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ORIGINAL RESEARCH

Prophylactic Norepinephrine and Phenylephrine Boluses to Prevent Postspinal Anesthesia Hypotension During Cesarean Section: A Randomized Sequential Allocation Dose-Finding Study

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Background: Norepinephrine and phenylephrine are widely used for obstetric anesthesia. Our central objective was to determine the ED (effective dose) 90 and potency ratio of prophylactic norepinephrine and phenylephrine boluses for preventing postspinal anesthesia hypotension during cesarean section.

Methods: Patients scheduled for elective cesarean section (n = 80) were randomly allocated to receive prophylactic norepinephrine (NE) or phenylephrine (PE) boluses immediately after induction of spinal anesthesia. An initial dose of NE (3 μg) and PE (37.5 μg) was given to the first patient, and an up-and-down sequential allocation method was used to determine the next dose level according to the responses (the effectiveness for preventing postspinal anesthesia hypotension [defined as SBP < 80% of baseline value]). Primary outcomes were ED90 and the potency ratio of prophylactic norepinephrine and phenylephrine boluses. Secondary outcomes were the incidence of postspinal anesthesia hypotension, severe postspinal anesthesia hypotension, nausea, vomiting, bradycardia, hypertension, umbilical artery blood gas values, and Apgar scores.

Results: The ED90 values for prophylactic norepinephrine and phenylephrine boluses were 8.0 μg (95% CI 7.1–11.0 μg) and 90.9 μg (95% CI 82.0–123.9 μg), respectively. The estimated relative potency ratio was 11.4:1. The incidence of bradycardia was lower in the NE group (2.5% vs 20%, $P = 0.034$). Other outcomes were comparable between the two groups.

Conclusion: An 8-μg prophylactic bolus of norepinephrine and a 90-μg prophylactic bolus of phenylephrine can effectively prevent postspinal anesthesia hypotension in patients during cesarean section.

Keywords: cesarean section, norepinephrine, phenylephrine, postspinal anesthesia hypotension

Introduction

Spinal anesthesia is used during cesarean section to provide rapid onset and dense block of motor and sensory nerves, intraoperative analgesia, and help patients remain conscious.[1,2] To prevent and treat postspinal anesthesia hypotension during cesarean section, vasopressors are recommended. Vasopressors (especially potent α-adrenergic receptor agonists) help offset the decrease in arteriolar dilation and peripheral vascular resistance caused by sympathetic nerve blockade after spinal anesthesia and may be associated with decreased incidence of neonatal acidosis.[3,4] The vasopressors norepinephrine and phenylephrine, both widely used for obstetric anesthesia, have a fast onset and short duration of action, do not readily cross the placenta, and can be administered via intravenous bolus or infusion.[5–7]

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Maternal hypotension can occur within 3–6 min following spinal anesthesia. A prophylactic vasopressor infusion or bolus given after induction of spinal anesthesia may help offset arterial vasodilation.[8] In a recent consensus statement, prophylactic application of vasopressors was recommended for routine use. Compared to therapeutic measures, this prophylactic intervention can reduce the incidence of postspinal anesthesia hypotension, nausea, and vomiting both before and after delivery, and provide better hemodynamic stability during cesarean section.[9]

Few studies have focused on the preventive application of norepinephrine and phenylephrine boluses for postspinal anesthesia hypotension. However, prophylactic norepinephrine and phenylephrine boluses are still a choice of approach in some medical institutions. Here, we used an up-and-down sequential allocation method to determine the ED (effective dose) 90 and potency ratio of prophylactic norepinephrine and phenylephrine boluses combined with 6% hydroxyethyl starch (130/0.4) co-load for postspinal anesthesia hypotension during cesarean section.

Methods

We obtained Institutional Review Board (IRB # KYLL-2021-921) approval from the General Hospital of Ningxia Medical University, Yinchuan, China, and conducted this randomized sequential allocation dose-finding study between Sep 2022 and Jan 2023. The study adhered to the Declaration of Helsinki and all applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. Before enrollment, all patients who participated in the study provided written informed consent. The study was registered at clinicaltrials.gov under the identifier NCT05035888 on September 3, 2021 (Principal Investigator: Yi Chen).

We recruited singleton full-term pregnancy patients aged 18–40 who were scheduled for elective cesarean section under spinal anesthesia and had an American Society of Anesthesiologists physical status of 1 or 2. Patients were excluded if they had a body mass index (BMI) >35 kg/m^2, eclampsia or preexisting hypertension (baseline systolic blood pressure ≥160 mmHg), a known allergy to hydroxyethyl starch, a developmental anomaly, coagulation or renal function disorders, hemoglobin <7 g/dL, or fetal distress.

Baseline maternal systolic blood pressure (SBP) and heart rate (HR) were determined a total of three times and obtained in the supine position with left uterine displacement and resting state. SBP and HR were recorded at one-minute intervals prior to delivery and again at five-minute intervals after induction of spinal anesthesia. Norepinephrine or phenylephrine bolus, compound sodium chloride (0.85% NaCl, 0.03% KCl, and 0.033% $CaCl_2$), and 6% hydroxyethyl starch (130/0.4) injection were infused by an indwelling 18-gauge intravenous (IV) catheter in the arm. No premedication or fluid preload was given. Hyperbaric bupivacaine (0.5% w/v 12.5 mg) was injected for spinal anesthesia at what was estimated to be the interspace of L3-4 at the lateral decubitus position; then, the patient was placed in a supine position with approximately 15° of left uterine displacement. A sterile needle was used to assess sensory block height. Cesarean section was performed once sensory block exceeded T6.

Patients were randomly assigned to receive prophylactic norepinephrine (NE group) and phenylephrine (PE group) boluses combined with 500 mL 6% hydroxyethyl starch (130/0.4) co-load immediately after induction of spinal anesthesia. Randomization was performed using a computer-generated randomization sequence, and allocations were placed into opaque, sealed envelopes. Patients and researchers (not involved in anesthesia management) were blinded to the grouping of patients. Norepinephrine and phenylephrine were prepared at 1 μg/mL and 12.5 μg/mL concentrations, respectively, by dilution in 0.9% normal saline.

An initial 3-μg and 37.5-μg prophylactic bolus dose of norepinephrine and phenylephrine was administered simultaneously with spinal anesthesia for the first patient according to grouping. The up-and-down sequential allocation method was used to determine the next dose level according to the responses (the effectiveness for preventing postspinal anesthesia hypotension [defined as SBP < 80% of baseline value] within 15 min during cesarean section under spinal anesthesia) of previous patients. A gradient dose of 1 μg of norepinephrine and 12.5 μg of phenylephrine was administered according to grouping. Three identical and consecutive doses were effective for responses, and a gradient dose was decreased to the next lower dose level. Patients received a continuous compound sodium chloride infusion (6 mL/kg/h) after delivery.

Primary outcomes included the doses of prophylactic norepinephrine and phenylephrine boluses that would be effective in preventing postspinal anesthesia hypotension in 90% (ED90) and their potency ratio. Secondary outcomes were the incidence of the postspinal anesthesia hypotension and severe postspinal anesthesia hypotension (defined as SBP <80% and 60% of

baseline value, respectively, treated with a 6-μg IV bolus of NE or a 75-μg IV bolus of PE according to grouping), nausea or vomiting, bradycardia (HR <60 BPM, handled with 0.5 mg IV atropine), and hypertension (SBP >120% of baseline value). Neonatal outcomes, including umbilical artery blood gas values and Apgar scores, were also recorded.

Statistical Analysis

Because of nonindependent data distribution, accurate sample size estimation is difficult; however, stable estimates for ED calculations of the target dose were used to enroll 20–40 patients for the up-and-down method.[10] Forty patients were allocated to each group based on the stopping rule.

SPSS version 22.0 (IBM SPSS, Inc., Chicago, IL, USA) was used for data analysis, and values of P <0.05 were considered significant. The Kolmogorov–Smirnov test was used to examine the normality of continuous variables. The unpaired t-test and the Mann–Whitney U-test were used to analyze normally distributed variables (presented as mean ± SD) and non-normally distributed variables (presented as median ([interquartile range, IQR]), respectively. A Chi-square test was used to analyze categorical variables (presented as number [%]). A probit regression model providing a conditional probability of an observation belonging to a particular category was used to determine the ED90 for effective prophylactic norepinephrine and phenylephrine doses of boluses.

Results

Eighty patients were randomly allocated to the PE and NE groups and were included in the final data analysis. A flow diagram detailing patient enrollment is shown in Figure 1. Patient characteristics, including baseline SBP and HR, were comparable between the two groups (Table 1).

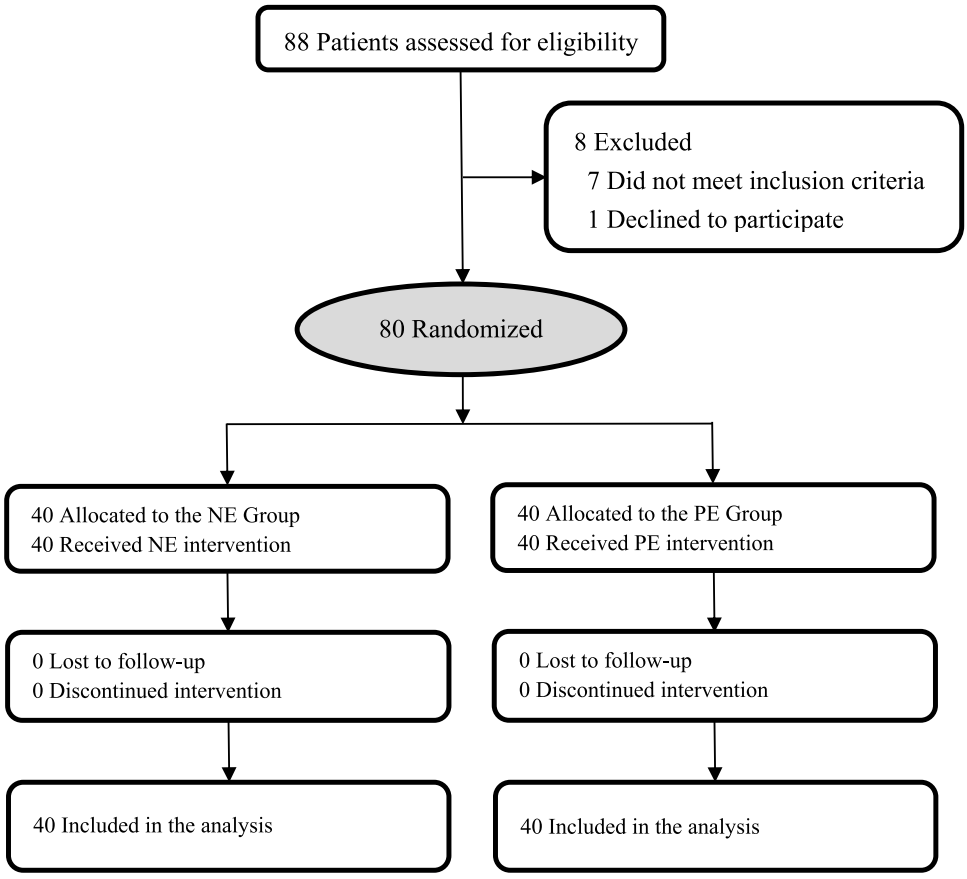

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1 Patient Characteristics

	NE Group (n = 40)	PE Group (n = 40)	*P* value
Age (yr)	31.7 ± 4.0	31.8 ± 4.5	0.884
Height (cm)	163.1 ± 4.2	161.2 ± 5.9	0.118
Weight (kg)	71.6 ± 10.0	72.7 ± 9.7	0.596
BMI (kg/m^2)	26.9 ± 3.6	28.5 ± 3.4	0.177
Gestational age (weeks)	38 (37, 39)	38 (37, 40)	0.431
Baseline characteristics			
Systolic blood pressure (mmHg)	119.2 ± 12.5	119.2 ± 12.4	0.715
Heart rate (bpm)	93.4 ± 10.7	95.9 ± 14.2	0.097
Block height	T6 (T5, T6)	T6 (T4, T6)	0.737
Spinal anesthesia to fetal delivery interval (min)	13.9 ± 2.7	14.7 ± 4.4	0.773
Skin incision to fetal delivery interval (min)	2.7 ± 0.9	3.4 ± 1.6	0.900
Estimated blood loss (mL)	400 (400, 500)	400 (400, 400)	0.502
Length of postoperative stay (days)	3.5 ± 0.8	3.5 ± 0.7	0.257

Note: Data are showed as mean ± SD and median (IQR).
Abbreviations: NE, norepinephrine; PE, phenylephrine; BMI, body mass index.

Patients with effective or ineffective responses to the prophylactic bolus dose of norepinephrine and phenylephrine are shown in Figure 2A and B. The response rates for doses of prophylactic norepinephrine and phenylephrine boluses are shown in Table 2.

The dose–response curve of a prophylactic bolus dose of norepinephrine or phenylephrine for preventing postspinal anesthesia hypotension is shown in Figure 3. The ED90 values were 8.0 μg (95% CI 7.1–11.0 μg) and 90.9 μg (95% CI 82.0–123.9 μg), respectively, for prophylactic bolus of norepinephrine and phenylephrine. The estimated relative potency ratio was 11.4:1.

The incidence of bradycardia was lower in the NE group (2.5% vs 20%, $P = 0.034$). Maternal adverse events, including postspinal anesthesia hypotension, nausea and vomiting, and hypertension and neonatal outcomes were comparable between the two groups (Table 3 and Table 4).

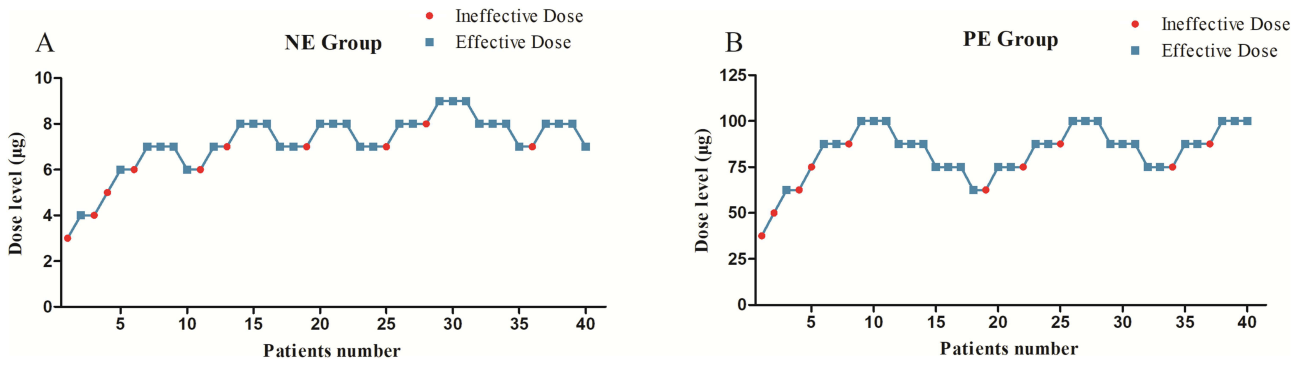

Figure 2 Patients with effective or ineffective response to the prophylactic bolus dose of norepinephrine ((**A**); NE Group) or phenylephrine ((**B**); PE Group).

Table 2 Response Rates for Doses of Prophylactic Phenylephrine and Norepinephrine Boluses

Assigned Dose (ug)	Number of Successes	Number of Patients	Response Rate (%)
Phenylephrine			
37.5	0	1	0.0
50	0	1	0.0
62.5	2	4	50.0
75	7	10	70.0
87.5	12	15	80.0
100	9	9	100.0
Norepinephrine			
3	0	1	0.0
4	1	2	50.0
5	0	1	0.0
6	2	4	50.0
7	9	13	69.2
8	12	14	85.7
9	5	5	100.0

Discussion

Spinal anesthesia can lead to hypotension in patients undergoing cesarean section. To determine the effective bolus doses of norepinephrine and phenylephrine for preventing postspinal anesthesia hypotension, we performed a randomized sequential allocation dose-finding study.

Few previous studies have assessed the ED90 of prophylactic norepinephrine and phenylephrine boluses for the prevention of postspinal anesthesia hypotension. Using the truncated Dixon and Mood method and the isotonic regression method, Onwochei et al[11] found that the ED90 of prophylactic norepinephrine boluses were 5.49 μg (95% CI 5.15–5.83 μg) and 5.80 μg (95% CI 5.01–6.59 μg) to prevent postspinal anesthesia hypotension. We found that for a prophylactic bolus of norepinephrine, the ED90 value was 8.0 μg (95% CI 7.1–11.0 μg). The lower ED90 of prophylactic norepinephrine boluses found by Onwochei et al may have resulted from their applied fluid infusion rate (15 to 30 mL/min). In our study, a fixed volume of 500 mL 6% hydroxyethyl starch (130/0.4) co-load was applied. Because fluid co-load contributes to increased intravascular volume, which coincides with the vasodilation effect after induction of spinal anesthesia,[12] a higher volume co-load may better compensate for this effect. Tanaka et al[13] used a logistic model with non-log-transformed doses to explore the ED95 of intermittent boluses of phenylephrine and estimated that 159 μg (95% CI 122–371 μg) with a bolus of at least 122 μg was needed to prevent pre-delivery spinal-induced hypotension and/or nausea. They also set the target value of SBP to ≥100% of baseline. As this standard is much stricter, their estimated ED95 of prophylactic phenylephrine boluses was higher than in our study (97.6 μg [95% CI 87.2–145.5 μg]). Likewise, they considered that the suggested prophylactic phenylephrine bolus was higher than standard practice (100 μg).

In a random-allocation, graded dose–response study by Ngan Kee et al,[14] the estimated ED50 values of norepinephrine and phenylephrine boluses to treat the first episode of postspinal anesthesia hypotension for cesarean delivery were 10 μg (95% CI 6–17 μg) and 137 μg (95% CI 79–236 μg), respectively, and the estimated dose of norepinephrine (8 μg) equivalent to phenylephrine (100 μg), and its relative potency ratio was 13.1:1. Mohta et al[5] used the up-and-down sequential allocation method to evaluate the dose–response comparison of norepinephrine and phenylephrine by IV

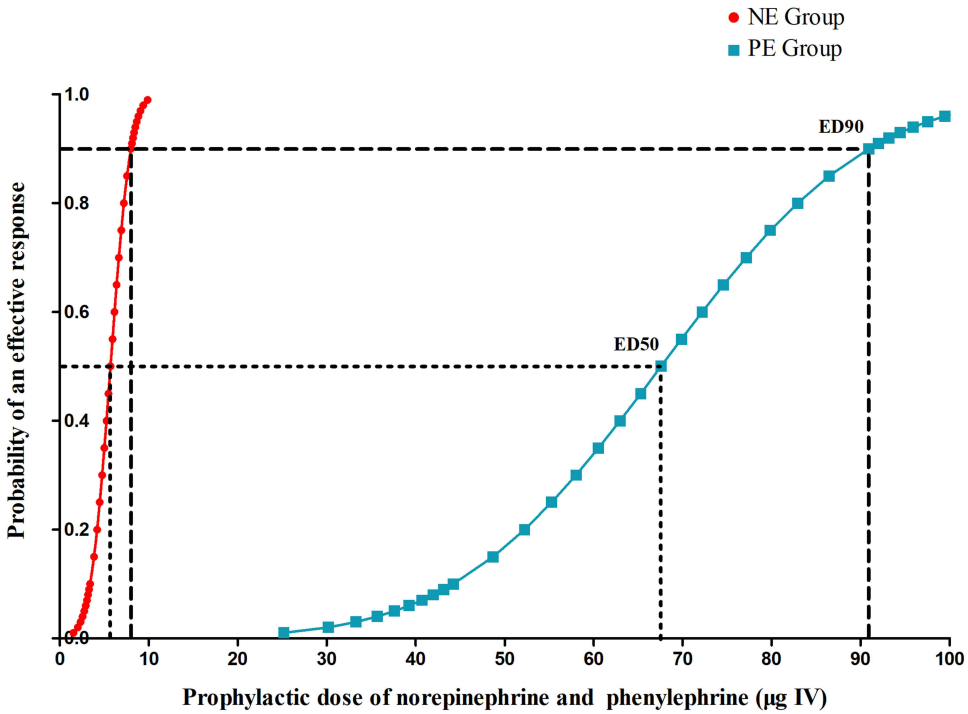

Figure 3 The dose–response curve of a prophylactic bolus dose of norepinephrine or phenylephrine for preventing postspinal anesthesia hypotension.
Abbreviation: ED, effective dose.

bolus, and the ED95 for postspinal anesthesia hypotension and reported estimates of 3.7 μg (95% CI 3.5–4.7 μg) and 43.1 μg (95% CI 39.5–65.0 μg), respectively. They found a relative potency ratio of 11.3:1. Our finding of a relative potency ratio of 11.4:1 for prophylactic norepinephrine and phenylephrine boluses is similar to the therapeutic boluses reported by both Ngan Kee and Mohta et al. Notably, Ngan Kee et al[14] used a nonlinear regression rather than the up-and-down sequential allocation method to evaluate the ED 50. Despite using an identical up-and-down sequential allocation method to evaluate the ED 90 and their similar relative potency ratio relative to our study, Mohta et al[5] found that the ED90 of norepinephrine and phenylephrine was smaller for therapeutic boluses.

Currently, phenylephrine is considered the first-line vasopressor for the prevention of postspinal anesthesia hypotension.[4] Notably, phenylephrine is often associated with a dose-related, baroreceptor-mediated decrease in heart rate (HR) and a subsequent reduction in cardiac output (CO).[9] This effect can occur even at modest doses, even if blood

Table 3 Adverse Events

	NE Group (n=40)	PE Group (n=40)	*P* value
Bradycardia, n (%)	1 (2.5)	8 (20.0)	0.034
Postspinal anesthesia hypotension, n (%)	11 (27.5)	11 (27.5)	1.000
Severe postspinal anesthesia hypotension, n (%)	0 (0.0)	1 (2.5)	1.000
Number of vasopressor boluses	1 (1, 2)	2(1, 3)	0.332
Nausea, n (%)	3 (7.5)	4 (10.0)	1.000
Vomiting, n (%)	2 (5.0)	1 (2.5)	1.000
Hypertension, n (%)	2 (5.0)	1 (2.5)	1.000

Note: Data are presented as number (%).
Abbreviations: NE, norepinephrine; PE, phenylephrine.

Table 4 Neonatal Outcomes

	NE Group (n = 40)	PE Group (n = 40)	*P* value
pH	7.36 ± 0.03	7.35 ± 0.03	0.456
pH < 7.2, n (%)	0 (0.0)	0 (0.0)	1.000
PCO_2 (mmHg)	41.5 ± 5.5	40.8 ± 5.7	0.731
PO_2 (mmHg)	21.5 ± 4.9	22.8 ± 5.0	0.374
BE (mmol/L)	−2.7 ± 1.5	−2.9 ± 1.5	0.579
Apgar score, 1 min	9 (9, 9)	9 (9, 9)	1.000
<7 at 1 min, n (%)	0 (0.0)	1 (1.5)	1.000
Apgar score, 5 min	10 (10, 10)	10 (9, 10)	1.000
<7 at 5 min, n (%)	0 (0.0)	0 (0.0)	1.000

Note: Data are presented as mean ± SD, number (%) and median (IQR).
Abbreviations: NE, norepinephrine; PE, phenylephrine; PCO_2, partial pressure of carbon dioxide; BE, base excess; PO_2, partial pressure of oxygen.

pressure has not exceeded baseline.[15] Maternal CO, rather than blood pressure, correlates closely with uteroplacental blood flow.[16] However, reduction in CO caused by the application of phenylephrine generally shows no negative impact on fetal acid–base status or Apgar scores in healthy patients and it is frequently maintained higher than baseline levels due to the compensatory increase in CO following sympathetic nerve blockade.[2] In addition, the reduced HR may return to baseline (increase) after ceasing administration of phenylephrine in most patients and seems to be negligible in healthy patients.[17,18] However, significant alterations in HR and CO remain a concern in particular conditions where the patient and fetus are already compromised, such as maternal cardiac disease, preeclampsia, uteroplacental insufficiency, or fetal distress.[11,17]

In contrast, the effect of norepinephrine on CO and HR is considered approximately neutral, as positive chronotropic action caused by weak β-adrenergic properties counteracts the negative chronotropic action caused by strong α-adrenergic properties.[6,19] Our previous randomized, controlled, dose-finding trial indicated that the norepinephrine prophylactic infusion effectively reduced the incidence of hypotension induced by spinal anesthesia and maintained the SBP closer to the baseline.[20] Because norepinephrine better maintains CO, reduces the incidence of bradycardia, and improves hemodynamic stability, it was recently put forward as an advantageous alternative to phenylephrine.[21] We found that the incidence of bradycardia was significantly lower in the norepinephrine group relative to the PE group. However, other maternal adverse events and neonatal outcomes were comparable between the two groups. Norepinephrine may be an appropriate choice for patients with low baseline HR or compromised cardiac function.[22]

Our study has some limitations. Because of their short duration of action, prophylactic norepinephrine and phenylephrine boluses may not be adequate to prevent postspinal anesthesia hypotension for the length of an operation. Prophylactic norepinephrine and phenylephrine infusion may provide better hemodynamic stability relative to bolus, despite exposure to more vasopressors. A fixed volume of 500 mL 6% hydroxyethyl starch (130/0.4) co-load may inadequately decrease the incidence rate of postspinal anesthesia hypotension and provide hemodynamic stability. Future studies investigating the optimal volume of colloid co-load are warranted.

Conclusion

Prophylactic norepinephrine and phenylephrine boluses can effectively prevent the occurrence of postspinal anesthesia hypotension. An 8 μg and 90 μg prophylactic bolus of norepinephrine and phenylephrine effectively prevented postspinal anesthesia hypotension for 90% of patients during cesarean section.

Data Sharing Statement

The data that support the study findings are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare no conflict of interest.

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