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Up-and-down determination of prophylactic norepinephrine boluses combined with crystalloid co-load for preventing post-spinal anesthesia hypotension during cesarean section

Chengfei Xu[1†], Peipei Zhang[2†], Chunying Dai[1], Jingjun Zhang[1], Honghao Wu[1], Qianying Liu[1], Zhiqiang Zhang[1], Fengwei Yin[1], Huadong Ni[3*] and Liang Cheng[1*]

Abstract

Background The use of a fluid co-load has been shown to enhance hemodynamic stability and diminish the occurrence of hypotension after spinal anesthesia when paired with prophylactic norepinephrine. This research aimed to identify the effective dosages (ED_{90} and ED_{50}) of prophylactic norepinephrine boluses, in conjunction with a crystalloid co-load, for the prevention of hypotension after spinal anesthesia in cesarean delivery patients.

Methods Patients were administered crystalloid co-loads at a dosage of 10 mL/kg, in addition to preventive norepinephrine dosages direct following spinal anesthesia administration. The dosages of norepinephrine were established employing the up-and-down sequential allocation technique, starting with 8 μg and progressively rising by 1 μg increments. The primary objective was to detect the effective dosage (ED_{90} and ED_{50}) of norepinephrine necessary to avoid hypotension following spinal anesthesia.

Results The ED_{90} for a single norepinephrine bolus, in combination with a crystalloid co-load, was calculated to be 5.35 μg (95% CI: 4.75 to 7.13). The ED_{50} was determined to be 4.05 μg (95% CI: 3.68 to 4.46) using the up-and-down method and 3.926 μg (95% CI: 3.362 to 4.422) through the probit regression model.

Conclusion A prophylactic norepinephrine bolus of 5.35 μg, administered with a crystalloid co-load, effectively prevents hypotension following the spinal anesthesia in cesarean delivery patients.

Keywords Crystalloid co-load, Norepinephrine, Post-spinal anesthesia hypotension, Cesarean section

[†]Chengfei Xu and Peipei Zhang contributed equally to this work.

*Correspondence:
Huadong Ni
huadongni@zjxu.edu.cn
Liang Cheng
bbchengliang@163.com

[1]Department of Anesthesiology, The Third People's Hospital of Bengbu, 38 Shengli Middle Road, Bengbu 233000, China
[2]Department of Obstetrics and Gynecology, The Third People's Hospital of Bengbu, 38 Shengli Middle Road, Bengbu 233000, China
[3]Department of Anesthesiology and Pain Research center, The Affiliated Hospital of Jiaxing University, 1882 Zhonghuan South Road, Jiaxing 314001, China

Introduction

Spinal anesthesia is the favored technique for cesarean delivery, yet it is often accompanied by hypotension after the spinal anesthesia, which remains the most prevalent complication related to maternity. This hypotension can lead to serious issues such as nausea, vomiting, reduced placental perfusion, and fetal acidosis [1]. To both prevent and manage this condition, vasopressors and fluid loading are essential, as these measures help stabilize hemodynamics [2, 3]. Fluid loading is particularly vital in addressing post-spinal anesthesia hypotension by maintaining intravascular volume, promoting sufficient tissue perfusion, and mitigating the hypotensive effects of sympathetic blockade [4]. Furthermore, fluid loading lessens dependence on vasopressors while enhancing the hemodynamic stability achieved through prophylactic vasopressor administration [3, 5].

The timing of fluid loading is critical for maximizing its effectiveness. Historically, preloading—conducted 15 to 30 min before spinal anesthesia—was commonly used during cesarean Sect. [6]. However, research has indicated that a 30 mL/kg crystalloid preload is inadequate in preventing hypotension following spinal anesthesia [7]. Consequently, clinical practice has increasingly favored co-loading, where fluids are administered immediately after spinal anesthesia induction. Co-loading has shown greater efficacy in augmenting intravascular volume during the time of maximal arterial expansion resulting from sympathetic blockade [8]. Recent studies have confirmed that co-loading with 10 mL/kg of crystalloids, together with prophylactic vasopressor infusion, successfully prevents post-anesthetic hypotension [9]. Nonetheless, the precise effective doses (ED_{90} and ED_{50}) of prophylactic norepinephrine in conjunction with a crystalloid co-load remain uncertain [10, 11].

Despite guidelines supporting prophylactic infusions to avert spinal hypotension [3], many anesthesiologists continue to prefer intravenous bolus administration [12]. Additionally, intermittent intravenous norepinephrine boluses have proven to be an effective strategy for avoiding hypotension caused by spinal anesthesia in obstetric patients, with minimal adverse effects [13]. In this investigation, we applied the up-and-down sequential allocation technique to ascertain the ED_{90} and ED_{50} of prophylactic norepinephrine boluses, administered alongside crystalloid co-loading, to prevent hypotension after the spinal anesthesia in the course of cesarean delivery.

Patients and methods

This prospective, double-blind, sequential allocation dose-finding study was authorized by the Research Ethics Board of the Third People's Hospital of Bengbu, China (Approval No. 2024-k21; June 24, 2024). Conducted between July 2024 and August 2024, the study utilized an up-and-down design to determine dose efficacy [14]. The study enrolled non-laboring women at term scheduled for elective cesarean delivery. Written informed permission was obtained from everyone involved in the study, and the trial had been registered in ClinicalTrials.gov (NCT06498115, 2024/07/11).

Study population

Inclusion criteria for participants included a healthy singleton pregnancy at full term (above 37 weeks of pregnancy), elective cesarean delivery under spinal anesthesia, the weight of the participant ranging from 50 to 100 kg, American Society of Anesthesiologists (ASA) physical status classification of I or II [15], height ranging from 150 to 180 cm, and a fasting duration exceeding 6 h. To ensure adherence to current standardized guidelines for patient evaluation, the most recent European Society of Anaesthesiology and Intensive Care (ESAIC) Guidelines were also referenced [16]. Exclusion criteria included allergies or hypersensitivity to norepinephrine, hypertension, cardiovascular diseases, arrhythmias, preeclampsia, fetal abnormalities, spinal cord malformations, and patient refusal to participate.

Monitoring and anesthesia

On the morning of the surgery, baseline systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were detected in the supine position using non-invasive methods. Initial SBP was established as the average of three successive readings obtained at 1-minute intervals employing an automatic blood pressure monitor. Blood pressure was measured at baseline and then at 1-minute intervals during the first 10 min after spinal anesthesia to monitor rapid hemodynamic changes. Thereafter, measurements were taken every 5 min until the end of the surgical procedure. During the procedure, continuous standard monitoring was performed, pulse oximetry, like non-invasive blood pressure, and electrocardiography using a monitoring system for the patient (MX550; Philips, Netherlands). Premedication was not administered. Particpants were positioned in the left lateral decubitus position before spinal anesthesia. A 16-gauge epidural needle was used to puncture the L3-L4 interspace, followed by the insertion of a 25-gauge Whitacre needle. Upon confirmation of cerebrospinal fluid outflow, indicating successful subarachnoid space entry, 0.6% ropivacaine was intrathecally injected at a rate of 0.1 ml/sec. The ropivacaine solution was prepared by diluting 1.5 ml of 1% ropivacaine (Shijiazhuang Four Drugs Co., Ltd.) with 1 ml of cerebrospinal fluid, a dosage based on previous studies [17–19]. After the injection, patients were situated supine with a 15-degree left lateral tilt to achieve left uterine displacement [20]. Oxygen was administered at 5 L per minute via mask. The degree of the spinal

sensory blockage was evaluated employing the pinprick technique and verified to fall within the interval of thoracic (T) 4–6. Investigation eliminated individuals who failed to meet this criterion.

Study protocol

A crystalloid preload was supplied at a dosage of 5 ml/kg over 20 min after an 18-gauge intravenous catheter was inserted into the right forearm prior to anesthesia administration. After spinal anesthesia was initiated, a crystalloid co-load solution consisting of complex sodium chloride (0.85% NaCl, 0.03% KCl, and 0.033% $CaCl_2$) was infused at 10 ml/kg over 10–15 min, then a preservation infusion rate of 0.1 ml/kg/min was conducted. To produce the investigation bolus dosage, the anesthesiologist assistant, who did not participate in patient treatment or gathering information but was responsible for dose preparation, added 2 mg of norepinephrine (Yuanda Pharmaceutical Co., Ltd.) to 500 ml of physiological saline. There was blinding of the patient and the participating anesthesiologist to group assignment, and the anesthesiologist in charge of collecting data was likewise blinded to the specific medication type and dose.

Based on prior research [21, 22], the first participant underwent a primary prophylactic bolus dose of 8 μg norepinephrine simultaneously with spinal anesthesia. This approach, validated in a randomized, double-blinded study comparing norepinephrine and phenylephrine, highlights the ability of an 8 μg norepinephrine bolus to maintain cardiac output and reduce the incidence of bradycardia [23]. In our study, this dosage was adopted to build upon prior evidence and ensure optimal maternal hemodynamic stability during elective cesarean sections. Subsequent norepinephrine doses were adjusted in 1 μg increments, depending on their effectiveness in avoiding hypotension after spinal anesthesia, defined as an SBP drop below 80% of baseline. The up-and-down sequential allocation approach directed these modifications [24, 25]. This method is a sequential allocation technique designed to estimate the ED_{50} and ED_{90} based on individual patient responses to varying doses of norepinephrine. The randomization process in our study was based on the patient's response to the initial dose. Initially, the patient was administered a starting dose of 8 μg of norepinephrine. If the patient experienced hypotension, the dose was adjusted increased by 1 μg for the next patient. If the patient did not experience hypotension, the dose was downward by 1 μg for the next patient. This "Up-and-Down" process continued until sufficient data was collected to estimate the effective dose range. This method allows for rapid adjustments in response to individual variability, enabling us to identify the dose range that most effectively prevents hypotension during spinal anesthesia for cesarean section.

Outcome measurement

The primary finding was to determine the effective doses of prophylactic norepinephrine essential to avoid hypotension following the spinal anesthesia in 90% (ED_{90}) and 50% (ED_{50}) of patients. Hypotension was known as a SBP falling below 80% of baseline, while the goal was to maintain SBP within 95% of baseline. An increase in SBP of 20% or more from baseline was considered hypertension. Successful treatment was identified as achieving an SBP within 95% of baseline within 1 min post-administration. Provided that the SBP kept below 80% of the initial level, 6 mg of ephedrine was provided. Treatment for bradycardia, which is defined as a pulse rate under 50 beats per minute, included the administration of 0.5 mg of atropine. Systematic documentation of maternal consequences, like infusion volume, bleeding, urination, and adverse reactions (like bradycardia, nausea, vomiting, hypertension, and hypotension), was conducted. Furthermore, the study assessed the fetal heart rates prior to and following spinal anesthesia, the Apgar ratings at 1 and 5 min, and the umbilical arterial blood gases.

Statistical analysis

Due to the non-independent and unknown data distribution inherent in the up-and-down study design, theoretical guidelines for precise sample size calculations to estimate the effective dose interval ED_{90} were not applicable [26]. Simulation studies indicate that a sample size of 20–40 patients generally yields stable dose estimates across various scenarios [26]. To enhance the reliability of our results, we included 51 patients in the study. The ED_{50} was determined with a 95% confidence interval (CI) using the up-and-down method. Probit regression analysis was also conducted to estimate both ED_{50} and ED_{90}. Visualization of data was conducted employing version 9.5.1of GraphPad Prism, and statistical analysis was done utilizing version 20.0 of the SPSS program.

Results

Patient recruitment

Figure 1 provides a detailed flow chart outlining the enrollment, exclusion, follow-up, and analysis of participants. Following the application of exclusion criteria and completion of follow-up techniques, 51 out of the 60 patients originally planned for optional cesarean sections using spinal anesthesia fulfilled the last criteria for inclusion and were enrolled in the investigation. Table 1 summarizes maternal demographics and surgical characteristics. Participants average age was 30.55 ± 5.07 years, and mean body mass index (BMI) was 29.12 ± 3.36 kg/m^2. Baseline SBP and DBP were 125.51 ± 6.84 mmHg and 74.65 ± 4.45 mmHg, respectively. The spinal block level ranged from T4 to T6, and the average duration of surgery was 49.20 ± 6.47 min.

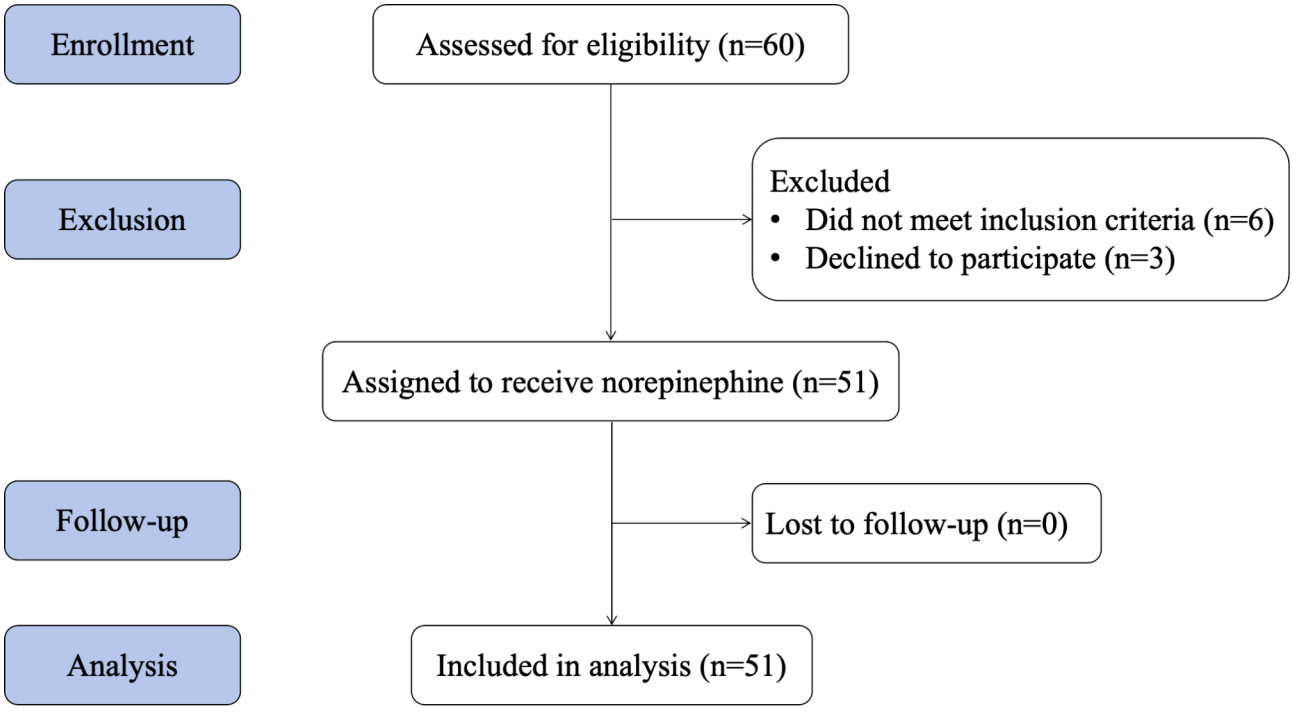

Fig. 1 Flowchart depicting the patient recruitment process, including stages of enrollment, exclusion criteria, follow-up procedures, and final analysis

Table 1 Patient demographics and surgical characteristics

Characteristics	Index ($n=51$)
Age (years)	30.55 ± 5.07
Weight (kg)	76.96 ± 8.37
Height (cm)	162.70 ± 4.85
Body mass index (kg/m^2)	29.12 ± 3.36
Gestation (weeks)	38.21 ± 0.99
SBP at baseline (mmHg)	125.51 ± 6.84
DBP at baseline (mmHg)	74.65 ± 4.45
HR at baseline (beats/min)	84.16 ± 12.57
Block level (T)	T5 (T4, T6)
Induction to delivery (min)	11.20 ± 2.50
Duration of surgery (min)	49.20 ± 6.47

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Data are presented as mean ± SD and median (IQR)

Primary outcomes

Figure 2 illustrates the sequences of patient responses to prophylactic norepinephrine dosages, categorized as effective or ineffective based on the up-and-down sequential technique. Figure 3 presents dose-response curves for prophylactic norepinephrine, which have been obtained using probit regression analysis. Isotonic regression analysis determined the ED_{50} for prophylactic norepinephrine to be 4.05 μg (95% CI: 3.68 to 4.46). Probit regression analysis estimated the ED_{50} to be 3.926 μg (95% CI: 3.362 to 4.422) and the ED_{90} to be 5.35 μg (95% CI: 4.75 to 7.13). Table 2 details the response rates for various prophylactic norepinephrine doses.

Maternal and neonatal outcomes

Patients received a crystalloid pre-load of 365 ml and a crystalloid co-load of 730 ml, as detailed in Table 3. Maternal outcomes are summarized in Table 4. Hypotension occurred in 23 patients (45.10%), while 1 patient experienced hypertension. Additionally, 3 patients reported nausea, 2 experienced vomiting, and 3 exhibited bradycardia. Neonatal outcomes are detailed in Table 5. A range of 3.14 ± 1.88 for umbilical artery base excess values and 7.33 ± 0.04 for pH values were detected. All pH values were within the normal range [27], with no neonates presenting with fetal acidosis (pH < 7.2). At both 1 min and 5 min, all newborns achieved Apgar scores of 8 or above.

Discussion

Our study determined the effective dose of norepinephrine required to prevent hypotension following the spinal anesthesia, establishing the ED_{90} as 5.35 μg (95% CI: 4.75 to 7.13) when administered with a crystalloid co-load. This finding highlights a significant reduction in norepinephrine dose compared to previous studies [13]. The ED_{50} in our study was approximately 4 μg, as estimated by isotonic regression analysis (4.05 μg, 95% CI: 3.68 to 4.46) and probit regression analysis (3.926 μg, 95% CI: 3.362 to 4.422), which is notably lower than ED_{50} values reported in earlier research [28].

Fluid loading, whether used independently or in combination with vasopressors, is a well-established approach for avoiding and managing post-spinal anesthesia

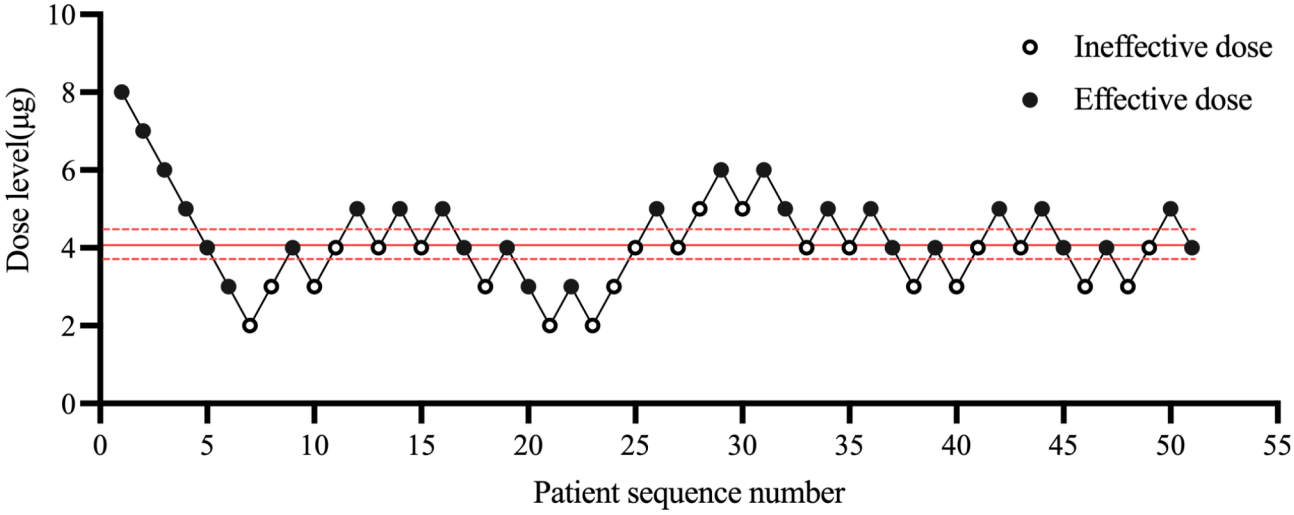

Fig. 2 Graph showing the distribution of patient responses to different norepinephrine bolus doses, categorizing them as either effective or ineffective

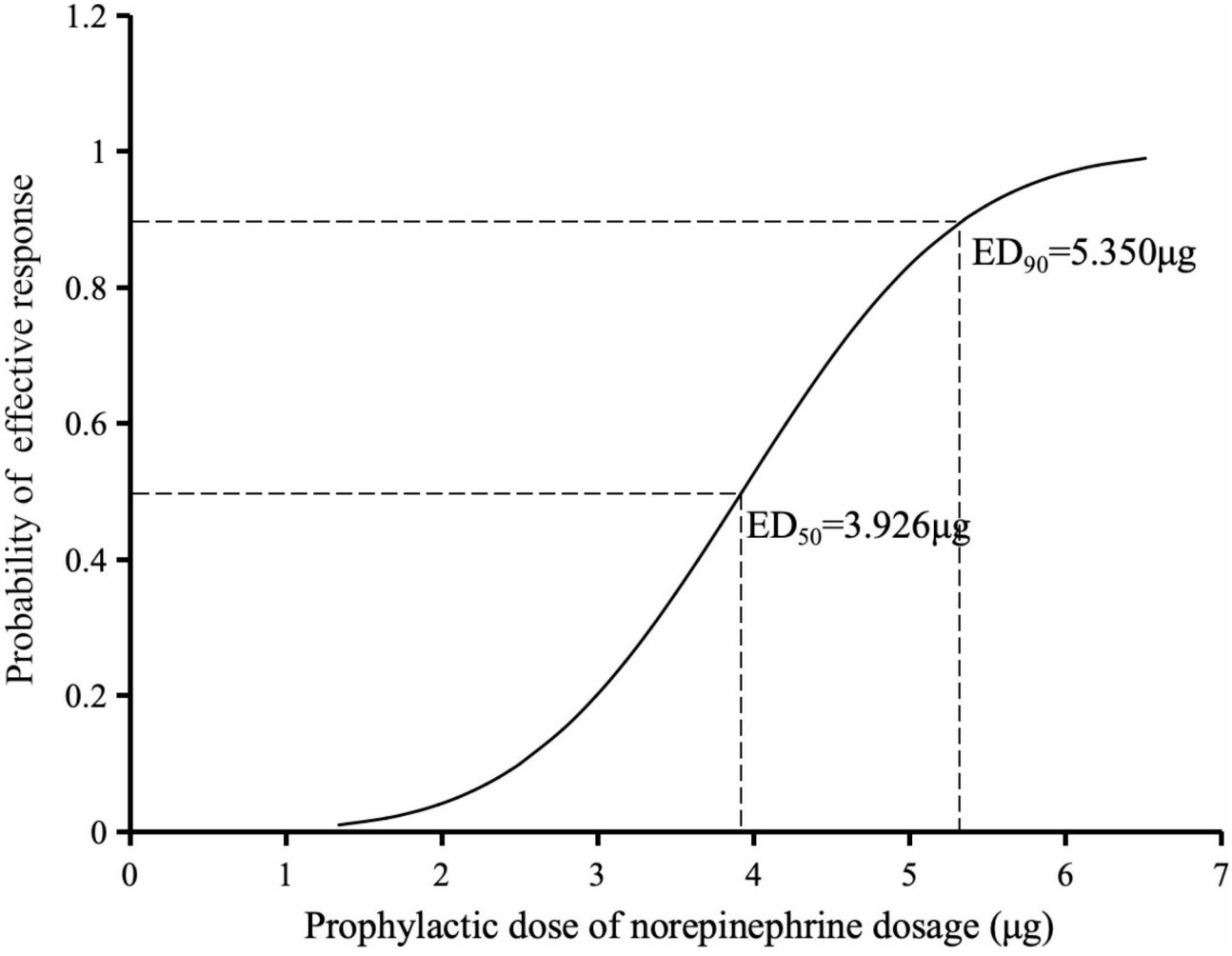

Fig. 3 Dose-response curve for norepinephrine: This graph illustrates the relationship between various norepinephrine dosages and the proportion of participants achieving effective treatment, identified as the restoration of systolic blood pressure (SBP) to within 95% of baseline values. The ED_{50} and ED_{90} values were calculated employing probit regression analysis

Table 2 Response rates for doses of prophylactic norepinephrine

Assigned dose of norepinephrine (ug)	Number of successes	Total number	Response rate (%)
2	0	3	0.00
3	3	11	27.27
4	9	19	47.37
5	11	13	84.62
6	3	3	100.00
7	2	2	100.00
8	1	1	100.00

Data are presented as number (%)

Table 3 Volumes of patient fluid intake and output

Parameters	Index ($n=51$)
Crystalloid pre-load (ml)	365 (332.50, 410.00)
Crystalloid co-load (ml)	730 (665.00, 820.00)
Bleeding volume (ml)	246.08 ± 93.19
Urine volume (ml)	119.61 ± 51.07

Data are presented as mean ± SD and median (IQR)

Table 4 Maternal outcomes

Outcome	Index ($n=51$)
Hypotension	23 (45.10%)
Hypertension	1 (1.96%)
Nausea	3 (5.88%)
Vomiting	2 (3.92%)
Bradycardia	3 (5.88%)

Data are presented as number (%)

Table 5 Neonatal umbilical artery outcomes

Outcome	Index ($n=51$)
PO_2 (mmHg)	21.39 ± 3.27
PCO_2 (mmHg)	51.22 ± 6.14
pH	7.33 ± 0.04
HCO_3^- (mmol/l)	22.65 ± 1.42
Base excess (mmol/l)	-3.14 ± 1.88
Apgar score at 1 min	9.00 (8.00, 9.00)
Apgar score < 7 at 1 min, n (%)	0 (0)
Apgar score at 5 min	10.00 (9.00, 10.00)
Apgar score < 7 at 5 min, n (%)	0 (0)

Data are presented as mean ± SD, median (IQR) and number (%)

hypotension after spinal [29]. Various fluid loading techniques, differing in their nature (crystalloid vs. colloid), time (preload vs. co-load), and volume, have demonstrated efficacy in reducing, but not entirely eradicating, post-spinal hypotension. The Vasopressor usage, therefore, plays a vital role in enhancing outcomes [30]. Chen et al. [31] have proposed that colloid co-loading does not provide any further advantages compared to crystalloid co-loading when used with prophylactic norepinephrine infusions. This supports the recommendation for crystalloid in large co-load volumes, like 10 mL/kg, for optimal outcomes. Our study's use of a 10 mL/kg crystalloid co-load aligns with these findings. While a crystalloid preload can partially address pre-operative hypovolemia and improve cardiac output prior to spinal anesthesia, it often fails to fully maintain systolic blood pressure (SBP) and correct flow time, thus not entirely eliminating post-spinal hypotension [32, 33]. In contrast, a crystalloid co-load offers more efficient growth of volume inside the vessel with slower redistribution [34]. Colloids, owing to their greater molecular size, tend to remain in the intravascular space longer compared to crystalloids, enhancing intravascular volume growth and osmotic pressure [35, 36]. Recently, a study conducted by Theodoraki et al. revealed that the incidence of hypotension after spinal anesthesia was equally low whether utilizing either colloid preload or crystalloid co-load in conjunction with infusion of prophylactic norepinephrine [37]. This finding underscores the possible benefits of employing crystalloids in this particular scenario.

While prophylactic infusion of vasopressors is commonly recommended to manage spinal hypotension and stabilize hemodynamic fluctuations, it is connected with an elevated risk of reactive hypertension [3]. In contrast to bolus regimens, infusion procedures often need a greater total dosage of phenylephrine to sustain maternal arterial blood pressure at the initial level during the pre-delivery interval [38]. The bolus approach allows for the immediate administration of an efficient dosage of phenylephrine, which can rapidly restore maternal vascular resistance throughout spinal blockade. As a result, many anesthesiologists prefer bolus administration and are accustomed to providing frequent dosages rather than initiating an infusion throughout spinal anesthesia [39]. In this study, we employed a norepinephrine bolus, a method familiar to most anesthesiologists. Currently, there is limited research specifically defining the ED_{50} and ED_{90} of norepinephrine used with crystalloid co-loading for optional cesarean delivery using spinal anesthesia. Norepinephrine boluses application in conjunction with crystalloid co-loading for hypotension management in this context remains inadequately explored.

Previous studies have provided varying estimates for the ED_{90} of prophylactic norepinephrine combined with crystalloid co-loading. ED_{90} values for prophylactic norepinephrine boluses were determined by Onwochei et al. [13]. to be 5.49 μg (95% CI: 5.15–5.83 μg) and 5.80 μg (95% CI: 5.01–6.59 μg). Their study utilized lactated Ringer's solution for crystalloid preload, introduced as a bolus infusion at 10 mL/kg with a maximum volume of 1000 mL via a pressure bag set at 250 mm Hg. It is important to note that their study focused on preload rather than co-load. Network meta-analyses have indicated that crystalloid co-loading is more effective than crystalloid

preload in managing spinal hypotension during elective cesarean Sect. [5]. Preload volumes can rapidly redistribute into the interstitial space due to sympathetic blockade, which may lead to atrial chamber distension and increased secretion of atrial natriuretic peptide [40]. This peptide causes peripheral vasodilation and diuresis. In contrast, co-loading can reduce these effects by minimizing fluid redistribution into the interstitial space and decreasing hydrostatic pressure during spinal-induced vasodilation [37, 41]. Guo et al. [22] discovered the ED_{90} for a bolus of prophylactic norepinephrine, administered with hydroxyethyl starch (130/0.4) co-load, to be 8.0 μg (95% CI: 7.1 to 11.0 μg). This higher ED_{90} might be attributable to the relatively smaller co-load volume of 500 mL used in their study. Their findings also suggested no significant difference between colloid and crystalloid co-loading [31].

This discussion integrates findings from our study with existing literature, highlighting the relevance of crystalloid co-loading and bolus administration in managing spinal hypotension during cesarean sections. Further research is needed to refine these parameters and optimize clinical practice. This investigation has some restrictions that should be considered. First, the investigation concentrated exclusively on the initial incidence of hypotension following spinal anesthesia and did not account for subsequent episodes throughout the surgical procedure, which may have distinct response patterns. Second, variability in individual sensitivity to vasoactive agents could have influenced the study's outcomes. Third, the geographic homogeneity of the study population may limit the generalizability of the results to more diverse and broader populations. Finally, the lack of a control group constrains our ability to establish definitive causal relationships.

This investigation has some restrictions that should be considered. First, the investigation concentrated exclusively on the initial incidence of hypotension following spinal anesthesia and did not account for subsequent episodes throughout the surgical procedure, which may have distinct response patterns. Second, the high incidence of hypotension (45.10%) observed in our study warrants further discussion. One contributing factor may be the pharmacodynamic properties of norepinephrine, which has an onset time of 1–2 min. In our study, a treatment was considered successful if systolic blood pressure (SBP) returned to ≥ 95% of baseline within 1 min after norepinephrine administration. This strict criterion may have categorized cases as hypotensive before the drug fully took effect. Furthermore, norepinephrine's short duration of action increases the likelihood of transient hypotensive episodes between doses, especially if redosing is delayed. This time-sensitive nature of norepinephrine administration reflects the challenges in managing maternal hemodynamics during spinal anesthesia. These factors likely contributed to the high incidence of hypotension in our study, highlighting an inherent limitation of the study protocol and the practical challenges in optimizing maternal hemodynamics with vasopressor boluses. Third, variability in individual sensitivity to vasoactive agents could have influenced the study's outcomes. Finally, the geographic homogeneity of the study population may limit the generalizability of the results to more diverse and broader populations.

In conclusion, this study determines that the ED_{90} of norepinephrine administered with a crystalloid co-load is 5.35 μg (95% CI: 4.75 to 7.13), based on probit regression analysis. The ED_{50} values for a single norepinephrine bolus to avoid hypotension throughout elective cesarean section were found to be 4.05 μg (95% CI: 3.68 to 4.46) using the up-and-down method and 3.926 μg (95% CI: 3.362 to 4.422) according to the probit regression model.

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Author contributions
CX and PZ conducted the majority of the experiments and wrote the manuscript. CD, JZ and HW conceived and designed the study. QL, and ZZ performed the data analysis. FY collected the data. LC and HN coordinated and supervised the experiments. All authors read and approved the final manuscript.

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Data availability
Access to the datasets utilized and/or analyzed in the present work may be obtained from the corresponding author upon an acceptable request.

Declarations

Ethics approval and consent to participate
The present study was approved by the Research Ethics Board of the Third People's Hospital of Bengbu (Anhui, China) and registered in the ClinicalTrials.gov (NCT06498115, 2024/07/11). All of the participants who participated in the study provided written informed consent at the time of enrolment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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