ORIGINAL CLINICAL RESEARCH REPORT

CME

Optimal Infusion Rate of Norepinephrine for Prevention of Spinal Hypotension for Cesarean Delivery: A Randomized Controlled Trial, Using Up-Down Sequential Allocation

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BACKGROUND: Norepinephrine has recently been suggested to be as effective as phenylephrine for the prevention of hypotension after spinal anesthesia for cesarean delivery. Moreover, compared to phenylephrine, norepinephrine may be superior in maintaining heart rate (HR) and consequently, cardiac output (CO). A recent study demonstrated that norepinephrine given as a single intravenous bolus is approximately 13 times more potent than phenylephrine. However, it is uncertain whether this finding can be applied when these vasopressors are administered as infusions. Therefore, the optimum infusion rate of norepinephrine remains unknown. We aimed to determine the median effective dose (ED_{50}; defined as the rate of vasopressor infusion required to prevent spinal hypotension in 50% of subjects) of both drugs needed to maintain maternal systolic blood pressure within 20% of the baseline after spinal anesthesia for cesarean delivery and to derive the relative potency ratio.

METHODS: Sixty healthy patients undergoing elective cesarean delivery with standardized spinal anesthesia were randomized into 2 groups. The first patient in group 1 received phenylephrine 1200 µg in normal saline 0.9% w/v 60 mL at 60 mL/h infusion rate (20 $\mu g.min^{-1}$). The first patient in group 2 received norepinephrine 96 µg in normal saline 0.9% w/v 60 mL at 60 mL/h infusion rate (1.6 $\mu g.min^{-1}$). Using up-down sequential allocation technique, the vasopressor dose for every subsequent patient was determined by the response in the previous patient. If effective, the next patient received a dose reduced by 150 µg of phenylephrine (2.5 $\mu g.min^{-1}$) or 12 µg (0.2 $\mu g.min^{-1}$) of norepinephrine. If ineffective, the dose for the next patient was increased by the same amount. The ED50s were determined according to the Dixon-Massey formula. Stroke volume (SV), HR, and CO were also measured.

RESULTS: The ED_{50} was 12.7 $\mu g.min^{-1}$ (95% CI, 10.5–14.9) for phenylephrine and 1.01 $\mu g.min^{-1}$ (95% CI, 0.84–1.18) for norepinephrine, giving a potency ratio of 12.6 (95% CI, 9.92–15.9). HR, SV, and CO did not differ between the groups.

CONCLUSIONS: Norepinephrine is more potent than phenylephrine by a factor of approximately 13 when administered as infusion for equivalent maternal blood pressure control. Based on these findings, we recommend a variable rate prophylactic infusion of norepinephrine to be initiated at 1.9 to 3.8 µg.min−1 for the management of hypotension during cesarean delivery under spinal anesthesia. (Anesth Analg 2025;141:17–25)

KEY POINTS

- **Question:** What is the optimal infusion rate of norepinephrine for prevention of hypotension after spinal anesthesia for cesarean delivery?
- **Findings:** A relative potency ratio of norepinephrine: phenylephrine is 12.6 (95% confidence interval [CI], 9.92–15.9) when administered as an infusion and the median effective dose (ED_{50}) of norepinephrine is 1.01 $\mu g.min^{-1}$.
- **Meaning:** Norepinephrine infusion initiated at a rate of 1.9 to 3.8 $\mu g.min^{-1}$ can serve as a safe alternative to phenylephrine for prevention of hypotension after spinal anesthesia for cesarean delivery.

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The prophylactic use of a vasopressors is considered the most effective method for preventing spinal hypotension during cesarean delivery. Based on the best supporting evidence, the international consensus statement[1] on the management of spinal hypotension during cesarean delivery recommends phenylephrine administered as an infusion to be the most appropriate vasopressor. However, vasopressors with β-adrenergic receptor agonist activity may offer a better hemodynamic profile than phenylephrine which is associated with dose-related reflex bradycardia and a corresponding decrease in cardiac output (CO). Comparative studies[2,3] have demonstrated norepinephrine to be as effective as phenylephrine for maintaining blood pressure (BP) and associated with an increased heart rate (HR) and consequent improvement in CO. The direct positive chronotropic effect of norepinephrine offsets the baroreceptor-mediated reflex bradycardia, resulting in a preservation of HR and CO. These positive findings have prompted further studies to investigate the appropriate dose of norepinephrine for this purpose. A subsequent dose-response study[4] showed that the calculated potency ratio for norepinephrine: phenylephrine was 13.1 (95% confidence interval [CI], 10.4–15.8) when given as a single intravenous bolus for restoring BP in patients undergoing cesarean delivery under spinal anesthesia. However, it is uncertain whether this potency ratio of these vasopressors can be extrapolated to its use by infusion.

The objective of this prospective randomized controlled trial using a sequential allocation methodology was to determine the median effective dose (ED_{50}) of norepinephrine and phenylephrine, and their relative potency ratio to derive the optimal infusion rate of norepinephrine for prevention of spinal hypotension during cesarean delivery. The ED_{50} is defined as the rate of vasopressor infusion required to prevent spinal hypotension in 50% of subjects.

METHODS

Study Design

This was a single center, prospective, randomized, patient—clinician—evaluator blinded, up-down sequential allocation study. The trial (HMC—IRB 16192/16) was approved by the Institutional Review Board (IRB) and Ethical Committee of Hamad Medical Corporation of Qatar and was prospectively registered in the Australian New Zealand Clinical Trials Registry (ANZCTR registration No. ACTRN12618000244202; principal investigator: Dr M. Kocarev, MD, DESAIC, date of registration: February 15, 2018). This article adheres to the applicable Consolidated Standards Of Reporting Trials (CONSORT) guidelines. The study was executed from February 18, 2018 to March 20, 2018, at the largest government-sponsored maternity hospital in Qatar. All patients provided written informed consent.

Study Population

Sixty parturients older than 18 years with an American Society of Anesthesiologists (ASA) physical status II, body mass index (BMI) 25 to 40 kg/m^2, height 150 to 180 cm, normal singleton pregnancy beyond 36 weeks' gestational age, scheduled for elective cesarean delivery under spinal anesthesia were included in the study. Exclusion criteria included the onset of labor, patients with gestational hypertension, history of diabetes, baseline arterial BP >140/90, or HR <60 or >110 beats per minute, cardiovascular and cerebrovascular problems, fetal abnormalities, and patients taking monoamine oxidase inhibitors or tricyclic antidepressants.

Computer-generated codes were used to randomize the 2 study groups into 15 blocks of 4 patients with a 1:1 ratio. One of the investigators, who did not have any other role in performing the study, was responsible for the coded randomization of patients as well as determining and preparing the exact dose of each drug. Both vasopressors, phenylephrine hydrochloride, and norepinephrine bitartrate, were made up in identical 60-mL syringes (labeled as the study drug) to a total volume of 60 mL using normal saline 0.9% w/v. A SyramedμSP6000 (Arcomed AG Medical Systems) syringe driver infusion pump was used at a fixed rate of 60 mL/h throughout the study period. The anesthetist assigned for the routine clinical management of the patient had no involvement in the study and was unaware of the contents of the syringe. Moreover, the investigator responsible for data collection was also unaware of the contents of the syringe.

Study Procedure

All the patients were administered pantoprazole 40mg orally as routine antacid prophylaxis on the morning of the surgery on the ward. Intravenous access was established with a 16-G cannula in the left hand, but no fluid or vasopressor infusion was commenced at that time. On arrival to the operating theater, patients were placed in a supine position with a left lateral tilt, and standard monitoring was initiated which included electrocardiography, noninvasive BP cuff (NIBP) applied on the right arm and pulse oximetry. A noninvasive hemodynamic monitoring system, ClearSight (Edwards Lifesciences), was attached to the left index finger using a dedicated finger sensor. NIBP was used to monitor BP and guide appropriate intervention as per the study protocol. The ClearSight device was used for

measurements of stroke volume (SV), systemic vascular resistance (SVR), and CO. Baseline systolic BP, HR, CO, SV, and SVR were defined as a mean of 3 consecutive measurements taken 3 minutes apart. Patients were then placed in the sitting position and administered a spinal injection of hyperbaric bupivacaine 0.5% w/v 12.5 mg, with fentanyl 15 µg using a 26-G Whitacre needle in the L3–L4 or L4–L5 interspace by the anesthetist who was involved in the patient's direct clinical care. After intrathecal injection, an infusion of the allocated vasopressor and Ringer Lactate (500 mL) at a rate of 999 mL/h using a volumetric infusion pump (Imed Gemini PC-2TX, Alaris Medical Systems) were initiated through the intravenous line attached to a unidirectional valve. All parameters were recorded every minute until the delivery of the fetus. The cranial sensory levels of subarachnoid block were tested with cold sensation using an ethyl chloride (cold) spray to ensure a block height of ≥T4 at 10 minutes.

Based on the findings of previous studies,[2,4–6] the initial dose of each vasopressor was approximated to a potency ratio of norepinephrine: phenylephrine at 12.5:1. The first patient in the phenylephrine group received phenylephrine 1200 µg in normal saline 0.9% w/v 60 mL at an infusion rate of 60 mL/h (20 $\mu g.min^{-1}$). The first patient in the norepinephrine group received norepinephrine 96 µg in normal saline 0.9% w/v 60 mL at an infusion rate of 60 mL/h (1.6 $\mu g.min^{-1}$). The dose of vasopressor for the subsequent patient was determined by the efficacy of the dose (whether the previous dose was either effective or ineffective in the previous patient), according to the technique of up-down sequential allocation. The presence of hypotension, hypertension, tachycardia, and bradycardia were recorded until the delivery of the baby, or 30 minutes after intrathecal injection, whichever was earlier to assess the efficacy of each solution. Hypotension was defined as a fall in systolic arterial pressure to <80% of the baseline value. Hypertension was defined as an increase in systolic arterial pressure to >120% of the baseline value. Tachycardia was defined as a rise in HR to >130 beats/min and bradycardia as a fall to <60 beats/min. Hypotension was treated with a bolus of phenylephrine 50 µg if the HR was >60 beats/min or a bolus of ephedrine 6mg if the HR was <60 beats/min. Bradycardia was treated with intravenous glycopyrronium 200 µg. The absence of hypotension classified the dose of infusion which was used as effective. After an effective outcome, the next patient in the phenylephrine group received a dose reduced by 150 µg of phenylephrine and the next patient in norepinephrine group received a dose reduced by 12 µg of norepinephrine. After an ineffective outcome, the dose for the next patient were increased by the same amount, in the respective group.

Outcomes

The primary outcome measure was the ED_{50} of norepinephrine and phenylephrine in the prevention of hypotension between the intrathecal injection and the delivery of the fetus and to derive the relative potency ratio. Secondary outcomes included changes in CO, SV, and SVR expressed as a percentage in comparison to the baseline value, APGAR scores at 1 and 5 minutes; uterine arterial and venous pH, Po_2, Pco_2, and standardized base excess; maternal nausea and vomiting scored on a scale of 0 to 2 (0, no nausea; 1, nausea but no vomiting; 2, nausea and vomiting); need for anticholinergics, time interval between intrathecal injection and delivery time, time interval from incision to delivery time.

Statistical Analysis

Using the phenylephrine data from a previous study,[6] with a conservative coefficient of variation of 14%, a minimum of 28 patients per vasopressor would be required to estimate the ED_{50} with a precision of ±20% precision with 90% probability for this up-down design. Simulation studies also suggest that dose-finding studies based on the biased-coin up-and-down sequential allocation design, enrolling at least 20 to 40 patients will provide stable estimates of the target dose for drugs.[7,8] The sequences were analyzed using the up-down method of Dixon and Massey[9] (Supplemental Digital Content 1, Supplementary 1, http://links.lww.com/AA/F40) and with loglogistic regression to estimate the ED_{50} and 95% CI for each vasopressor. The potency ratio with 95% CI was estimated using the Fieller method. The ED95 was estimated from the calculated ED_{50} multiplied by the appropriate standard deviation (SD) for the desired point estimate. Extreme point estimates such as ED95 is often an extrapolation beyond the range of doses tested during the study, quoted for general information only and should not be solely relied on for clinical use. Patient characteristics and the secondary outcomes were compared descriptively across various time interval groups. Data are presented as mean (SD), median [interquartile], and count (%). Analyses included Student *t* test, Mann-Whitny *U* test, and expanded Fisher exact statistics. Time-based data were analyzed using repeated measures analysis of variance (RMANOVA) with Geisser-Greenhouse corrections. Analyses were performed using Excel 2312 (Microsoft Inc), Minitab 14 (Minitab Inc), Number Cruncher Statistical Systems 2020 (NCSS; NCSS Inc), and GraphPad Prism7 (GraphPad Software). Two-sided $P < .05$ was defined as significant.

RESULTS

The CONSORT flow diagram for patient recruitment is shown in Figure 1. Seventy-eight patients presenting for elective cesarean delivery were screened for eligibility. Eight patients did not meet our inclusion criteria, 8 patients declined to participate, and 2 patients were excluded—1 was in active labor and the other 1 was found to have high BP after enrollment. Sixty patients were therefore consented and randomized for inclusion into the study and successfully completed the trial. Data from all participants were analyzed according to their assigned group.

Maternal demographics, operative data, and baseline hemodynamic parameters are summarized in Table 1. Maternal characteristics were comparable in both groups except the mean maternal age was 3.6 years higher in the norepinephrine group compared to the phenylephrine group at 33.3 years and 29.7 years, respectively, with a sampling probability $P = .003$.

According to the protocol, analysis of data for all outcomes were restricted to the period of intrathecal injection to the delivery of the fetus. All data were analyzed for the first 15 minutes from administration of spinal anesthesia as the relatively short intrathecal injection to delivery intervals caused loss of data beyond this period.

The noninvasive BP measurement was set to cycle every 1 minute. However, due to the differences of BP measurement time, the maternal systolic BP comparisons between the groups were made using each consecutive measurement.

The other hemodynamic parameters (SV, CO, and SVR) were analyzed only for patients who had an effective outcome. This was done to avoid the confounding effects of rescue vasopressors or anticholinergics on the SV, SVR, HR, and eventually the CO. Therefore, the data for 17 patients in the norepinephrine group and 16 patients in phenylephrine group who had effective outcomes were analyzed for these parameters.

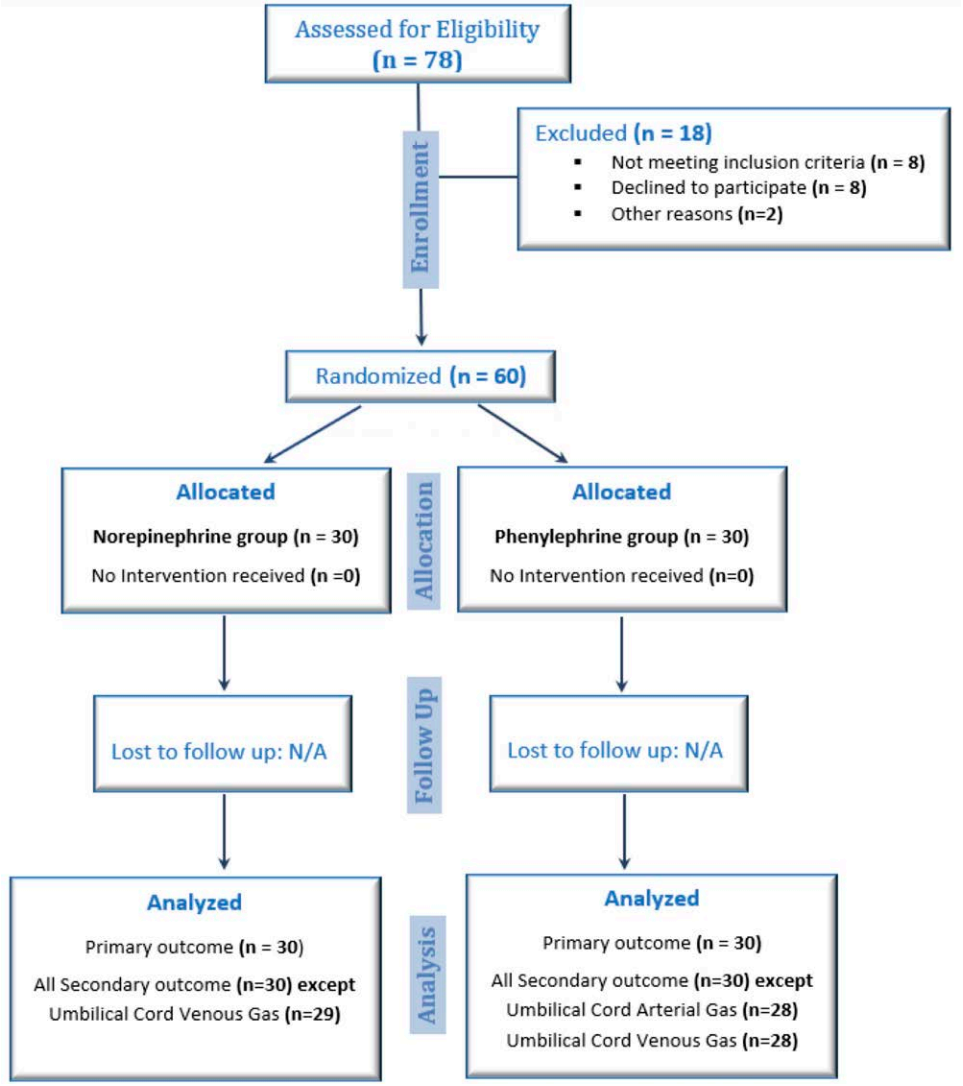

Figure 1. CONSORT chart detailing patient recruitment. CONSORT indicates Consolidated Standards of Reporting Trials.

Table 1. Maternal Demographics, Operative Data, and Baseline Hemodynamic Parameters

	Norepinephrine mean (SD)	Phenylephrine mean (SD)	Sampling probability
Age (y)	33.3 (4.67)	29.7 (4.29)	0.003
Weight (kg)	79.6 (16.6)	75.9 (13.9)	0.35
Height (m)	1.60 (0.05)	1.59 (0.04)	0.16
BMI (kg/m^2)	30.9 (5.75)	30.1 (4.97)	0.59
Gestational age (wks)	38.8 (0.71)	38.7 (0.88)	0.27
Baseline systolic blood pressure (mm Hg)	116 (10.5)	113 (11.3)	0.15
Baseline heart rate (beats/min)	87 (10.5)	88.2 (9.5)	0.32
Baseline cardiac output (L/min)	8.1 (1.28)	7.98 (0.97)	0.68
Baseline stroke volume (mL)	93.7 (15.1)	91.5 (12.3)	0.54
Baseline systemic vascular resistance (dyne · s · cm^{-5})	818 (153)	812 (129)	0.86
Block height at 10 min	T4 [3–4]	T4 [3–4]	0.91
Spinal to delivery Interval (min)	20.4 (3.6)	21.9 (4.7)	0.08
Incision to delivery interval (min)	8.97 (3.8)	8.33 (5.05)	0.29

Abbreviations: BMI, body mass index; SD, standard deviation.

Umbilical cord arterial gas analysis was not performed in 1 neonate in the phenylephrine group due to a technical issue with the measurement. There was an insufficient blood sample to perform umbilical cord venous gas analysis in 1 neonate in the norepinephrine group and 2 neonates in the phenylephrine group.

Primary Outcome

The up-down sequential allocation of the infusion rates for both vasopressors are shown in Figure 2. The ED_{50} was 1.01 µg.min^{-1} (95% CI, 0.84–1.18) for norepinephrine and 12.7 µg.min^{-1} (95% CI, 10.5–14.9) for phenylephrine (Supplemental Digital Content 2, Supplementary 2, http://links.lww.com/AA/F41). The calculated potency ratio of norepinephrine: phenylephrine from this method was 12.6 (95% CI, 9.92–15.9). Probit regression analysis, used as a back-up or sensitivity test, showed similar results with ED_{50} for norepinephrine at 0.96 µg.min^{-1} (95% CI, 0.8–1.12) and for phenylephrine at 12.4 µg.min^{-1} (95% CI, 10.4–14.5), which gave a potency ratio of 12.9 (95% CI, 10.3–16.3). The dose-response curves for both vasopressors are shown in Figure 3.

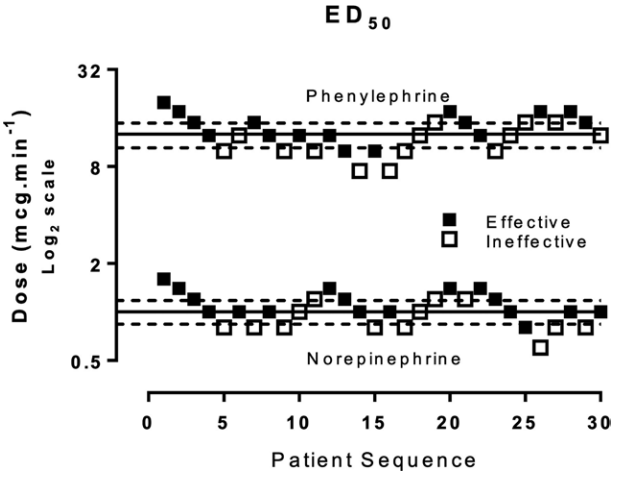

Figure 2. The up-down sequential allocation of the infusion rates for phenylephrine and norepinephrine µg.min^{-1}.

Secondary Outcome

Results for hemodynamic outcomes are shown in Figure 4. There were no significant differences in the hemodynamic parameters between the 2 groups. However, there was a small but statistically significant decrease in the HR and CO observed over time as compared to the baseline in both groups, which was associated with slight increase in SVR. SV was generally well maintained.

Two patients in the norepinephrine group developed bradycardia requiring glycopyrronium. In both these patients, bradycardia was preceded by severe hypotension for which they received multiple boluses of phenylephrine and ephedrine.

Baseline nausea and vomiting scores were similar for both groups. Among patients with an effective outcome, only 1 patient in the norepinephrine group had nausea.

There were no significant differences in neonatal outcome between the groups (Table 2).

DISCUSSION

This randomized triple-blind up-down sequential allocation study demonstrated the relative potency ratio of norepinephrine to phenylephrine to be approximately 13:1 when administered as an infusion for the prevention of spinal hypotension during cesarean delivery. The ratio can serve as a guide for the initial infusion rate of norepinephrine to provide similar clinical efficacy with a reduced incidence of side effects compared to a phenylephrine infusion.

The ED50s for norepinephrine and phenylephrine were 1.01 µg.min^{-1} (95% CI, 0.84–1.18) and 12.7 µg.min^{-1} (95% CI, 10.5–14.9), respectively. The derived ED95 (effective dose to prevent hypotension in 95% of patients) estimates were 1.50 µg.min^{-1} (95% CI, 0.99–2.05) and 19.8 µg.min^{-1} (95% CI, 12.5–27.0), respectively.

Previously published studies used a variety of methods where norepinephrine was administered as either a manually adjusted infusion, fixed rate infusion or

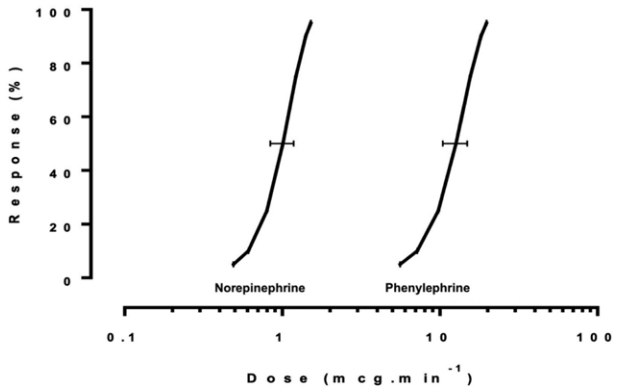

Figure 3. Dose-response curves of norepinephrine and phenylephrine infusions for prevention of spinal hypotension for cesarean delivery. The horizontal axis represents infusion rates on a logarithmic scale.

intermittent boluses.[10–14] In contrast, a well-established up-down method consisting of an adaptive dose-response design, using binary end points to determine the target benchmark dose (ED_{50}) for a drug, was used in our study. This methodology is more effective than the approach of treating equal numbers of patients at a predetermined set of equally spaced doses.

Although a few studies[2,3] have shown that norepinephrine has a better hemodynamic profile as it is associated with less reflex decreases in HR and CO as compared to phenylephrine, our study did not demonstrate a similar outcome. Among the subjects with effective maintenance of systolic BP, there was no difference in SV and HR, and consequently CO between the 2 groups. One of the possible explanations for this discrepancy could be the different dose regimens used in these studies. In our dose-finding study, the primary aim was to determine ED_{50}. Therefore, the dosages used for both phenylephrine and norepinephrine were not sufficient to demonstrate either the beta effect of norepinephrine or reflex bradycardia described with phenylephrine. The studies[2,3] that showed a higher CO in the norepinephrine group used higher infusion rates ranging from 2.35 to 3.5 $\mu g.min^{-1}$ as compared to a mean infusion rate of 1.15 $\mu g.min^{-1}$ among the patients with an effective outcome in our study. In contrast, a few studies, where similarly higher doses of norepinephrine was used, failed to demonstrate these hemodynamic benefits.[15,16] Caution should be taken when interpretating the different outcomes observed in the previous studies as well as the current study, owing to the heterogeneity among these studies in terms of study design, types of monitors used to measure CO, techniques of administration of medications, amount, and types of cohydration fluid, target SBP for intervention and types of rescue vasopressors used.

In our study, we used the ClearSight device (Edwards Lifesciences), a noninvasive, noncalibrated beat to beat pulse contour analysis monitor utilizing the volume clamp method. Although the reliability of such monitors could be markedly altered by rapid changes in the arterial tone which occurs after administration of spinal anesthesia and vasopressors,[17,18] the ClearSight device may still be useful in tracking the hemodynamic changes from baseline and suited for trend analysis.[19]

There was no intergroup difference in umbilical cord variables and APGAR scores. These results are consistent with the findings of a randomized double-blind pragmatic non inferiority study of neonatal outcome.[20]

The incidence of maternal adverse effects including N&V, bradycardia and dizziness were similar between the groups. None of the patients in the norepinephrine group experienced local tissue ischemia during the infusion or afterwards. The highest concentration used in this study was 1.6 μg /mL and was administered through a large bore cannula. The concern of local tissue necrosis when norepinephrine is infused through peripheral vein is theoretical when administering dilute solutions; concentrated solutions as high as 32 μg /mL[21] are associated with a complication rate <2%.

Study Strengths

To the best of our knowledge, this is the only study which has used a robust method to determine the ED_{50} of norepinephrine for prevention of spinal hypotension during cesarean delivery. Although, the use of norepinephrine has been explored for almost a decade and several published studies have in fact demonstrated its potential hemodynamic benefits, there remains a reluctance among clinicians to incorporate it in routine practice. Uncertainty about the appropriate dosing regimens may be one of the main reasons. Another strength of this study is the precision used to titrate the infusion rate of both vasopressors, which is confirmed with the equivalence for the SBP control between the groups. The difference in percentage change in SBP between both vasopressors was minimal at 0.13% with a 95% CI of (−4.60 to 4.87), which is significantly ($P < .0001$) within an acceptable ±10% margin for equivalence.

Study Limitations

The study has some limitations. Mean maternal age was 3.6 years higher in the norepinephrine group compared to the phenylephrine group. Post hoc analysis of covariance (ANCOVA), adjusting for age, returned a similar potency ratio at 12.9 (95% CI, 11.4–14.7), suggesting no effect of age. While the sample size of this up-down sequential allocation design was sufficient to calculate the ED_{50}, it may not have been large enough to detect a statistically significant difference in the secondary outcomes. This study was designed at a time when

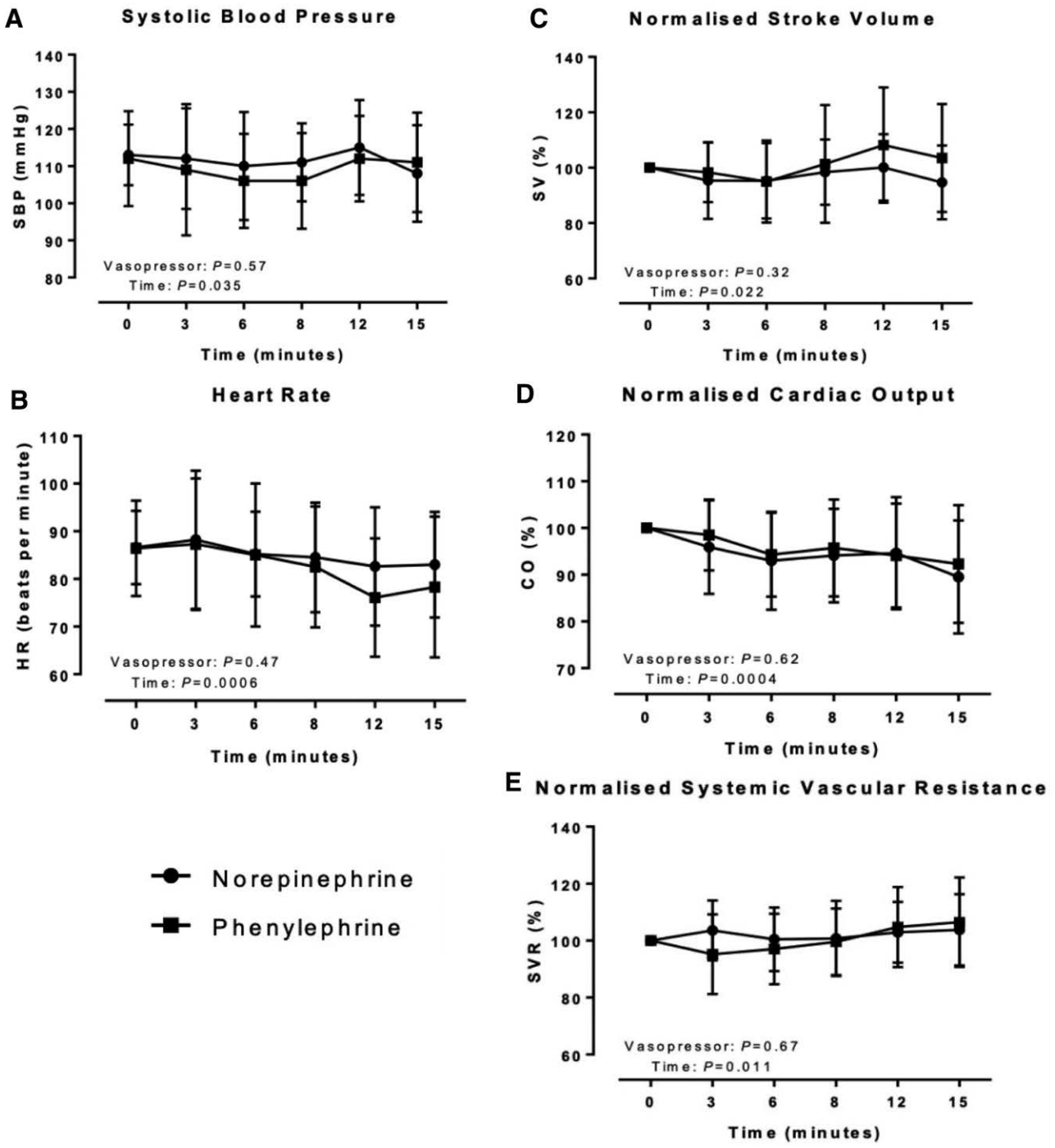

Figure 4. Hemodynamic changes after administration of spinal anesthesia to the delivery of the fetus: -Serial changes in systolic blood pressure (A) and heart rate (B). -Serial normalized changes in stroke volume (C), cardiac output (D), and systemic vascular resistance (E) in patients with effective outcomes.

the recommendation was to maintain maternal SBP at ≥80% of the baseline.[2,4,6] Consequently, our estimated ED_{50} and extrapolated ED95 doses for both vasopressors may be slightly lower than those required to maintain the SBP at ≥90% of the baseline, as per current recommendations.[1] However, these discrepancies should not impact the potency ratio. Future research could focus on evaluating the hemodynamic benefits of norepinephrine and its potential neonatal outcomes by estimating and testing at ED90 or ED95 doses.

In conclusion, this study successfully determined that norepinephrine is more potent than phenylephrine by a factor of approximately 13, when administered as an infusion for equivalent maternal BP control after spinal anesthesia for cesarean delivery.

Table 2. Neonatal Outcome

	Norepinephrine mean (SD)	Phenylephrine mean (SD)	*P* value
Apgar at 1 min	9 (0)	9 (0)	.99
Apgar at 5 min	10 (0)	10 (0)	.99
Umbilical arterial blood gases			
pH	7.31 (0.05)	7.31(0.05)	.83
Pco_2 (mm Hg)	54.1 (6.1)	54.6 (6.01)	.71
Po_2 (mm Hg)	14.3 (4.75)	13.1 (5.85)	.70
Base excess (mmol/L)	−0.03 (1.95)	−0.07 (1.92)	.94
Lactate (mmol/L)	1.57 (0.59)	1.74 (0.87)	.39
Glucose (mmol/L)	3.51(0.38)	3.33(0.54)	.22
Umbilical venous blood gases			
pH	7.35 (0.05)	7.35 (0.05)	.99
Pco_2 (mm Hg)	45.8(7.25)	45.1 (7.26)	.74
Po_2 (mm Hg)	24.2 (6.89)	22.7(4.84)	.35
Base excess (mmol/L)	−0.68 (1.47)	−0.77 (1.78)	.85
Lactate (mmol/L)	1.43 (0.40)	1.60 (0.75)	.30
Glucose (mmol/L)	4.01 (0.30)	3.85(0.51)	.16

Abbreviation: SD, standard deviation.

Therefore, based on this finding and the recommendation of the international consensus statement[1] where prophylactic infusion of phenylephrine should be initiated at 25 to 50 $\mu g.min^{-1}$, we suggest prophylactic infusion of norepinephrine to be initiated at 1.9 to 3.8 $\mu g.min^{-1}$ for the management of hypotension during cesarean delivery under spinal anesthesia. ■

DISCLOSURES

Conflicts of Interest: None. **Funding:** Support was provided solely from institutional sources. **This manuscript was handled by:** Jill M. Mhyre, MD.

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