SBP < 90 mmHg) did not improve for 3 consecutive minutes under this program, the patient could be given additional phenylephrine, additional ephedrine, or additional intravenous fluids, and the position could be adjusted. If all of the above treatments are still ineffective, patients could be given epinephrine. The dose of additional vasoactive drugs was determined by the anaesthesiologist.

A dose of 0.5 mg of atropine was administered for an HR < 50 bpm without hypotension. The total cumulative amount of metaraminol used before the end of surgery was recorded.

The 15° left-tilt angle of operating table was determined by phone (Simple Gradienter 5.5.6, Longjie Network Technology, Shanghai, China). Ringer's solution (10 mL/kg) was instilled quickly within 10–15 minutes until the SBP reached baseline and stabilized for more than 5 minutes; then, the infusion was changed to a uniform slow infusion.[13,20,21]

Immediately after the delivery of the foetus, UA blood and umbilical vein (UV) blood were taken from a double-clamped segment of the umbilical cord and transported by an investigator who was blinded to the group assignment to a GEM Premier 4000 blood gas analyser (Instrumentation Laboratory, MA, USA) within 30s. Apgar scores were rated at 1 and 5 minutes after delivery.

Statistical Analysis

The primary outcome was the UA pH. The secondary outcome indicators included blood gas analysis results of UA blood and UV blood and the presence of hypotension (SBP ≤ 80% baseline value or SBP < 90 mmHg), nausea (the patient was queried at the end of the operation), vomiting (vomiting 10 mL or more of liquid or vomiting solids or the observation that the patient retched), and bradycardia (HR was ≤50 bpm) before delivery.[22] Patients with reactive hypertension (SBP ≥ 120% of the baseline value), 1-minute and 5-minute Apgar scores, SBP within 20 minutes after the end of spinal anaesthesia, and use of metaraminol and duration of hypotension were included in the exploratory analysis. The 20-minute collection time of SBP was based on the duration from spinal anaesthesia to delivery at our medical centre. The analysis was by "intent to treat".[22]

Data analysis was performed using SPSS 21.0 (SPSS, Inc., Chicago, IL). For quantitative data, we used the K–S test to evaluate for a normal distribution: normally distributed data (such as age and BMI) are expressed as the mean ± standard deviation (X ± S) and were compared with unpaired t tests. Nonnormally distributed data are expressed as the median (M) and interquartile range (IQR). The Mann–Whitney *U*-test was used to compare data between groups. The median difference was calculated with the use of the Hodges–Lehmann estimate based on the Mann–Whitney *U*-test. The repeated measurement data were compared using a generalized linear mixed model. Count data are expressed as proportions. A *P* value less than or equal to 0.05 was considered to indicate statistical significance.

Sample size calculation was performed using PASS 15.0 (NCSS, LLC, Kaysville, USA) software. The primary outcome of the trial is the UA pH.[2,23] Based on previous studies, we determined that a UA-pH difference of 0.03 would lead to differences in clinical outcomes, especially the risk of fetus acidosis.[2,24,25] A trial performed by Crawford et al determined that a 15° tilt could cause a difference of 0.039 in the UA pH, which led to the 15° tilt position being widely used clinically; therefore, we estimate that a UA pH difference of 0.03 has clinical significance.[2] A tolerance limit of 0.021 (70% of 0.03) was chosen because this magnitude of difference was regarded as not having any clinical importance. We estimated (based on pilot data) within-group SDs of 0.03. With one-sided $\alpha = 0.025$ and $\beta = 0.1$, a total of 88 patients were included.

In addition, metabolic acidosis and hence hypoxia have also been accurately measured by base excess of the umbilical artery (UA-BE). Based on a study by Lee et al, we determined that a UA-BE difference of 2 mmol/L would lead to differences in clinical outcomes, and a tolerance limit of 1 mm was chosen.[11] We estimated (based on pilot data) within-group SDs of 1.5 mm. With one-sided $\alpha = 0.025$ and $\beta = 0.1$, a total of 98 patients were obtained.

Two outcomes require 88 and 98 patients, respectively.

Considering the possibility of dropping out and having more type II errors, each group included 62 patients.

Results

A total of 274 women were screened during the trial, 124 of whom met the inclusion criteria and were randomized (supine group, n = 62; tilt group, n = 62). Figure 1 shows the CONSORT flow diagram. Data from 124 patients were included in the analysis. Two patients in each group did not collect primary outcome.

Baseline Data

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

Neonatal Outcomes

UA blood was not collected from 2 patients in the supine group and 2 patients in the tilt group; UV blood was not collected from 5 patients in the supine group and 5 patients in the tilt group.

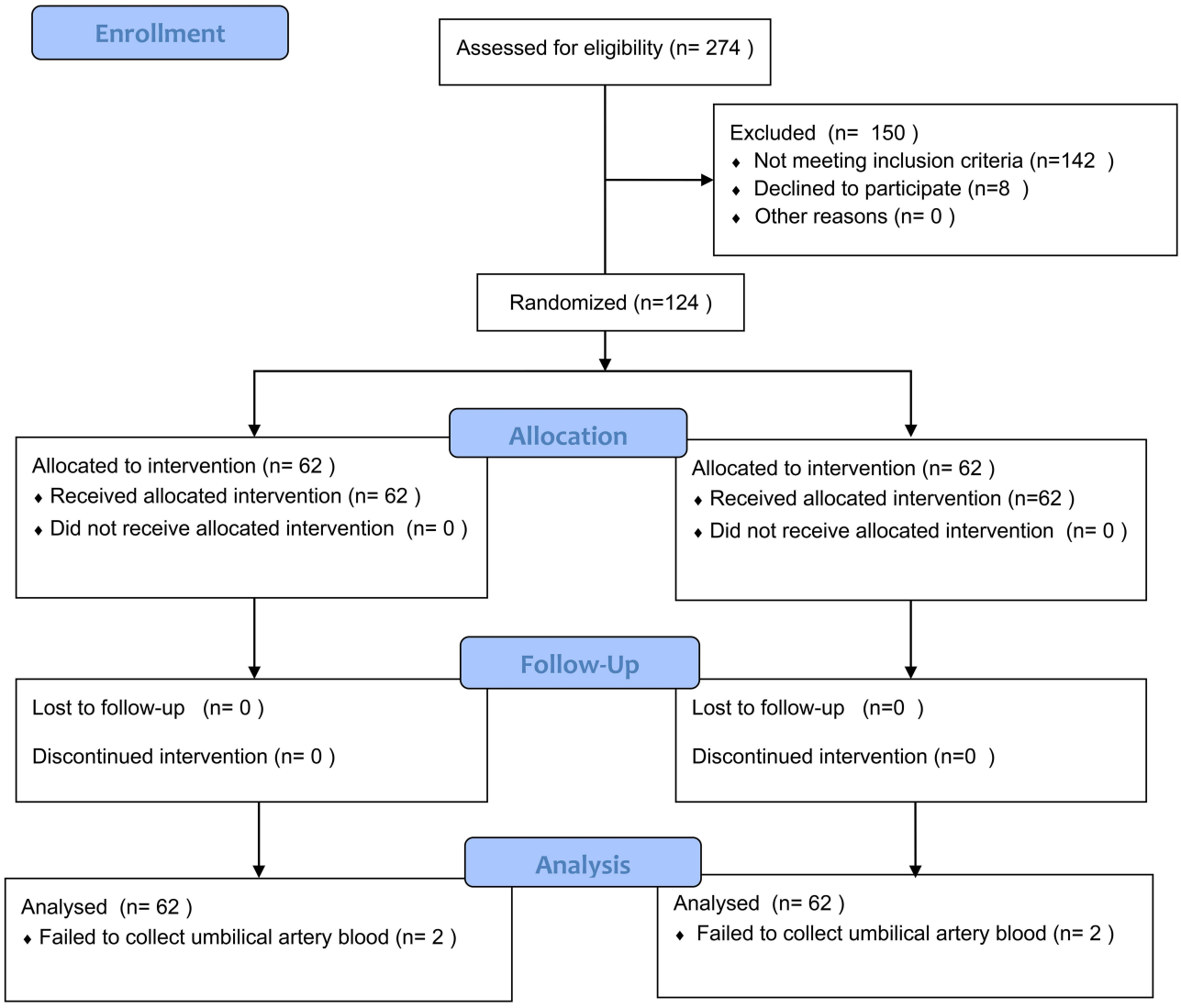

Figure 1 CONSORT flow diagram.

The neonatal UA-pH did not significantly differ between the two groups (tilt group: 7.33 (7.3, 7.35) vs supine group: 7.325 (7.29, 7.35), P = 0.76), with a mean (SD) of 7.319 (0.05) vs 7.316 (0.05), respectively. The estimated median (95% CI) difference in arterial pH between the groups was 0 (−0.02–0.01). The lower bound of the two-sided 95% CI of the estimated difference in treatment effect was −0.02, above the pre-determined lower boundary of clinical non-inferiority of −0.021, indicating that supine position was non-inferior to left-tilt position. A box plot of the distribution of UA-pH by group is presented in Figure 2.

Neonatal UA-BE did not significantly differ between the two groups (tilt group: −0.98 (2.59) mM vs supine group: −0.92 (2.77) mM, P = 0.9; mean difference = −0.62). The estimated median (95% CI) difference in arterial pH between the groups was −0.62 (−0.91–1.03). The lower bound of the two-sided 95% CI of the estimated difference in treatment effect was −0.91, above the pre-determined lower boundary of clinical non-inferiority of −1, indicating that supine position was non-inferior to left-tilt position. A box plot of the distribution of UA-pH by group is presented in Figure S1.

No significant difference was found in the UV-BE or UV-pH. No neonates had low Apgar scores at 1 minute or 5 minutes after delivery, and these scores were not significantly different between the two groups (Table 2).

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.

Maternal Systolic Blood Pressure

We used a generalized linear mixed model to analyse the SBP within 20 minutes after anaesthesia (Figure 3). The time * group interaction term was not statistically significant (P = 0.31), which suggested that the trends in SBP over time did not differ between the two groups. Figure 3 shows no significant difference in the SBP between the two groups (P = 0.16).

Other Outcome Measures

There was no significant difference in the use of metaraminol between the two groups (supine group: 2880 (2268, 3878) μg vs tilt group: 2662 (1958, 3275) μg, P = 0.11), and no mothers needed vasoactive drugs other than atropine (Table 3).

There was no significant difference in the incidence of hypotension between the two groups (6 patients in the supine group and 5 patients in the tilt group, P = 0.75).

The incidence of hypertension (52% of patients in the supine group and 21% of patients in the tilt group) was significantly lower in the tilt group (P < 0.001). There was no significant difference in the duration of hypotension

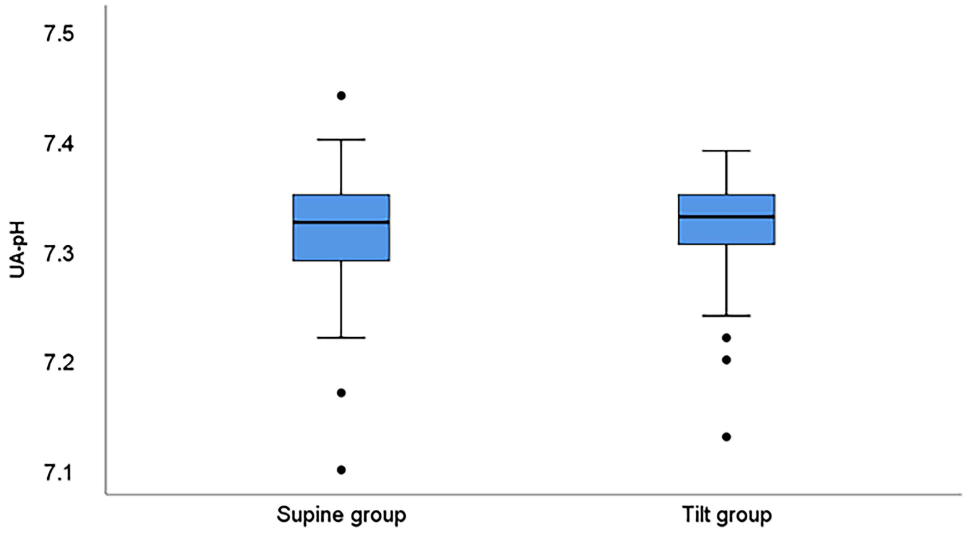

Figure 2 Box plot of the distribution of the pH of the umbilical artery by group. The line outlier median, box outlier interquartile range, whisker outlier 2.5th percentile and 97.5th percentile and dots represent outlier values.

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.

between the two groups (P = 0.82). All six patients in the supine group experienced 1 minute of hypotension, while five patients in the tilt group experienced an average of 1.8 minutes of hypotension (two patients for 1 minute, two patients for 2 minutes, and one patient for 3 minutes). The incidence of bradycardia (13% of patients in the supine group and 6% of patients in the tilt group) was not significantly different between the two groups (P = 0.22). Patients in the two groups did not experience nausea or vomiting before delivery (Table 3).

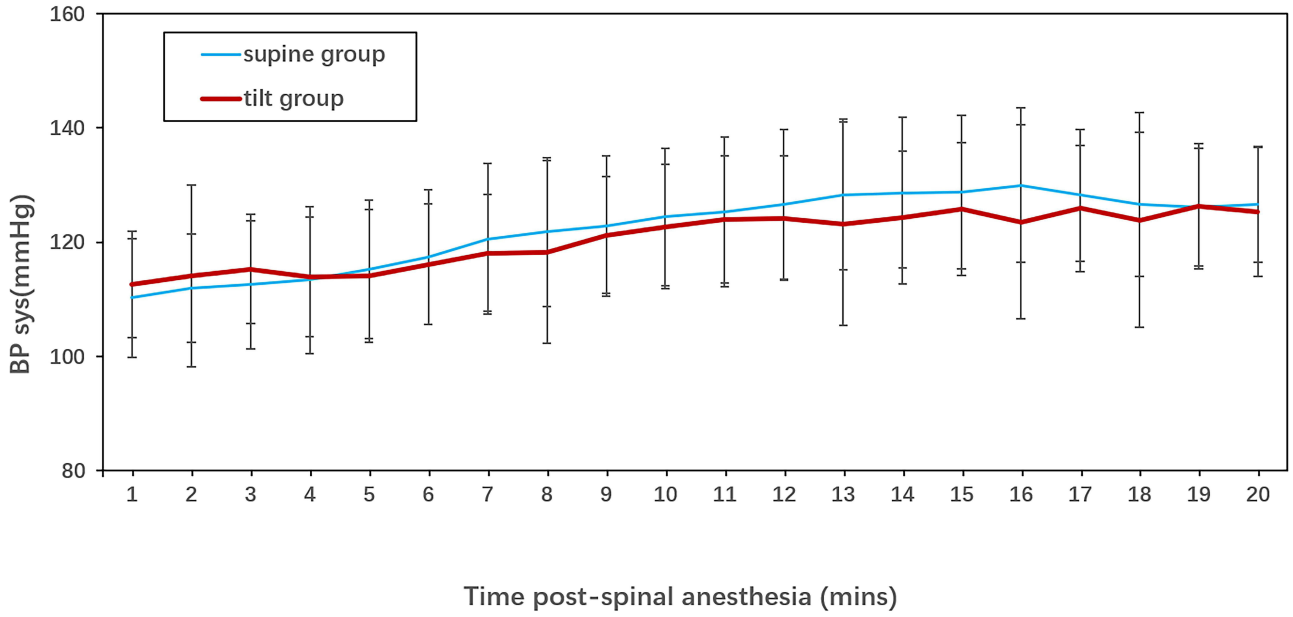

Figure 3 Differences in the SBP within 20 minutes after spinal anaesthesia between the two groups. The whiskers represent the standard deviation. All patients were followed up until delivery or 20 minutes after spinal anaesthesia. P value of time × group interaction = 0.31, P value of group = 0.16.

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.

Discussion

Our most notable finding is that, compared to infusion in the 15° left-tilt position, infusion of metaraminol at a higher initial rate in mothers in the supine position did not impair fetal acid–base balance and did not increase the incidence of hypotension. There was no significant difference in UA pH (P = 0.76) or UA-BE (P = 0.9) between the two groups; the incidences of hypotension (P = 0.75) and SBP within 20 minutes after spinal anaesthesia (P = 0.16) in the supine group were not significantly worse than those in the tilt group. Our research results indicate that for women who undergo elective caesarean delivery without complications and who have a BMI below 35 kg/m^2, the tilt position may not be necessary.

As recommended by guidelines, the 15° left tilt position has been used for more than 50 years; however, contemporary practice that utilizes a fluid coload and prophylactic vasopressor infusions to manage hypotension associated with spinal anaesthesia has lessened the need for intraoperative left uterine displacement to support maternal blood pressure, and drawbacks of the 15° left tilt position are emerging.[4,26] Both anaesthesiologists, surgeons, and patients are dissatisfied with a 15° left tilt.[5,6] The use of tilt and wedges for caesarean section may increase the risk of sciatic nerve disease.[9,10]

Lee et al administered phenylephrine infusion at the same initial rate as phenylephrine infusion in both the supine and tilt positions of mothers in an attempt to prove that the tilted position is unnecessary.[11] There was no significant difference in fetal acid–base balance between the two groups; however, the SBP and cardiac output of the mothers were significantly lower in the supine position, and higher doses of phenylephrine were required to maintain this balance.[11] The instability of maternal haemodynamics causes concern among anaesthesiologists, leading to the continued preservation of the tilted position.[12,27]

One study demonstrated that the use of the ED90 of weight-adjusted infusions of different vasoactive drugs for preventive hypotension during caesarean delivery can achieve similar effects on fetal acid–base balance and maternal haemodynamics.[28] These findings inspired researchers to explore the ability of the ED90 of metaraminol in the supine position to prevent hypotension during caesarean delivery.[14] In this study, we used different weight-adjusted infusion doses of metaraminol for women in the supine (2.7 μg kg^{-1} min^{-1}) and tilt (2 μg kg^{-1} min^{-1}) positions, and the incidences of hypotension were 9.6% and 8%, respectively.[13,14] This indicates that the previously determined dose is effective. The short duration of hypotension in both groups (1 minute on average for the supine group and 1.8 minutes on average for the tilt group) could explain the similar fetal acid–base balance between the two groups and demonstrates that anaesthesiologists in the two groups spent minimal effort treating hypotension.

Notably, although there was no significant difference in the incidence of hypotension or maternal SBP between the two groups, the incidence of reactive hypertension in the supine position group was significantly greater than that in the tilt position group (52% vs 21%, P < 0.001). Anaesthesiologists in the supine group needed to reduce the infusion rate of metaraminol more frequently to prevent hypertension; therefore, there was no significant difference in the use of metaraminol between the two groups (P = 0.11). The maternal SBP in the tilt group was slightly (but not significantly) greater than that in the supine position group in the first 4 minutes after the end of spinal anaesthesia (Figure 3); this may be because maternal SVR and blood pressure can decrease rapidly in the first 1–5 minutes (during surgical preparation) after spinal drug administration.[29,30] In summary, the tilt position still contributed to haemodynamic stability. Excessive

use of vasoactive drugs may lead to reactive hypertension, and failure to promptly discontinue the vasopressor may result in a hypertensive crisis,[31] especially in mothers with preeclampsia, for whom the tilt position still holds clinical significance.

However, we believe that this limited benefit cannot offset the inconvenience caused by the tilt position in healthy mothers. We still recommend routine use of the supine position for mothers without complications and with a BMI less than 35 kg/m^2 for elective caesarean delivery.

Limitations

We included only singleton pregnant mothers without complications, especially mothers with preeclampsia, and our conclusions should be interpreted with caution. In addition, the BMI of all patients was <35 kg/m^2. Obese women may have different responses to symptomatic blocks of spatial anisotropy (per hip having different symptomatic tones at baseline) or to the use of vasopressors. Mothers with larger uteri (eg, macrosomia, polyhydramnios, multiple gestation) were excluded from this research. However, these patients may be at a higher risk of experiencing more significant aortocaval compression. These limitations limit the generalizability of this trial.

Because only the ED90s of metaraminol were determined in both the supine and tilted positions, we chose metaraminol rather than other commonly used vasoactive drugs.[13,14] According to reports, the use of the ED90 of weight-adjusted infusions of phenylephrine, norepinephrine and metaraminol can achieve similar effects on fetal acid–base balance and maternal haemodynamics.[28] In the future, we still look forward to more trials to determine the ED90s of other vasoactive drugs in the supine position to guide clinical practice.

We used 9 mg of bupivacaine for spinal anaesthesia instead of 12–14 mg, which was based on the practice of our medical centre and the dosage used by Fei et al (10 mg of bupivacaine),[13] which means that our findings may not be applicable to patients who receive larger doses of spinal anaesthesia. In addition, Liu et al did not use intrathecal opioid drugs when exploring the ED90 of metaraminol in supine position, so we did not use opioid drugs.[14] However, almost all of our patients achieved T4-T6 levels of anaesthesia with single-shot spinal anaesthesia (only 3 patients required additional anaesthesia) and the incidence of hypotension in both groups is close to the 10%, which indicates that our conclusions are clinically applicable.

We did not collect data on patient satisfaction from mothers in different positions, which may have limited our conclusions.

Summary Statement

Compared to infusion in the 15° left-tilt position, the infusion of metaraminol at a higher initial rate in mothers in the supine position did not impair fetal acid–base balance and did not increase the incidence of hypotension.

Conclusions

If maternal blood pressure is maintained using the higher weight-based dose of metaraminol, the left tilted position may not be necessary among healthy patients (with a BMI less than 35 kg/m^2) undergoing elective caesarean delivery with spinal anaesthesia.

Ethics

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.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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.

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Disclosure

This paper is available as a preprint on SSRN at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4865065. The authors report no conflicts of interest in this work.

References

1. Dyer RA, Reed AR, van Dyk D, et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology*. 2009;111(4):753–765. doi:10.1097/ALN.0b013e3181b437e0
2. FFARCSBMPD JSELWYNCRAWFORD, M.sc PHD, Davies P. TIME AND LATERAL TILT AT CAESAREAN SECTION. *Br J Anaesth*. 1972;44(5):477–484. doi:10.1093/bja/44.5.477
3. Downing JW, Coleman AJ, Mahomedy MC, Jeal DE, Mahomedy YH. Lateral table tilt for Caesarean section. *Anaesthesia*. 1974;29(6):696–703. doi:10.1111/j.1365-2044.1974.tb00755.x
4. JL Apfelbaum, JL Hawkins, M Agarkar. Practice Guidelines for Obstetric Anesthesia: an Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. *Anesthesiology*. 2016;124(2):270–300. doi:10.1097/ALN.0000000000000935
5. Jones SKS, Kinsella SM, Donald FA. Donald FA Comparison of measured and estimated angles of table tilt at Caesarean section. *Br J Anaesth*. 2003;2003(90):86–87. doi:10.1093/bja/aeg003
6. Wiesmann HASKMKT, Koehler S, Kuehnert M, Wiesmann T. Guideline-recommended 15° left lateral table tilt during cesarean section in regional anesthesia—practical aspects An observational study. *Journal of Clinical Anesthesia*. 2016;32:47–53. doi:10.1016/j.jclinane.2015.12.041
7. Ellington C, Katz VL, Watson WJ, Spielman FJ. The effect of lateral tilt on maternal and fetal hemodynamic variables. *Obstet Gynecol*. 1991;77(2):201–203. doi:10.1097/00006250-199102000-00007
8. Bamber JH, Dresner M. Aortocaval compression in pregnancy: the effect of changing the degree and direction of lateral tilt on maternal cardiac output. *Anesth Analg*. 2003;97(1):256–258. doi:10.1213/01.ane.0000067400.79654.30
9. Roy S, Levine AB, Herbison GJ, Jacobs SR. Intraoperative positioning during cesarean as a cause of sciatic neuropathy. *Obstet Gynecol*. 2002;99(4):652–653. doi:10.1016/s0029-7844(01)01700-8
10. Postaci A, Karabeyoglu I, Erdogan G, Turan O, Dikmen B. A case of sciatic neuropathy after caesarean section under spinal anaesthesia. *Int J Obstet Anesth*. 2006;15(4):317–319. doi:10.1016/j.ijoa.2006.02.004
11. Lee AJ, Landau R, Mattingly JL, et al. Left Lateral Table Tilt for Elective Cesarean Delivery under Spinal Anesthesia Has No Effect on Neonatal Acid-Base Status: a Randomized Controlled Trial. *Anesthesiology*. 2017;127(2):241–249. doi:10.1097/aln.0000000000001737
12. Shayegan B, Khorasani A, Knezevic NN. Left Lateral Table Tilt for Elective Cesarean Delivery under Spinal Anesthesia Should Not Be Abandoned. *Anesthesiology*. 2018;128(4):860–861. doi:10.1097/ALN.0000000000002095
13. Xiao F, Xu WP, Yao HQ, Fan JM, Chen XZ. A Randomized Double-Blinded Dose-dependent Study of Metaraminol for Preventing Spinal-Induced Hypotension in Caesarean Delivery. *Front Pharmacol*. 2021;12:608198. doi:10.3389/fphar.2021.608198
14. Liu T, Gao X, Zou S, et al. Randomised double-blind dose-response study of weight-adjusted infusions of metaraminol for preventing hypotension with combined spinal-epidural anaesthesia for elective Caesarean delivery in the supine position. *Br J Anaesth*. 2022;128(1):e20–e22. doi:10.1016/j.bja.2021.09.040
15. McDonnell NJ, Paech MJ, Muchatuta NA, Hillyard S, Nathan EA. A randomised double-blind trial of phenylephrine and metaraminol infusions for prevention of hypotension during spinal and combined spinal–epidural anaesthesia for elective caesarean section. *Anaesthesia*. 2017;72(5):609–617. doi:10.1111/anae.13836
16. Fitzgerald JP, Fedoruk KA, Jadin SM, Carvalho B, Halpern SH. Prevention of hypotension after spinal anaesthesia for caesarean section: a systematic review and network meta-analysis of randomised controlled trials. *Anaesthesia*. 2020;75(1):109–121. doi:10.1111/anae.14841
17. Singh PM, Singh NP, Reschke M, Ngan Kee WD, Palanisamy A, Monks DT. Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes. *Br J Anaesth*. 2020;124(3):e95–e107. doi:10.1016/j.bja.2019.09.045
18. Schulz KFAD, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152(11)::726–32. doi:10.7326/0003-4819-152-11-201006010-00232
19. Nor NM, Russell IF. Assessing blocks after spinal anaesthesia for elective caesarean section: how different questions affect findings from the same stimulus. *Int J Obstet Anesth*. 2013;22(4):294–297. doi:10.1016/j.ijoa.2013.05.010
20. Fu F, Xiao F, Chen W, et al. A randomised double-blind dose-response study of weight-adjusted infusions of norepinephrine for preventing hypotension during combined spinal-epidural anaesthesia for Caesarean delivery. *Br J Anaesth*. 2020;124(3):e108–e114. doi:10.1016/j.bja.2019.12.019
21. Xiao F, Shen B, Xu WP, Feng Y, Ngan Kee WD, Chen XZ. Dose-Response Study of 4 Weight-Based Phenylephrine Infusion Regimens for Preventing Hypotension During Cesarean Delivery Under Combined Spinal-Epidural Anesthesia. *Anesth Analg*. 2020;130(1):187–193. doi:10.1213/ANE.0000000000004092
22. Saravanan S, Kocarev M, Wilson RC, Watkins E, Columb MO, Lyons G. Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. *Br J Anaesth*. 2006;96(1):95–99. doi:10.1093/bja/aei265
23. Julious SA. Sample sizes for clinical trials with normal data. *Stat Med*. 2004;23(12):1921–1986. doi:10.1002/sim.1783

24. Victory R, Penava D, Da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. *Am J Obstet Gynecol*. 2004;191(6):2021–2028. doi:10.1016/j.ajog.2004.04.026
25. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2009;111(3):506–512. doi:10.1097/ALN.0b013e3181b160a3
26. Massoth C, Chappell D, Kranke P, Wenk M. Supine hypotensive syndrome of pregnancy: a review of current knowledge. *Eur J Anaesthesiol*. 2022;39(3):236–243. doi:10.1097/EJA.0000000000001554
27. Lee AJ, Landau R, Smiley RM. In Reply. *Anesthesiology*. 2018;128(4):861–862. doi:10.1097/ALN.0000000000002096
28. Liu T, Cheng Z, Zou S, et al. Effect of Weight-Adjusted Phenylephrine, Norepinephrine, and Metaraminol for Elective Cesarean Delivery on Neonatal Acid-Base Status: a Randomized Controlled Trial. *Drug Des Devel Ther*. 2022;16:3215–3223. doi:10.2147/DDDT.S381048
29. Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, doubleblind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. *Anesthesiology*. 2008;109(5):856–863. doi:10.1097/ALN.0b013e31818a401f
30. Liu T, Zou S, Guo L, et al. Effect of Different Positions During Surgical Preparation With Combined Spinal-Epidural Anesthesia for Elective Cesarean Delivery: a Randomized Controlled Trial. *Anesth Analg*. 2021;133(5):1235–1243. doi:10.1213/ANE.0000000000005320
31. Newell CP, Seller C, Vizhi M, Turner N. Case report: spontaneous coronary artery dissection during elective caesarean section under spinal anaesthesia. *Anaesthesia*. 2011;66(7):615–619. doi:10.1111/j.1365-2044.2011.06697.x