

Determination of the ED₅₀ and ED₉₅ of intravenous bolus of norepinephrine for the treatment of hypotension during spinal anesthesia for cesarean delivery

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Abstract. Norepinephrine is considered as a potential alternative for blood pressure stabilization during spinal anesthesia for cesarean delivery, as it maintains a better maternal heart rate and cardiac output compared with phenylephrine. However, its use as a bolus dose for hypotension treatment remains largely unexplored. Therefore, the present study investigated the ED₅₀ and ED₉₅ of norepinephrine as a bolus for maternal hypotension during cesarean delivery. In the present prospective trial, 42 patients were enrolled for elective delivery under spinal anesthesia. The dose of norepinephrine was decided by the up-and-down sequential allocation method (UDM) with an initial dose of 0.075 µg/kg and a 0.025 µg/kg increment. The 42 patients received a bolus of norepinephrine when systolic blood pressure fell to <80% of baseline. The ED₅₀ was calculated by the sequential method and the probit regression model. The ED₉₅ was then calculated using the probit regression model. The ED₅₀ of norepinephrine, which was determined by the UDM, was 0.067 µg/kg (95% CI, 0.056-0.081). The probit regression model calculated an ED₅₀ of 0.072 µg/kg (95% CI, 0.056-0.088) and an ED₉₅ of 0.121 µg/kg (95% CI, 0.1-0.207). In summary, the present results suggested the ED₅₀ of a bolus norepinephrine for preventing hypotension in elective CD is 0.067 µg/kg (95% CI, 0.056-0.081), with an ED₉₅ of 0.121 µg/kg (95% CI, 0.1-0.207).

Introduction

Spinal anesthesia is a widely used anesthetic method for cesarean delivery (CD), and is associated with a high incidence of maternal hypotension, at 70-80% (1). Persistent hypotension can lead to maternal nausea and vomiting, as well as fetal acidosis owing to reduced uterine blood flow (2). Therefore, common vasopressors such as ephedrine, phenylephrine and norepinephrine are recommended to decrease the occurrence of hypotension (3). However, controversies exist regarding the choice and use of vasopressors (3). Compared with ephedrine, phenylephrine is associated with improved fetal acid-base status (4) and is considered a better choice for hypotension prevention during cesarean delivery (5,6). However, phenylephrine has a potential risk of maternal bradycardia, with significant effects on maternal heart rate (HR) and cardiac output (CO) (7). Norepinephrine has pharmacologic characteristics that make it a potential alternative to phenylephrine for blood pressure stabilization during spinal anesthesia (8). In comparison with phenylephrine, norepinephrine is a potent α-adrenergic receptor agonist that can also excite β-adrenergic receptors (3). A recent study demonstrated that norepinephrine may be a useful vasopressor for stabilizing blood pressure with fewer side effects, such as reducing HR and CO (9). However, there are limited studies on the use of norepinephrine for treating hypotension during spinal anesthesia, and few studies have reported its application in obstetric patients. Norepinephrine infusion has been used to prevent hypotension during spinal anesthesia (10) but the use of this drug as a bolus has not been fully investigated.

Although the ED₉₀ of norepinephrine that prevents hypotension during spinal anesthesia has been assessed (11), the use of ED₅₀ and ED₉₅ for treating hypotension has not been completely defined. The objective of the present study was to determine the intravenous bolus dose of norepinephrine in treating maternal hypotension in 50% (ED₅₀) and 95% (ED₉₅) of puerperas undergoing spinal anesthesia. The secondary outcomes of the present study included maternal anesthetic block level, hemodynamic changes, bradycardia, adverse

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effects, umbilical arterial blood gases, Apgar scores and the ratio of hypotensive patients to hypertensive patients following treatment.

Patients and methods

Patient characteristics. A total of 42 patients were enrolled into the present study between 3rd November 2018 and 31st December 2018. The present study was conducted in Jiaxing Maternity and Child Healthcare Hospital (Jiaxing, China), and informed consent was provided by each participating patient. Inclusion criteria were elective cesarean delivery under spinal anesthesia, healthy singleton full-term pregnancy beyond 37 weeks of gestation, American Society of Anesthesiologists physical status I or II (12), weight of 50-100 kg, height of 150-180 cm, and fasting for >6 h. Exclusion criteria were hypertension, cardiovascular diseases, preeclampsia, anisorrhhythmia, diabetes mellitus, spinal cord malformation, abnormal fetus and patient refusal. The included puerperas received different doses of norepinephrine (0.025, 0.050, 0.075, 0.100 and 0.125 $\mu\text{g}/\text{kg}$) to stabilize blood pressure. The present prospective, double-blinded study was approved by the Ethical Committee of Jiaxing Maternity and Child Healthcare Hospital, and was registered in the Chinese Clinical Registry Center (registration no. ChiCTR1800018474).

Patient monitoring. No patients received premedication. Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were recorded in the supine position on the morning of the surgery. Baseline systolic arterial BP was the average of three continuous measurements at 1 min intervals using an automated device for non-invasive BP assessment on the morning of surgery. In the operating room, patients underwent continuous standard monitoring throughout the whole surgery, including electrocardiography, non-invasive blood pressure measurement and pulse oximetry on a patient monitor system (B650; GE Healthcare Finland Oy). A 18G intravenous catheter cannula was inserted into a right forearm vein and infused with Ringer's lactate solution at 10 ml/kg within 20 min of infusion, followed by a maintained dose of 20 ml/min. The patients were placed in the left lateral position. Spinal anesthesia was performed using a 16G epidural puncture needle, with a 25G Whitacre needle at the Lumbar 3-4 interspace. Upon entry into the subarachnoid space and noticing the cerebrospinal fluid flowing out, 0.5% bupivacaine, which was obtained by mixing 2 ml 0.75% bupivacaine (Shanghai Hefeng Pharmaceutical Co., Ltd.) with 1 ml sterile saline, and was administered intrathecally at the rate of 0.1 ml/sec. The dose of bupivacaine is referred to in the Harten dose table, and was adjusted according to the height and weight of a patient (13). Then, the patient was placed in the supine position with left uterine displacement by tilting the bed to the left by 15° (14). Oxygen was administered via a mask at 5 l/min. The spinal sensory block level was evaluated by pinprick and confirmed to be within Thoracic (T) 4-6. If not, the case was excluded from the current study.

Treatment preparation. Prior to treatment, the anesthesiologist assistant, who was not involved in patient management or data acquisition, prepared the study bolus dose by adding

a measured volume of 2 mg norepinephrine (Changzhou Yuanda Pharmaceutical Chemical Co. Ltd.) to 500 ml of physiological saline. The patient and the attending anesthetic manager were blinded to group allocation. Based on patient weight, the corresponding dose of the drug was determined by the assistant anesthesiologist. The anesthetic manager who collected the data was blinded to the drug and its dose. After delivery, 5U oxytocin (Nanjing Xinbai Pharmaceutical Co., Ltd.) was administered slowly by intravenous infusion, and an additional 5U oxytocin was injected into the uterine muscle. Meanwhile, the pediatric nurse, who was unaware of the study, assessed Apgar scores (15) at 1 and 5 min, including activity, pulse, grimace, appearance and respiration. Arterial blood specimens were collected from the clamped umbilical cord for immediate blood gas analysis using a blood gas analyzer (COBAS B123; Roche Diagnostics).

Treatment regime. Previous studies have suggested that a 100 μg dose of phenylephrine approximates an 8 μg dose of norepinephrine (16), though a dose 100 μg of phenylephrine is a suitable dosage (17,18), and the use of a 6 μg bolus norepinephrine appears sufficient to prevent hypotension (11). In the present trial, the dosage of norepinephrine was decided by the up-and-down sequential allocation method with an initial dose of 0.075 $\mu\text{g}/\text{kg}$ and a 0.025 $\mu\text{g}/\text{kg}$ gradient. For the dose finding study by the up-and-down method, the data distribution was unknown and non-independent (19-21). As required by the sequential approach, the dose level for the next patient was determined by the response of the preceding patient. In the present study, the first patient received a dose of 0.075 $\mu\text{g}/\text{kg}$, which was thought to be closest to the estimated dose. If the first patient showed a positive response, the second patient would be exposed to a lower dose (0.05 $\mu\text{g}/\text{kg}$). In case of a negative response by the first patient at 0.075 $\mu\text{g}/\text{kg}$, the second patient would be exposed to a next higher dose (0.1 $\mu\text{g}/\text{kg}$). Successive patients were assigned respective doses similarly based on the responses of the preceding participants.

In the present study the norepinephrine regimen was started immediately after intrathecal injection. According to our standard practice, SBP was assessed every min, beginning immediately after intrathecal injection until delivery. The study drug was administered manually by the attending anesthetic manager whenever SBP was <80% of baseline, to maintain SBP within the 95% baseline value. Hypotension was defined as SBP <80% of baseline, and hypertension as a 20% increase from baseline. In case SBP returned to within the 95% baseline value within 1 min after administration, treatment was considered to be successful. If SBP was still <80% of baseline, 6 mg ephedrine was administered. Bradycardia, which is a heart rate below 50 beats per minute, was treated with 0.5 mg atropine.

SBP, DBP and HR were recorded at baseline and 1 min after administration. The times of norepinephrine injection before delivery and throughout the surgery were recorded. Maternal infusion volume, blood loss, urine output and adverse effects such as nausea, vomiting, bradycardia, hypertension and hypotension were also recorded. In addition, fetal heart rates before and after spinal anesthesia, Apgar scores at 1 and 5 min, and umbilical arterial blood gases were assessed.

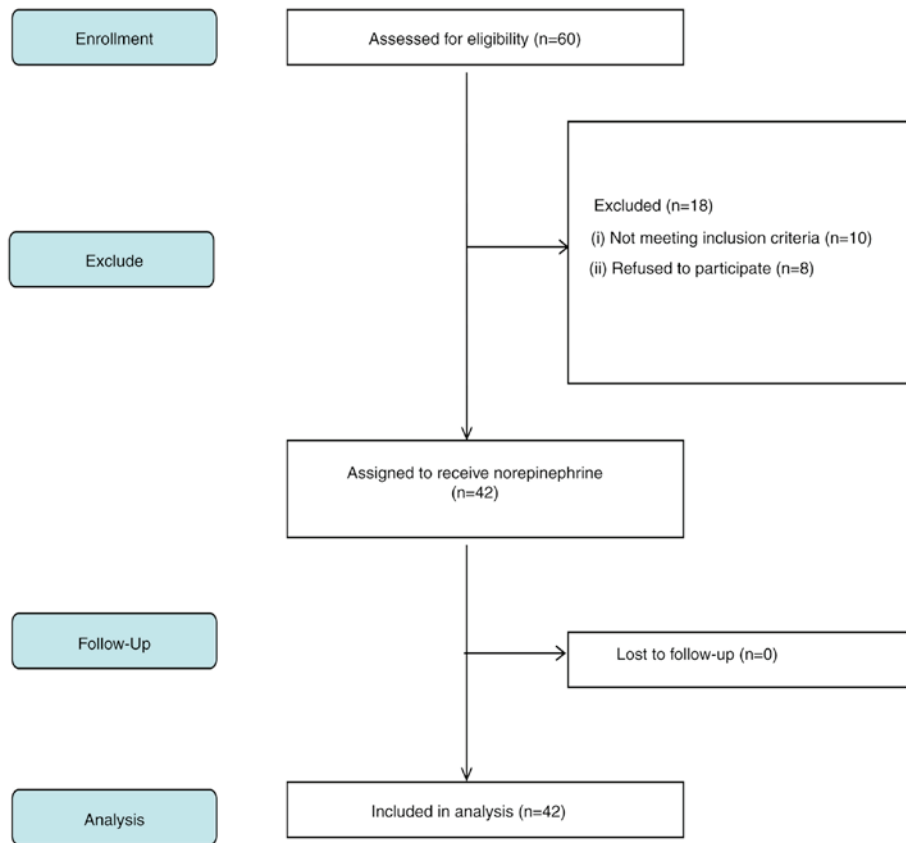


Figure 1. Flowchart of patient recruitment.

Statistical analysis. In the present UDM study, data distribution was non-independent and unknown, which prevents the development of theoretical rules for determining the necessary sample size from an accurate estimation of the ED_{50} (21). Simulation studies suggested that a stopping rule with 20-40 patients would provide stable estimates of the study dose for most realistic cases (21). The present study required a sample size of 42 patients for the stopping rule. The data were used to calculate the ED_{50} with 95% CI, using the up-and-down method. Data were further analyzed using the probit regression model to calculate the ED_{50} and ED_{95} . The sequential method was performed according to the following formula: $ED_{50} = \lg^{-1} \sum r \lg C / \sum r C$, where C is the dose, r is the number of injections. The standard error was calculated as $S_{\lg ED_{50}} = d \{ \sum [p(1-p)/(r-1)] \}^{1/2}$, where p is the effective rate. The 95% CI was determined for the ED_{50} obtained by the sequential method as $\lg^{-1} (\lg ED_{50} \pm 1.96 S_{\lg ED_{50}})$ (22). Data analysis was performed using the SPSS 20.0 software (IBM Corp.).

Results

Patient recruitment. A total of 60 patients undergoing elective cesarean delivery under spinal anesthesia were recruited in the present study, and 42 were included in the final analysis. Fig. 1 indicates a flow diagram detailing patient enrolment. The demographics of the mothers are presented in Table I, with parameters presented as mean \pm SD or number. The mean age of the participants was 30.4 ± 4.3 years, the mean body weight

was 70.5 ± 8.4 kg. The anesthesia block level was between T4 and T6.

Neonatal measurements. Umbilical arterial blood gas data after delivery are presented as mean \pm SD (Table II). Umbilical artery base excess values ranged from -7.5 to -0.4 mEq/l. The pH values ranged from 7.23-7.34. All pH values were within the normal range, and no neonate experienced fetal acidosis defined as pH <7.2, which is the lower limit of normal (data not shown) (23). Values in blood gas analysis of the umbilical artery fluctuated within the normal range without obvious abnormality. Apgar scores at 1 and 5 min were eight or above for all cases. No neonates required intubation or ventilation.

Maternal outcomes. Side effects observed after treatment included nausea, vomiting, bradycardia, hypertension and hypotension (Table III). Of the eight patients (19.1%) who developed nausea, six received a dose <0.1 $\mu\text{g}/\text{kg}$, and one case (2.4%) had vomiting symptoms. Of the 19 patients (45.2%) who developed hypotension, 12 received bolus norepinephrine doses <0.075 $\mu\text{g}/\text{kg}$ (data not shown). Table IV indicates the observed response rates for various norepinephrine dose levels. A total of 21 participants reported the norepinephrine dosage to be effective, and 21 considered their received dosage to be ineffective.

Norepinephrine dose response. Effective and ineffective responses were evaluated at various norepinephrine dose levels, including 0.025, 0.05, 0.075, 0.1 and 0.125 $\mu\text{g}/\text{kg}$. Fig. 2

Table I. Demographic data and surgical characteristics. Data are presented as mean \pm SD.

Characteristic	Index
Age, years	30.4 \pm 4.3
Weight, kg	70.5 \pm 8.4
Height, cm	159.2 \pm 6.3
Gestation, weeks	38.0 \pm 1.4
SBP at baseline, mmHg	120.4 \pm 11.4
DBP at baseline, mmHg	71.5 \pm 6.1
HR at baseline, beats/min	77.8 \pm 11.2
Block level (T)	T5(T4 to T6)

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table II. Neonatal umbilical artery outcomes.

Parameters	Index
PO ₂ , mm Hg	21.4 \pm 4.8
PCO ₂ , mm Hg	46.4 \pm 4.1
pH	7.3 \pm 0.1
HCO ₃ ⁻ , mmol/l	24.6 \pm 2.5
Base excess, mEq/l	-3.2 \pm 2.0
Apgar score at 1 min	8.7 \pm 0.5
Apgar score at 5 min	8.8 \pm 0.4

Data are presented as mean \pm SD. SD, standard deviation.

Table III. Maternal outcomes.

Parameter	Index
Nausea	8 (19.1%)
Vomiting	1 (2.4%)
Bradycardia	2 (4.8%)
Hypertension	2 (4.8%)
Hypotension	19 (45.2%)
Transfusion volume, ml	871.4 \pm 74.2
Bleeding volume, ml	260.7 \pm 59.0
Urine volume, ml	104.3 \pm 15.3

Data are presented as number (%) or mean \pm SD. SD, standard deviation.

showed each dose, anesthetic result and subsequent dosing. The ED₅₀ of norepinephrine determined by the up-and-down sequential allocation method was 0.067 μ g/kg (Fig. 2; 95% CI, 0.056-0.081). In addition, effective and ineffective responses to norepinephrine were evaluated by the probit regression model. The ED₅₀ of norepinephrine was 0.072 μ g/kg (95% CI, 0.056-0.088) and the ED₉₅ identified by the probit regression model was 0.121 μ g/kg (Fig. 3; 95% CI, 0.1-0.207).

Table IV. Observed response rate.

Groups	Assigned dose, μ g/kg	Effective	Total number	Effective rate
NE 1	0.025	0	3	0.00
NE 2	0.050	3	12	0.3
NE 3	0.075	9	16	0.6
NE 4	0.100	7	9	0.8
NE 5	0.125	2	2	1.00

NE, norepinephrine.

Discussion

The present study determined the weight-based dose of norepinephrine given as a bolus to treat the first episode of hypotension in patients undergoing spinal anesthesia for elective CD. The present results suggested that ED₅₀ values for norepinephrine were 0.067 μ g/kg (95% CI, 0.056-0.081) and 0.072 μ g/kg (95% CI, 0.056-0.088) as assessed by the up-and-down method and the probit regression model, respectively. The ED₉₅ calculated by the probit regression model was 0.121 μ g/kg (95% CI, 0.1-0.207). The ED₅₀ measured by the up-and-down method was close to that obtained by the probit regression model. No significant adverse effects were identified in the present study; however, it is possible that the low incidence of side effects was due to the small sample size. For the dosage determination study by the up-and-down method, data distribution was unknown and non-independent. As required by the sequential approach, the dose for the subsequent patient was determined by the response of the preceding patient (21). Using the sequential approach to calculate median effective dose, once six pairs of reversal of sequence was achieved, it was possible to consider the sample size as adequate (20,24). The present study had >6 pairs of reversal of sequence, so the sample size was sufficient. In addition, previous simulation studies suggest that including \geq 20-40 patients will provide stable estimates of the target dose for most realistic scenarios (19). The present study required a sample size of 42 patients for the stopping rule.

A previous study reported an ED₉₀ preventing hypotension for norepinephrine of 6 μ g (11), however the weight based ED₅₀ and ED₉₅ of norepinephrine have not been widely investigated in patients. Therefore, the present study assessed the ED₅₀ and ED₉₅ of norepinephrine. Understanding the ED₅₀ of a drug is important as it is located in the most sensitive portion of the dose-response curve, and small adjustments are expected to have significant increases in therapeutic response (25). In addition, determining the ED₅₀ can potentially limit the total number of patients enrolled in a clinical trial, which is important when there is limited published information related to the side effects of a drug. The present study used the up-and-down method to determine the effective dose of norepinephrine, when the starting dose approximates the therapeutic scope for the drug, which resulted in the identification of the ED₅₀ in a limited number of patients. A limitation of the up-and-down method is the inability to accurately determine the ED₉₅ (26);

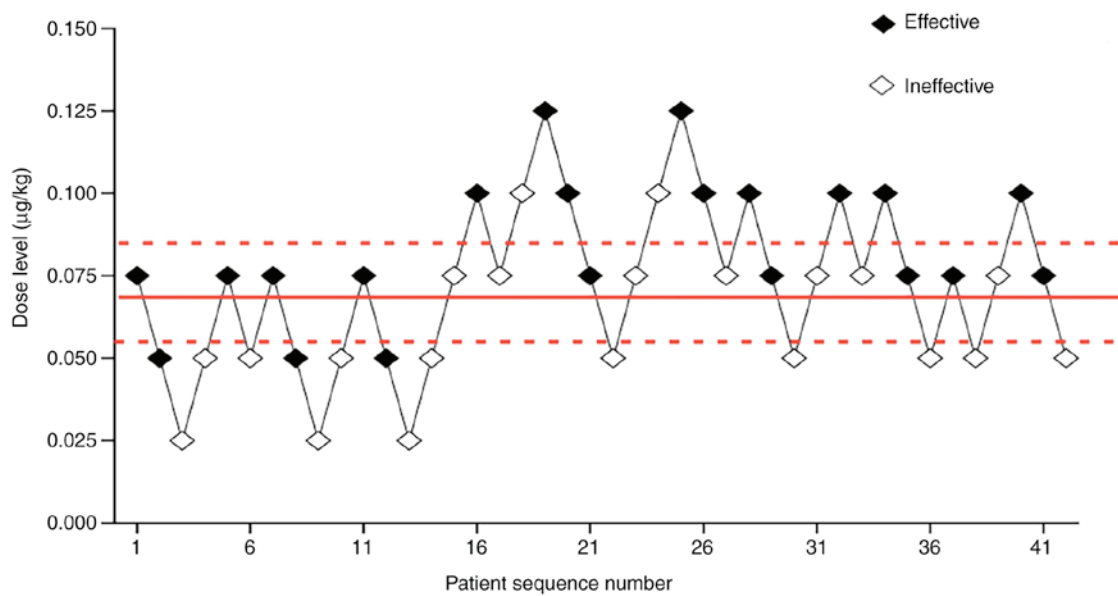


Figure 2. Sequential test diagram. Scatter plot showing effective, represented by a solid dot, and ineffective, represented by an open dot, doses for all 42 participants. Median effective dosage was 0.067 $\mu\text{g}/\text{kg}$ (95% CI, 0.056-0.081).

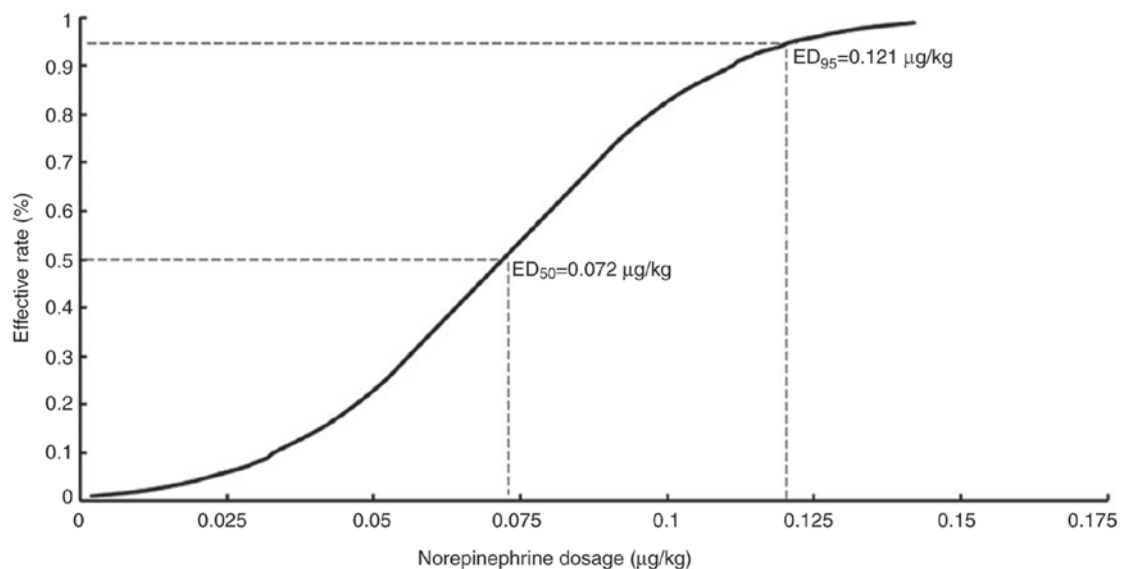


Figure 3. Norepinephrine dose-effective probability curve. The dose-response curve identified the relationship between the norepinephrine dosage in the patients and the proportion of patients reporting the effectiveness (defined as the SBP returned to within 95% of the baseline value). The ED_{50} and ED_{95} were estimated using probit regression model. SBP, systolic blood pressure.

therefore, the probit regression model was used for this purpose.

Ngan Kee *et al* (16) conducted a random-allocation, graded dose-response study of norepinephrine and phenylephrine and the authors estimated the ED_{50} (dose yielding a 50% response) of norepinephrine at 10 μg (95% CI, 6 to 17 μg), which was different from the results of the present study. With dose-response analysis, the value represents the dose that results in responses of 50% magnitude, which differs from the same term in the more traditional quantal dose-response methodology (27). In the present study, the intrathecal anesthetic dose was 11 mg hyperbaric bupivacaine 0.5% w/v and 15 μg fentanyl, while the dose of bupivacaine was 10 mg

bupivacaine (2 ml 0.75% bupivacaine). The magnitude of response is measured as the percentage of full restoration of SBP to baseline (16), which is different to the present study where SBP returning to within 95% of the baseline value was satisfactory. The ED_{50} calculated was much higher in the study by Ngan Kee *et al* (16) than the ED_{50} values for norepinephrine in the present study. This variation could be attributed to the differing study designs. Compared with the random-allocation graded dose-response study, the present study used the sequential method to collect cases, with the advantage of obtaining the effective dose with a fewer number of patients. Differences in patient populations could have also affected the study results.

A previous study has suggested that the incidence of maternal hypotension is 50-80% depending upon the position of the patient, the rate of spinal anesthetic agent injected, intravenous fluid loading and whether the women is laboring or has associated morbidity, including pregnancy induced hypertension (28). Anesthesiologists are required to be careful since hypotension is common during cesarean delivery under spinal anesthesia (28). Commonly used vasopressors include ephedrine, phenylephrine and norepinephrine (3). Ephedrine has been previously considered the most appropriate vasopressor during spinal anesthesia (28). However, ephedrine is associated with decreased umbilical artery pH compared with other vasopressors such as phenylephrine (29). In addition, ephedrine does not completely prevent hypotension, nausea and vomiting and fetal acidosis (9). On the contrary, it may cause reactive hypertension in some patients (30). Phenylephrine is more effective for venoconstriction than arterial constriction, and predictably increases blood pressure by elevating both systemic vascular resistance and preload (28). In addition, due to its minimal β -2 receptor activity, phenylephrine does not cause tachycardia, and instead induces reflex bradycardia with increasing blood pressure (28).

Ali Elnabity and Selim (3) compared ephedrine and norepinephrine, and found that the latter is associated with reduced numbers of hypotension and hypertension episodes as well as decreased frequencies of bradycardia and tachycardia, while maintaining maternal blood pressure and uterine artery blood flow during cesarean delivery. Furthermore, the study also found that the number of norepinephrine boluses used during spinal anesthesia is lower compared with that of ephedrine. Norepinephrine does not readily cross the placental barrier, because of the ability of the placenta to degrade catecholamines (31). However, it is a mild β -adrenergic and a potent α -adrenergic receptor agonist (7,8). Hence, norepinephrine may be a more appropriate choice for stabilizing maternal blood pressure with fewer adverse effects on HR and cardiac output in the setting of elective cesarean delivery under spinal anesthesia.

Although prophylactic infusion is the recommended method for treating spinal hypotension to reduce hemodynamic fluctuation and maternal side effects, it may be associated with a higher incidence of reactive hypertension (32). Doherty *et al* (33) reported that no significant difference could be found in maintaining baseline maternal CO and providing BP stability between both options of an infusion regimen and a bolus dose of phenylephrine in elective cesarean delivery under spinal anesthesia. Compared with the bolus regimen, the infusion regimen required a higher total dose of phenylephrine to maintain maternal arterial blood pressure at baseline during the pre-delivery period (33). Administration of the bolus regimen resulted in a smaller reduction in baseline SBP in the initial minutes after intrathecal injection. The bolus regimen allows faster delivery of an effective dose of phenylephrine recovering maternal vascular resistance rapidly during the establishment of spinal blockade. Of note, many anesthesiologists may favor bolus doses of vasopressors, while being prepared for repeated doses rather than selecting infusion initially during spinal anesthesia (34). Therefore, the present study selected a bolus dose of norepinephrine, which may be familiar to the majority of anesthesiologists. To the best of our knowledge, no previous study has precisely determined

the ED₅₀ and ED₉₅ of weight-based norepinephrine as a bolus in the setting of elective cesarean delivery under spinal anesthesia. Furthermore, using norepinephrine as a bolus to treat hypotension during cesarean delivery is not well understood.

Chen *et al* (10) performed a randomized double-blinded controlled study of 120 patients for elective section delivery under spinal anesthesia; the patients treated by infusion were assigned to four groups, and administered saline or norepinephrine at 5, 10 and 15 $\mu\text{g}/\text{kg}/\text{h}$, respectively. Onwochei *et al* (11) carried out a prospective, double-blind sequential allocation dose-finding study, using the biased coin up-and-down design. In the latter trial, 40 pregnant women received a set intermittent norepinephrine bolus of 3, 4, 5, 6, 7 or 8 μg , when systolic blood pressure fell below 100% of baseline. Vallejo *et al* (14) conducted an open-label randomized controlled clinical trial including 85 patients undergoing spinal anesthesia for elective cesarean delivery, who were randomized to the phenylephrine (0.1 $\mu\text{g}/\text{kg}/\text{min}$) and norepinephrine (0.05 $\mu\text{g}/\text{kg}/\text{min}$) fixed-rate infusion groups. The present results suggested the ED₅₀ and ED₉₅ of norepinephrine were 0.067 $\mu\text{g}/\text{kg}$ (95% CI, 0.056-0.081) and 0.121 $\mu\text{g}/\text{kg}$ (95% CI, 0.1-0.207), respectively, during cesarean delivery, corroborating the previous studies.

The issue of tissue injury caused by bolus norepinephrine through peripheral venous catheters has become the main concern in the field (35). Previous studies have reported complications associated with norepinephrine administered through peripheral venous catheters, e.g. skin necrosis, with a 3.6% complication rate in 55 patients administered the vasopressor (36). However, a recent retrospective trial in neonates using vasopressors via peripheral venous catheters found no complications (37). In another prospective study, 55 patients received vasopressors via peripheral venous catheters, and the rate of complications (5.45%) was very low, with no significant morbidity (38). In the present study, the highest single bolus dose of norepinephrine was 0.125 $\mu\text{g}/\text{kg}$, and was associated with no complications.

However, the present study does have limitations that need to be mentioned. First, the present study, which was based on treatment for the first episode of hypotension following spinal anesthesia, was not extended until the end of surgery; responses to subsequent episodes of hypotension could be different. Secondly, the individual sensitivity to vasoactive drugs differs, which may impact the results. Thirdly, all participants were from the same geographic area. Finally, the present study had no control group.

In conclusion, the present results indicated that the ED₅₀ values of a single bolus of norepinephrine for preventing hypotension in elective CD were 0.067 $\mu\text{g}/\text{kg}$ (95% CI, 0.056-0.081) and 0.072 $\mu\text{g}/\text{kg}$ (95% CI, 0.056-0.088) by the up-and-down method and the probit regression model, respectively. The ED₉₅ obtained by the probit regression model was 0.121 $\mu\text{g}/\text{kg}$ (95% CI, 0.1-0.207).

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TW and QH conducted the majority of the experiments and wrote the manuscript. WZ and JZ conceived and designed the study. HN and RY performed the data analysis. QL and LX collected the data and MY coordinated and supervised the experiments. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of Jiaying Maternity and Child Healthcare Hospital (Zhejiang, China) and registered in the Chinese Clinical Registry Center (registration no. ChiCTR1800018474). All of the participants who participated in the study provided written informed consent at the time of enrolment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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