

The Median Effective Dose of Phenylephrine Infusion for Prevention of Spinal-Induced Hypotension During Cesarean Delivery in the 15° Left-Tilt vs. Supine Positions: A Randomised Control Study

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Background: Left uterine displacement is presumed to decrease vasopressor requirements during cesarean delivery due to decreased aortocaval compression, but studies have been equivocal. Our primary aim was to determine the median effective dose (ED₅₀) of prophylactic phenylephrine infusion in two positions—15° left lateral tilt versus supine—which remains unknown during elective cesarean delivery under combined spinal-epidural anesthesia. We hypothesized that a 15° left tilt would reduce phenylephrine requirements.

Methods: Eighty pregnant women were randomly allocated to be positioned either at a 15° left tilt (group L) or supine (group S) during elective cesarean delivery. A Prophylactic phenylephrine was started immediately after intrathecal injection. In each group, the first patient received phenylephrine infusion at 0.5 µg/kg/min. Each subsequent patient received an infusion with an incremental dose of 0.05 µg/kg/min above or below the initial dose, depending on the response of the preceding patient. ED₅₀ values for phenylephrine were calculated using the up-down sequential methodology and compared using relative median potency ratios.

Results: The ED₅₀ of a phenylephrine infusion was 0.33 µg/kg/min (95% confidence interval (CI), 0.23 to 0.39 µg/kg/min) in group L and 0.30 µg/kg/min (95% CI, 0.22 to 0.37 µg/kg/min) in group S. The relative median potency for phenylephrine in group L vs. group S was 1.06 (95% CI, 0.86 to 1.45).

Conclusion: A 15 left tilt did not significantly alter phenylephrine requirements; therefore, routine use of tilt solely to reduce vasopressor need may not be necessary.

Keywords: phenylephrine, spinal anesthesia, hypotension, cesarean delivery, left-tilt, supine

Introduction

Phenylephrine infusion is often administered prophylactically during cesarean delivery to reduce the risk of spinal-induced hypotension. In addition, pregnant women are typically positioned with a 15° tilt to the left to facilitate left uterine displacement (LUD) and prevent supine hypotension syndrome (SHS),^{1–3} which occurs due to the gravid uterus compressing the inferior vena cava (IVC). While LUD has been considered a standard practice in obstetric anesthesia for years,^{4,5} more recent studies^{6,7} have found that a 15° left tilt and even a 30° left tilt do not necessarily improve neonatal outcomes. Despite this, recent international consensus and systematic review from the Cochrane Database consistently support this dogma.^{8,9} Additionally, these studies have suggested that LUD decreases the consumption of vasopressors;

however, the results have been inconsistent. Therefore, it remains unclear how much phenylephrine requirement decreases when women are tilted at a 15° tilt to the left during cesarean delivery.

In the present study, we aimed to determine the 50% effective dose (ED50) of preventive phenylephrine infusion during elective cesarean delivery under combined spinal-epidural anesthesia by comparing the 15° left lateral tilt position with the supine position. Our hypothesis was that a 15° tilt would be tilted to the left, while cesarean delivery would decrease prophylactic phenylephrine requirements when compared to the supine position.

Materials and Methods

Study Setting

This study was conducted as a parallel-group, randomized, double-blinded trial and was approved by the Institutional Review Board at Jiaxing University Affiliated Women and Children Hospital on December 8, 2023. All participants provided written informed consent before participating in the study. The clinical trial was registered in the Chinese Clinical Trial Registry (ChiCTR2400081536, <https://www.chictr.org.cn/showproj.html?proj=207591>) before patient enrollment. We enrolled the first patient in this study on March 10, 2024, which marked the official start of our research protocol, and completed the study on December 13, 2024. This study complies with the Declaration of Helsinki.

Patients

Women with American Society of Anesthesiologists physical status II, Singleton pregnancy, aged 16–40 years, and scheduled to undergo elective cesarean delivery under neuraxial anesthesia at 37 weeks' gestation or later were eligible for study participation. Exclusion criteria included hypertensive disorders (including preeclampsia), diabetes, BMI >35 kg/m², contraindications to neuraxial anesthesia, known fetal anomalies, pre-existing bradycardia, cardiovascular diseases, and the use of cardiovascular medications or allergy to study drugs.

Study Protocol

All women who consented were required to have fasted from solids for at least 8 hours and from clear liquids for at least 2 hours. Peripheral venous access was created in the forearm via intravenous cannulation and no premedication was administered. Upon entering the theater, routine monitoring devices, including a non-invasive blood pressure cuff, pulse oximeter, and telemetry system, were attached. Following a short rest period, three consecutive measurements were obtained for systolic blood pressure (SBP) and heart rate (HR) at three-minute intervals, which were then averaged to derive the mean SBP and HR.

A combined spinal-epidural block was performed at the L3–L4 interspace using the needle-through-needle method, with the patient positioned in the left lateral decubitus position. After confirmation of proper needle placement by clear cerebrospinal fluid (CSF) return, a solution containing 10 mg hyperbaric bupivacaine and 5 µg sufentanil was administered intrathecally for 15 s. Subsequently, an epidural catheter was advanced 4 cm into the epidural cavity to allow for additional analgesic administration as needed. Immediately after the neuraxial procedure, 5 mL/kg of 37°C lactated Ringer's solution was administered intravenously for 20 min.

Patients were randomized into one of two groups in a 1:1 ratio: group L, which was placed at a 15° angle tilted to the left using a custom-made 15° wedge under the right side, or group S, which was in a supine position. Randomization was achieved by creating a computer-generated sequence of random numbers in Excel (IBM Corp., Armonk, NY, USA) prior to enrolling the first participant. Randomization groups were contained within sealed envelopes and disclosed upon enrollment. In cases where a neuraxial technique could not be completed as intended, the patient was excluded, and randomization allocation was applied again for the subsequent study.

The sensory level to pinprick was then assessed bilaterally along the midclavicular line every 2 min throughout the initial 10 min following intrathecal administration and subsequently every 5 min for the next 20 min. A lower level was observed in cases of asymmetric sensory block. After achieving a T6 dermatomal level, the obstetrician proceeded with the surgery. SBP and HR were recorded at one-minute intervals throughout the study period, defined as the interval from spinal injection to delivery of the baby.

At the start of each case, a single researcher (FX) determined the phenylephrine infusion rate to be used and affixed a non-transparent cover on the infusion pump's (TCI-III-B, Guangxi VERYARK Technology Co., Ltd., China, conduct calibration once a month) display to ensure blinding of clinicians. One of the three anesthesiologists (JQ, HJH, and LY) was responsible for the clinical care. These anesthesiologists could stop and/or restart phenylephrine infusion during surgery, but could not adjust the rate to maintain dose blinding. These anesthesiologists collected the data and reported that phenylephrine infusion was effective (defined as no hypotension occurred during the study period) or ineffective (defined as hypotension occurred during the study period) for FX and then assessed the infusion rate for the following patient.

The first patient in group L and group S received a phenylephrine infusion (100 µg/mL, 5 mg phenylephrine diluted with 50 mL saline prepared in an identical 50 mL syringe) via an infusion pump at 0.5 µg/kg/min starting with intrathecal injection. The infusion rate for subsequent subjects in each group was determined based on the reaction of the prior study subject via the up-down methodology described in previous reports.^{10,11} In cases in which an effective response to the study drug was observed, the subsequent patient's phenylephrine infusion was decreased in gradients of 0.05 µg/kg/min. Conversely, in cases where an ineffective response to phenylephrine was observed, the subsequent phenylephrine infusion was enhanced in gradients of 0.05 µg/kg/min.

Hypotension was characterized by a decrease in SBP exceeding 20% from the baseline and was treated with intravenous boluses of 50 µg phenylephrine. Hypertension was identified when SBP rose more than 20% above baseline, prompting discontinuation of phenylephrine infusion; resumption occurred only after SBP reverted to the baseline range. An HR of <55 beats/min was considered bradycardia. In cases accompanied by hypotension, bradycardia was managed with intravenous boluses of atropine (0.5 mg); in cases without concomitant hypotension, bradycardia was treated by stopping bump infusion. Upon delivery of the neonate, subsequent management of phenylephrine infusion was performed at the discretion of the anesthesiologist.

Measurements

The primary outcome of this study was to determine whether the administered dose of phenylephrine was effective. Subsequently, we determined the ED50 values of phenylephrine in each group based on the primary outcome. Secondary outcomes were as follows: adverse events, including hypotension, hypertension, bradycardia, nausea, vomiting, and shivering; neonatal outcomes were evaluated by determining Apgar scores at 1 and 5 min (by a single neonatologist) and measuring umbilical arterial blood pH; obstetrician satisfaction about the patient position was assessed using a simple Numeric Rating Scale (NRS) ranging from 0 to 10, where 0 indicated not satisfied at all and 10 indicated the most satisfied.

Sample Size Estimation

The decision to include 40 participants in each group was determined based on prior studies that suggested that a sample size of 20–40 subjects is adequate in a variety of clinical scenarios for estimating the ED50 using the up-down method.^{12,13} Furthermore, drawing on data from our earlier research¹¹ determining the ED50 of phenylephrine for preventing hypotension during cesarean delivery, sample size calculations indicated that enrolling at least 21 participants per group would provide greater than 90% statistical power to detect a 20% difference in phenylephrine ED50 between the groups, with a significance level set at $\alpha = 0.05$.

Statistical Analysis

The ED50 for phenylephrine infusion was established by computing the mean midpoint from successive pairs of parturients who transitioned from a nonresponsive to a responsive state (crossover point), as previously described.^{10,14} The method described by Choi¹⁵ was used to estimate the standard error and 95% confidence interval (CI) for ED50 values. As a sensitivity analysis, probit regression analysis was used to examine the combined totals of “effective” and “ineffective” outcomes across each dosage group for all subgroups.¹² In the subsequent analysis, we determined ED50 estimates for phenylephrine infusion rate in both groups and compared their values by calculating the relative mean effectiveness along with a 95% confidence interval using Fieller's method.

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Variables that followed a normal distribution were presented as mean $\pm$ standard deviation (SD) and compared using Student's *t*-test, while non-normally distributed variables were summarized as median and interquartile range (IQR) and analyzed using the Mann–Whitney *U*-test. Categorical variables were reported as frequency (percentage) and evaluated using Fisher's exact test.

Data analysis was performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA) and IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Statistical significance was set at $p < 0.05$.

Results

A total of 91 individuals were initially screened for eligibility, of whom three chose not to participate and seven failed to satisfy the inclusion criteria. Of the remaining 81 patients who were recruited, one did not complete spinal anesthesia; thus, 80 patients were ultimately included in the final analysis. [Figure 1](#) displays the flowchart of the Consolidated Standards of Reporting Trials (CONSORT) flowchart. Detailed demographic data and surgical timing are shown in [Table 1](#).

Patient responses to phenylephrine (effective vs. ineffective) and the sequential order of the subjects are shown in [Figure 2](#). The ED₅₀ of intravenous phenylephrine infusion rate was 0.33 $\mu\text{g/kg/min}$ (95% CI, 0.23 to 0.39 $\mu\text{g/kg/min}$) in group L and 0.30 $\mu\text{g/kg/min}$ (95% CI, 0.22 to 0.37 $\mu\text{g/kg/min}$) in group S. The ED₅₀ values assessed via probit analysis were 0.30 $\mu\text{g/kg/min}$ (95% CI, 0.24 to 0.35 $\mu\text{g/kg/min}$) and 0.28 $\mu\text{g/kg/min}$ (95% CI, 0.23 to 0.33 $\mu\text{g/kg/min}$) in group L and S, respectively. The relative median potency of phenylephrine in group L compared to group S was 1.06 (95% CI:

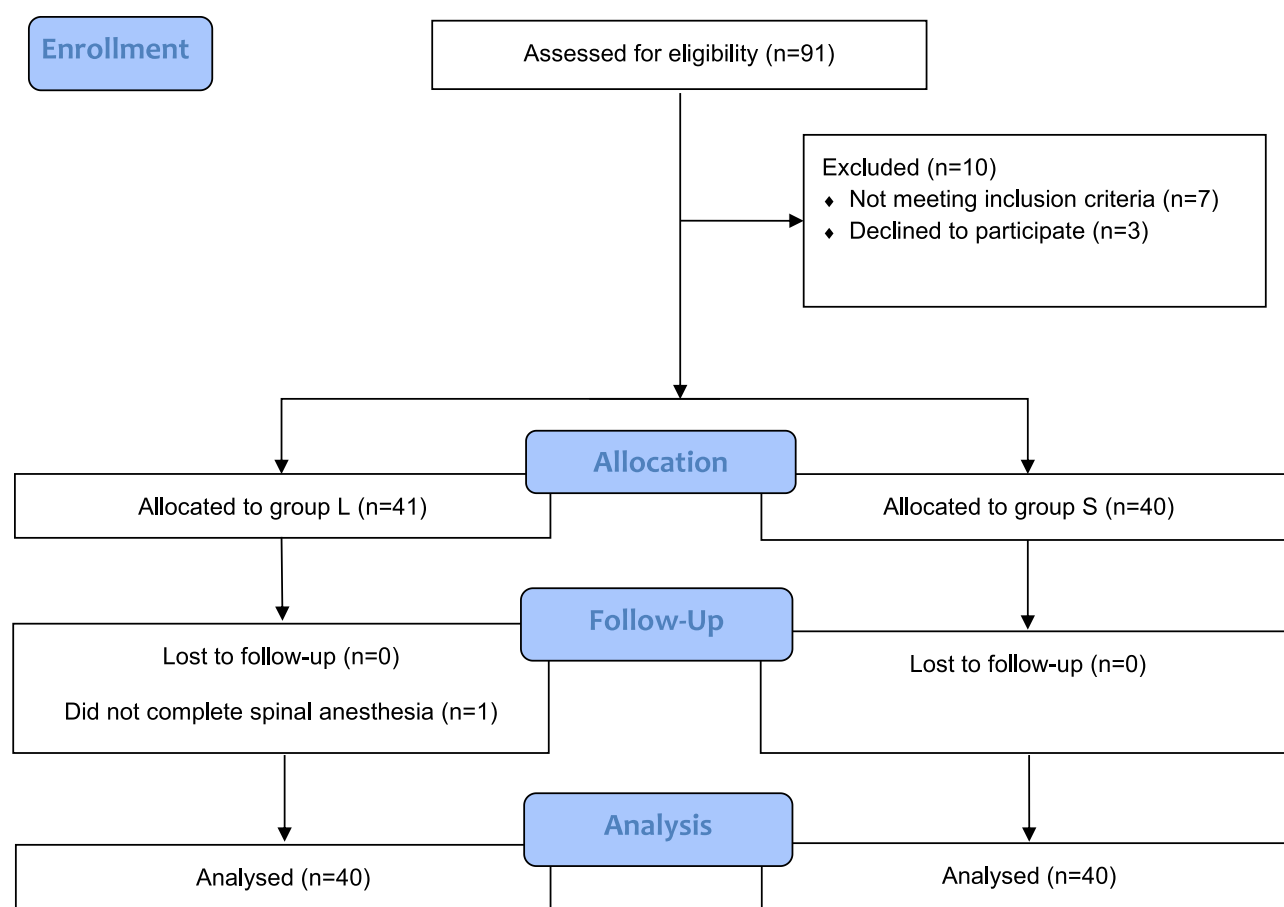


Figure 1 CONSORT diagram showing flow of patients in the study. CONSORT indicates Consolidated Standards of Reporting Trials.

Table 1 Demographic Data and Surgical Timing

Characteristic	Group L (n= 40)	Group S (n= 40)	P value
Age (years)	30.6±2.9	31.4±3.5	0.24*
Height (cm)	159.6±4.3	159.8±5.0	0.87*
Weight (kg)	72.2±9.0	69.7±7.8	0.19*
Gestational age (weeks ^a)	38.7±0.9	39.0±0.9	0.05*
Baseline SBP	122±18	117±15	0.16*
Baseline HR	88±9	87±11	0.51*
Sensory block level	T4 (T4 to T4)	T4 (T4 to T4)	0.81 [†]
Duration from intrathecal injection to infant delivery (minutes)	15.0 (13.0 to 18.0)	15.5 (13.0 to 18.0)	0.94 [†]

Notes: Data are presented as mean ± standard deviation or median (range). * Student's *t* test. [†]Mann-Whitney *U*-test.

0.86 to 1.45), indicating no statistically significant difference between the two groups. Dose–response relationships derived from probit regression analysis, as depicted in Figure 3, illustrate the infusion rate of phenylephrine required to prevent hypotension.

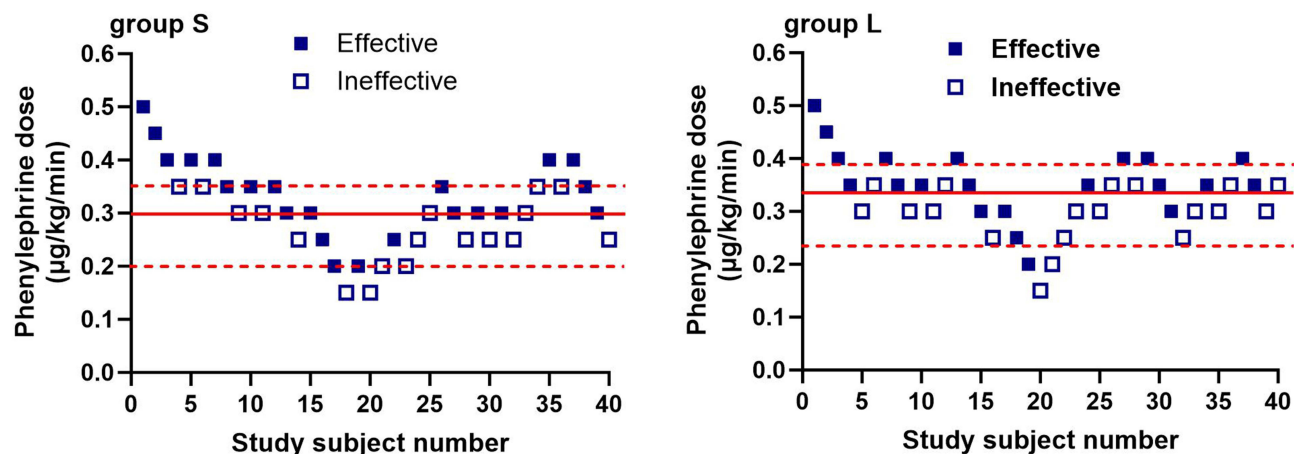


Figure 2 Individual response to prophylactic phenylephrine at corresponding infusion rate ($\mu\text{g/kg/min}$). The ED50 values of intravenous phenylephrine infusion rate calculated by up-and-down method was 0.33 $\mu\text{g/kg/min}$ (95% CI, 0.23–0.39 $\mu\text{g/kg/min}$) in group L and 0.30 $\mu\text{g/kg/min}$ (95% CI, 0.22–0.37 $\mu\text{g/kg/min}$) in group S. Solid lines represent the ED50 values, and dashed lines represent the 95% CI. CI indicates confidence interval; ED50, effective dose in 50% of subjects.

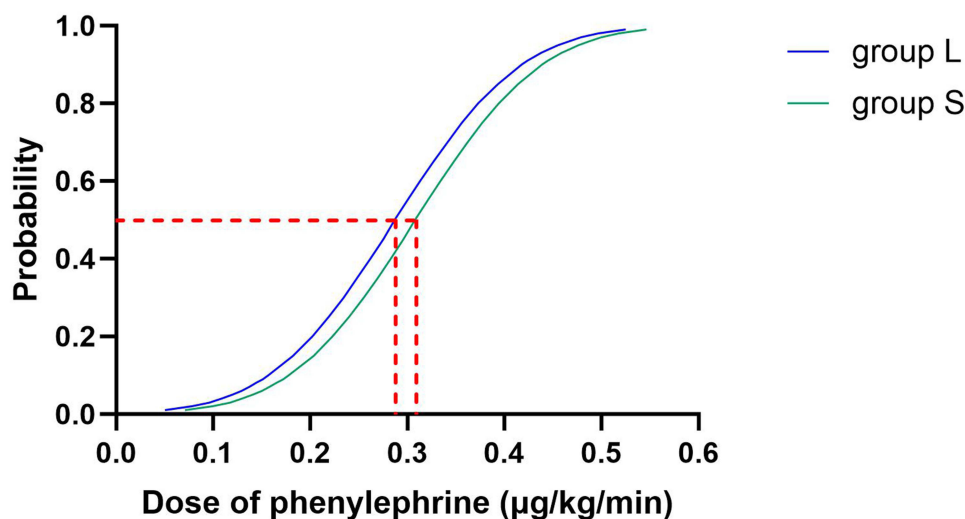


Figure 3 The dose-response curve for prophylactic phenylephrine infusions, designed to prevent hypotension, is constructed by plotting the estimated probabilities of an effective response (ranging from 1% to 99%) against the corresponding phenylephrine infusion rates, as determined through probit analysis.

Table 2 Side Effects, Total Consumption of Phenylephrine and Neonatal Outcomes

	Group L (n=40)	Group S (n=40)	P value
Hypotension	19 (47.5)	18 (45)	0.81 [#]
Total phenylephrine (mcg)	345 (290 to 443)	310 (243 to 390)	0.21 [†]
Hypertension	0 (0)	1 (2.5)	>0.99 [#]
Bradycardia	3 (7.5)	2 (5)	>0.99 [#]
Nausea and/or vomiting	2 (5)	3 (7.5)	>0.99 [#]
Shivering	4 (10)	4 (10)	0.71 [#]
1-minute Apgar score	9 (9 to 9)	9 (9 to 9)	>0.99 [†]
5-minute Apgar score	10 (10 to 10)	10 (10 to 10)	0.36 [†]
Base excess	0.85 (−0.85 to 1.98)	0.60 (−0.78 to 1.83)	0.67 [†]
Lactic acid	4.19 ± 1.08	3.88 ± 0.95	0.18*
Umbilical artery pH	7.28 ± 0.05	7.30 ± 0.05	0.29*

Notes: Data are presented as number (%), median (range) or mean ± standard deviation. *Student's *t* test. [†]Mann–Whitney *U*-test. [#]Chi-square test.

There was no significant difference in the incidence of side effects between the two groups (Table 2). No significant differences were observed in the Apgar scores or umbilical arterial pH between the groups. Obstetrician satisfaction was significantly lower in group L (6 [6–7]) than in group S (10 [9–10]; $P < 0.0001$).

Discussion

In the current study, we determined that the ED50 values for preventing phenylephrine in a 15° left-tilt vs. supine position was 0.33 and 0.30 µg/kg/min, respectively. We also found that obstetrician satisfaction was significantly lower in the 15° left-tilt position than in the supine position. The finding that the ED50 values for preventing phenylephrine were essentially the same in both positions suggests that the recommended practice of LUD during cesarean delivery may not have as significant an effect on vasopressor requirement for hypotension prevention, as previously thought.

One explanation for our ED50 findings is that the degree of left tilt may not have been sufficient to exert a hemodynamic benefit. Fujita et al,¹⁶ performed a comprehensive maternal MRI study and found that the IVC volume can only be increased when the left tilt reaches 30°. The authors also found no significant change in aortic volume between the 15° left lateral tilt and the supine posture. As such, the lack of difference in phenylephrine requirements in these two positions is likely related to insufficient displacement of the uterus off the major maternal blood vessels in the 15° left-tilt position when compared to the supine position. A study by Liu et al⁷ further supports this hypothesis, as it was only with a positioning of 30° left tilt that they found a significant reduction in hypotension and the consumption of phenylephrine and ephedrine.

Our findings also have important implications for neonatal outcomes. We found no significant differences in Apgar scores or umbilical arterial pH between the two positions, consistent with no clinically significant difference in uterine blood flow with a 15° left tilt. Lee et al⁶ and Liu et al⁷ also found that the 15° left-tilt position was no better than the supine position with regard to the neonatal acid-base status. Despite studies in the 1970s demonstrating improved clinical outcomes for neonates and better acid-base status through the implementation of maternal tilting during cesarean delivery,^{17–19} it appears that more recent research has disproven those findings.

As a 15° left tilt appears to be insufficient to decrease hypotension and improve neonatal outcomes, it would be logical to conclude that we should advocate a 30° left tilt. However, such a steep degree of tilting is associated with risks and disadvantages. First, patients with a 30° left tilt have an increased risk of falling out of the bed. Given the significant morbidity associated with inpatient falls, this risk outweighed the benefits of positioning. Second, tilting makes the surgery more challenging. Aust et al²⁰ reported that only 3% of obstetricians tolerated a 15° orientation tilted to the left. Additionally, in our study, a significant number of obstetricians expressed dissatisfaction with the 15° left tilt position due to the heightened challenges it poses for surgical access. Given that the risks and disadvantages of LUD and transient

hypotension do not appear to present a major risk of uteroplacental hypoperfusion, it may be necessary to perform many cesarean deliveries in the supine position. Further studies to examine whether there were objective difficulties in accessing the tilted position during surgery or more surgical complications could be highly valuable.

As with all studies, we must consider the important limitations. First, complete blinding was not possible given the study design; grouping can be easily distinguished based on whether they are in a supine or a 15° left tilt position. However, the researchers and patients were blinded to the randomization assignment prior to enrollment in the study. Furthermore, all patients were blinded to the phenylephrine dose. Second, it is important to acknowledge that the primary aim of our study was to evaluate how the potency and required dose of phenylephrine vary when administered in different positions, rather than establishing specific dosing recommendations such as ED90 or ED95 values. While we do not expect a difference in ED95 either, it is still a question that remains unanswered. Third, it remains uncertain whether our findings can be generalized to patients undergoing cesarean delivery under certain conditions in the exclusion criteria (such as BMI > 35), which might make them more susceptible to the effects of aortocaval compression. Finally, we were unable to evaluate changes in the left femoral vein diameter, which could directly and intuitively reflect the degree of compression on the vena cava, because the measurement procedure could interfere with surgical intervention. Further studies to investigate changes in the diameter of the left femoral vein in different patient positions may be of great interest.

Conclusion

A 15° left tilt did not significantly alter phenylephrine requirements; therefore, routine use of tilt solely to reduce vasopressor need may not be necessary.³

Abbreviations

ASA, American Standards Association; ED50, Median effective dose; CSF, cerebrospinal fluid; LUD, left uterine displacement; SHS, supine hypotension syndrome; IVC, inferior vena cava.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding author (Liu Yu) on reasonable requests.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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