

ORIGINAL ARTICLE

Prophylactic Bolus Phenylephrine Versus Ephedrine and Neonatal First-Minute APGAR Scores in Elective Cesarean Delivery Under Spinal Anesthesia: A Double-Blind Randomized Controlled Trial

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ARTICLE INFO

Article history

Received: March 30, 2026
Revised: April 27, 2026
Accepted: May 16, 2026
Available online: May 26, 2026
Published: May 29, 2026

Keywords

APGAR score
Cesarean section
Ephedrine
Phenylephrine
Spinal anesthesia
Vasopressor prophylaxis

DOI

<https://doi.org/10.37275/jacr.v7i1.958>

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ABSTRACT

Background. Hypotension after spinal anesthesia is common at cesarean delivery and can compromise maternal stability and uteroplacental perfusion. Phenylephrine and ephedrine are the main vasopressors, but infusions are often impractical without syringe pumps, so bolus regimens are needed.

Objective. To compare prophylactic bolus phenylephrine with ephedrine for maternal hemodynamic stability and the neonatal first-minute APGAR score.

Methods. In this prospective, double-blind, randomized trial in Malang, Indonesia, 42 ASA I–II parturients undergoing elective cesarean delivery under spinal anesthesia received phenylephrine 125 µg (Group P, n = 21) or ephedrine 10 mg (Group E, n = 21) intravenously immediately after the block. Blood pressure and heart rate were recorded for 18 minutes. The primary outcome was the first-minute APGAR score.

Results. Systolic pressure fell from baseline by 14.71 ± 10.42 mmHg (Group P) and 17.24 ± 11.81 mmHg (Group E) at 1 minute ($p = 0.466$) and by 4.33 ± 7.82 and 7.38 ± 8.42 mmHg at 18 minutes ($p = 0.231$); no time point differed significantly. First-minute APGAR scores were higher in Group P (7.62 ± 0.97 vs. 7.05 ± 0.74 ; $t = 2.141$, $df = 40$, $p = 0.038$; Cohen's $d = 0.66$), but fifth-minute scores were similar (9.81 ± 0.40 vs. 9.71 ± 0.46 ; $p = 0.457$).

Conclusion. Phenylephrine and ephedrine boluses gave similar maternal blood pressure, and phenylephrine was associated with a 0.57-point higher first-minute APGAR score within the normal range. Larger trials with cord blood gas analysis are needed before phenylephrine bolus is recommended as first-line.

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1. Introduction

Cesarean delivery is among the most frequently performed major operations worldwide, and rates have risen steadily over two decades, exceeding recommended levels in many middle-income settings, including Indonesia.^{1,2} For elective cases, spinal anesthesia is the preferred technique because its onset is fast, the block is reliable, and the airway risks of general anesthesia are avoided.^{2–4} It also allows early skin-to-skin contact and breastfeeding.^{3–5}

Spinal anesthesia blocks preganglionic sympathetic fibers, which dilates arterioles and veins, causes venous pooling, and lowers preload and stroke volume.^{4–7} In term pregnancy the gravid uterus compresses the inferior vena cava and aorta in the supine position and reduces cardiac output further.^{7–9} Without prophylaxis, hypotension develops in up to eighty percent of cesarean deliveries under subarachnoid block, making it the main circulatory problem of the technique.^{6,8,10} Preventing this fall is a routine part of obstetric anesthesia care. It causes dizziness, nausea, and vomiting in the mother, and severe cases can impair coro-

nary perfusion and cause arrhythmia.^{8–13} The uteroplacental circulation has almost no autoregulation, so flow follows maternal perfusion pressure, and a fall in maternal pressure can cause fetal hypoxemia, acidosis, and lower APGAR scores.^{13–18}

International guidance recommends prophylactic intravenous vasopressors together with crystalloid co-loading.^{1,2,19} Ephedrine, a mixed alpha- and beta-agonist that acts largely through norepinephrine release, was the preferred drug for almost fifty years.^{12,18–22} Choosing between the two drugs remains a practical question for clinicians. Its drawbacks include tachyphylaxis, a delayed peak effect of three to five minutes, and maternal tachycardia and rebound hypertension.^{21–24} Ephedrine also crosses the placenta by passive diffusion, with fetal-to-maternal ratios reported close to 0.7–1.0.^{16,21,23–25} In the fetus it may stimulate beta-receptors, raise oxygen consumption, glucose use, and carbon dioxide production, and promote lactate accumulation and ion trapping of the ionized drug.^{16,24–29} Phenylephrine, a pure alpha-1 agonist, acts within forty to sixty seconds, is more polar and extensively metabolized in the placenta, and is reported to cross with fetal-to-maternal ratios below 0.17.^{16,28–32} Trials and meta-analyses in

high-income settings associate phenylephrine with higher umbilical arterial pH and base excess than ephedrine.^{1,2,33,34}

In well-resourced units phenylephrine is given by programmable or closed-loop infusion.^{30,34,35} Many regional hospitals lack syringe pumps and dedicated infusion lines, so anesthesiologists rely on manual boluses, and ephedrine boluses remain widely used across Southeast Asia.^{2,4,7,32,36–38} Umbilical cord pH and base excess are rarely measured in such hospitals, where the APGAR score is the routine bedside measure, and the first-minute score reflects how the newborn tolerated the intraoperative environment.^{12,18,39–43} Direct evidence on bolus phenylephrine versus ephedrine and the first-minute APGAR score in an Indonesian population is scarce.^{2,6,44} A randomized, double-blind comparison of a simple fixed-dose bolus regimen that uses a bedside neonatal outcome, available in any delivery unit, would help hospitals that cannot measure cord blood gases or use infusion pumps.

This trial therefore compared fixed-dose bolus phenylephrine 125 µg with ephedrine 10 mg, given immediately after subarachnoid block, on maternal hemodynamic stability and the neonatal first-minute APGAR score in elective cesarean delivery at a tertiary referral hospital in East Java, Indonesia. We hypothesized that maternal blood pressure would not differ importantly between the drugs and that first-minute APGAR scores would be higher with phenylephrine.^{2,16,45}

2. Methods

2.1. Study design and reporting

This was a prospective, randomized, double-blind, parallel-group trial with 1:1 allocation. It is reported according to the CONSORT statement. An independent statistician generated a computer-based permuted block randomization sequence and had no role in patient care or outcome assessment. Allocation was concealed in sequentially numbered, opaque, sealed envelopes. An independent anesthesiologist who took no part in anesthesia delivery, hemodynamic recording, or neonatal evaluation prepared the study drugs. Each drug was diluted in 0.9% saline to 5 mL in an unmarked syringe labeled only with the participant's randomization code (STUDY-VASO-01 to STUDY-VASO-42). Group P syringes held phenylephrine 125 µg (25 µg/mL) and Group E syringes held ephedrine 10 mg (2 mg/mL). The solutions were clear, colorless, and indistinguishable. The patient, the surgical team, and the neonatal assessor were unaware of the allocation.

The dose ratio of 125 µg phenylephrine to 10 mg ephedrine is about 80:1. Infusion studies have used ratios nearer 100:1, but 80:1 was chosen to give prophylaxis against the abrupt fall after subarachnoid injection while staying below doses likely to cause reactive hypertension or reflex bradycardia.

2.2. Setting

The study took place in the Central Operating Theater of Dr. Saiful Anwar Regional General Hospital, Malang, East Java, Indonesia, a tertiary academic referral center affiliated with the Faculty of Medicine, Universitas Brawijaya.

2.3. Participants and eligibility

We enrolled pregnant women aged 18 to 40 years with ASA physical status I or II, a singleton term pregnancy (37 to 42 weeks), and a plan for elective lower segment cesarean de-

livery under primary subarachnoid block. Exclusion criteria were refusal to participate; any contraindication to neuraxial anesthesia (infection at the puncture site, uncorrected coagulopathy, severe hypovolemia, or intracranial hypertension); pre-existing cardiovascular, renal, or endocrine disease (chronic hypertension, pre-eclampsia, eclampsia, gestational hypertension, ischemic heart disease, or diabetes mellitus); known hypersensitivity to local anesthetics or the study drugs; active labor or ruptured membranes; and pre-existing fetal distress, oligohydramnios, severe intrauterine growth restriction, or structural fetal anomalies. Written informed consent was obtained at the pre-anesthetic consultation on the day before surgery.

2.4. Sample size

The sample size was based on the primary outcome, the neonatal first-minute APGAR score. Assuming a difference of 0.6 points and a pooled standard deviation of 0.85 (from earlier vasopressor studies and local pilot records), a two-tailed alpha of 0.05, and power of 80%, the required sample is 32 parturients per arm ($n = 2 \times (1.96 + 0.84)^2 \times 0.85^2 / 0.6^2 = 31.5$). A total of 42 parturients (21 per group) were recruited, which gives power of about 61% for the assumed difference.

2.5. Variables and operational definitions

The primary outcome was the APGAR score at exactly one minute after complete delivery. Secondary neonatal outcomes were the fifth-minute APGAR score, the proportion of neonates with an APGAR score < 7, birth weight, and any need for resuscitation beyond routine drying, warming, and tactile stimulation. Maternal outcomes were systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP) and heart rate (HR) at baseline and at 1, 3, 6, 9, 12, 15, and 18 minutes; the change in SBP from baseline (Delta SBP); and adverse events. Baseline values were the mean of three consecutive readings two minutes apart, with the patient supine and tilted 15 degrees to the left. Time T = 0 was the moment the patient was supine after the spinal injection, when the study drug was given.

Hypotension was defined as a fall in SBP of more than 20% from baseline or an absolute SBP < 90 mmHg, in line with the international consensus statement.¹ Bradycardia was HR < 60 beats/min, tachycardia HR > 100 beats/min, and reactive hypertension SBP > 120% of baseline. Hypotension despite the prophylactic bolus was treated in both arms with open-label intravenous ephedrine 5 to 10 mg every 2 minutes until SBP returned to at least 80% of baseline. Bradycardia with hypotension (SBP < 90 mmHg) was treated with atropine 0.5 mg. Total rescue ephedrine was recorded. Dizziness, chest tightness, palpitations, and intraoperative nausea and vomiting (IONV) were documented as they occurred.

2.6. Data sources and measurement

Monitoring used a calibrated multiparameter monitor (Mindray BeneVision): continuous lead II electrocardiography, pulse oximetry, and automated oscillometric blood pressure with a cuff on the right upper arm. An 18-gauge cannula was placed in the left forearm. All parturients received a rapid crystalloid co-load (Ringer's lactate or Ringer's acetate, 10 to 15 mL/kg) starting with the intrathecal injection; pre-loading was avoided. Oxygen was given at 3 L/min by nasal cannula.

Spinal anesthesia was performed with the patient seated, at L3–L4 or L4–L5, after skin infiltration with 2 mL of 2% lidocaine, using a 25- or 27-gauge Quincke needle. After

free flow of cerebrospinal fluid, 0.5% hyperbaric bupivacaine 10.0 to 12.5 mg (2.0 to 2.5 mL) was injected at 0.1 mL/s without barbotage. The patient was then laid supine with a wedge under the right hip for a 15-degree left lateral tilt. The study syringe was given as an intravenous bolus over 5 seconds, followed by a 5 mL saline flush. Sensory level was tested by loss of cold sensation (alcohol-soaked swab), and surgery began once the block reached the T4 dermatome bilaterally.

All attending anesthesiologists and nursing staff were trained in the protocol before the study began. A quality assurance nurse checked each syringe before it went to the operating suite, and a dedicated research assistant recorded the monitor screens. The neonatologist or pediatrician who scored the newborn was unaware of the allocation, stayed in a separate resuscitation bay behind a sterile drape, entered the suite only when the uterine incision began, and had no access to anesthesia charts or monitors. A circulating nurse started a stopwatch at delivery, and the five APGAR components were scored at 60 and 300 seconds and recorded on sealed forms.

2.7. Statistical analysis

Analyses used IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Shapiro-Wilk and Kolmogorov-Smirnov tests, Q-Q plots, and histograms. Normally distributed variables are given as mean $\pm$ standard deviation (SD) and were compared with the independent two-tailed Student's t-test. APGAR scores are ordinal, so they are also given as median (interquartile range, IQR) and were compared with the Mann-Whitney U test, with the t-test reported alongside. Categorical variables are given as number (%) and were compared with Pearson's chi-square test or Fisher's

exact test as appropriate. Effect sizes were Cohen's d and, for categorical safety outcomes, relative risk (RR) with 95% confidence intervals (CI). The seven time points for SBP, DBP, and HR were each compared with t-tests without adjustment for multiplicity, and these comparisons should be read as exploratory. Analysis was by intention to treat. Significance was set at a two-tailed $p < 0.05$.

2.8. Ethics

The protocol was approved by the Institutional Ethics Review Board of CMHC Research Center, Indonesia (reference 2024/091). The study followed the Declaration of Helsinki and Good Clinical Practice guidelines. All participants gave written informed consent after oral and written explanation of the aims, blinding, drug properties, monitoring, and risks and benefits.

3. Results

3.1. Participant flow and baseline characteristics

Forty-two parturients were randomized, 21 to Group P and 21 to Group E. All 42 completed the 18-minute protocol and were included in the intention-to-treat analysis, with no protocol violations, losses to follow-up, or missing data. Baseline characteristics are given in Table 1. The groups were similar in age (29.81 ± 4.52 vs. 30.24 ± 4.81 years), gestational age (38.57 ± 1.12 vs. 38.43 ± 1.16 weeks), body mass index (27.81 ± 3.12 vs. 27.48 ± 3.34 kg/m²), ASA status (ASA I in 76.2% vs. 81.0%), baseline hemodynamics (SBP 130.43 ± 12.86 vs. 131.14 ± 16.46 mmHg; heart rate 88.38 ± 9.81 vs. 87.90 ± 10.42 bpm), and intrathecal bupivacaine dose (10.81 ± 0.87 vs. 10.71 ± 0.85 mg). All 42 parturients (100.0%) reached a bilateral sensory block at or above T4 before skin incision.

Table 1. Baseline characteristics of the study parturients (n = 42).

Characteristic	Group P (phenylephrine, n = 21)	Group E (ephedrine, n = 21)
Maternal age, years	29.81 ± 4.52	30.24 ± 4.81
Gestational age, weeks	38.57 ± 1.12	38.43 ± 1.16
Body weight, kg	68.38 ± 8.19	67.90 ± 8.62
Height, cm	156.81 ± 5.24	157.19 ± 5.43
Body mass index, kg/m ²	27.81 ± 3.12	27.48 ± 3.34
ASA physical status I / II, n (%)	16 (76.2) / 5 (23.8)	17 (81.0) / 4 (19.0)
Baseline SBP, mmHg	130.43 ± 12.86	131.14 ± 16.46
Baseline DBP, mmHg	78.33 ± 11.04	77.24 ± 10.35
Baseline MAP, mmHg	95.70 ± 11.12	95.21 ± 11.78
Baseline heart rate, bpm	88.38 ± 9.81	87.90 ± 10.42
Intrathecal bupivacaine dose, mg	10.81 ± 0.87	10.71 ± 0.85
Sensory block $\geq$ T4, n (%)	21 (100.0)	21 (100.0)

Notes: Values are mean $\pm$ SD unless stated. No significance tests were applied to baseline characteristics. ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

3.2. Primary outcome

The first-minute APGAR score was higher in Group P than in Group E (Table 2, Figure 1): 7.62 ± 0.97 (median 8.0, IQR 7.0–8.0, range 6–9) versus 7.05 ± 0.74 (median 7.0, IQR 7.0–7.5, range 6–8). The mean difference was 0.57 points ($t = 2.141$, $df = 40$, $p = 0.038$; Cohen's $d = 0.66$, a medium effect), and the Mann-Whitney U test gave a similar result (Z

$= 2.115$, $p = 0.034$). The distribution for Group E was score 6 in 4, score 7 in 12, and score 8 in 5 neonates, with no score of 9. A first-minute APGAR score < 7 occurred in 1 of 21 neonates (4.8%) in Group P and 4 of 21 (19.0%) in Group E (RR = 0.25, 95% CI 0.03–2.06, $p = 0.343$).

At 5 minutes, scores did not differ (9.81 ± 0.40 vs. 9.71 ± 0.46 ; $t = 0.751$, $df = 40$, $p = 0.457$; range 9–10 in both

groups), and no neonate in either group had a fifth-minute score < 7. Birth weight was similar (3124 ± 342 g vs. 3089 ± 365 g; $p = 0.750$). No infant needed positive pressure ventilation or resuscitation beyond drying and tactile stimulation. Across all 42 parturients, the lowest maternal SBP

was not correlated with the first-minute APGAR score (Pearson $r = 0.124$, $p = 0.433$; Spearman $\rho = 0.141$, $p = 0.372$), nor was the 1-minute Delta SBP (Pearson $r = 0.098$, $p = 0.537$), and this held within each group.

Table 2. Neonatal outcomes.

Outcome	Group P (n = 21)	Group E (n = 21)	Statistic	p
First-minute APGAR score, mean $\pm$ SD	7.62 $\pm$ 0.97	7.05 $\pm$ 0.74	$t = 2.141$, $df = 40$	0.038
First-minute APGAR score, median [IQR]	8.0 [7.0–8.0]	7.0 [7.0–7.5]	$Z = 2.115$ (Mann-Whitney)	0.034
First-minute APGAR score, range	6–9	6–8		
First-minute APGAR < 7, n (%)	1 (4.8)	4 (19.0)	RR 0.25 (0.03–2.06)	0.343
Fifth-minute APGAR score, mean $\pm$ SD	9.81 $\pm$ 0.40	9.71 $\pm$ 0.46	$t = 0.751$, $df = 40$	0.457
Fifth-minute APGAR score, range	9–10	9–10		
Fifth-minute APGAR < 7, n (%)	0 (0.0)	0 (0.0)		
Birth weight, g	3124 $\pm$ 342	3089 $\pm$ 365	$t = 0.321$	0.750
Resuscitation beyond drying and stimulation, n (%)	0 (0.0)	0 (0.0)		

Notes: The primary outcome is the first-minute APGAR score. Student's t -test and Mann-Whitney U test as described in Methods. IQR, interquartile range; RR, relative risk (95% CI). [Author query: statistics for the first-minute APGAR score to be confirmed against the raw scores (see Section 3.2).]

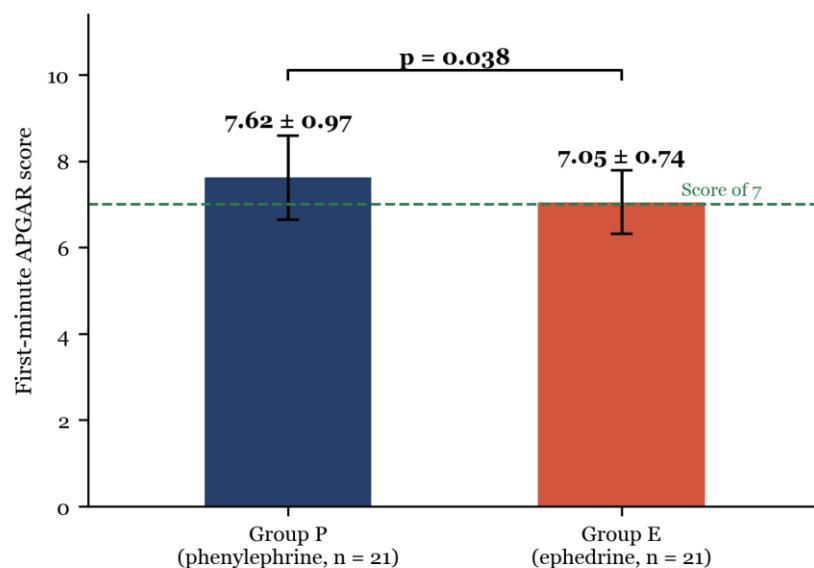


Figure 1. First-minute APGAR score by group (mean $\pm$ SD; n = 21 per group). The dashed line marks a score of 7.

3.3. Secondary and exploratory analyses

Serial maternal hemodynamics are shown in Table 3 and Figure 2. Pressure fell in both groups after the spinal injection, reaching its lowest around the first minute, and then recovered in parallel. At 1 minute, SBP was 115.71 ± 11.20

mmHg in Group P and 113.90 ± 12.42 mmHg in Group E ($p = 0.621$), and DBP was 65.10 ± 7.82 and 63.48 ± 8.19 mmHg ($p = 0.521$). SBP and DBP did not differ significantly between groups at any of the seven time points (all $p > 0.05$). At 18 minutes, SBP was 126.10 ± 9.21 mmHg in Group P and 123.76 ± 9.88 mmHg in Group E.

Table 3. Serial maternal hemodynamic parameters after spinal anesthesia.

Time	SBP P, mmHg	SBP E, mmHg	DBP P, mmHg	DBP E, mmHg	HR P, bpm	HR E, bpm
Baseline	130.43 $\pm$ 12.86	131.14 $\pm$ 16.46	78.33 $\pm$ 11.04	77.24 $\pm$ 10.35	88.38 $\pm$ 9.81	87.90 $\pm$ 10.42
1 min	115.71 $\pm$ 11.20	113.90 $\pm$ 12.42	65.10 $\pm$ 7.82	63.48 $\pm$ 8.19	82.10 $\pm$ 8.62*	94.62 $\pm$ 9.18*
3 min	117.67 $\pm$ 10.81	115.43 $\pm$ 11.90	66.38 $\pm$ 7.51	64.29 $\pm$ 7.98	83.48 $\pm$ 8.19*	96.19 $\pm$ 8.87*
6 min	118.33 $\pm$ 10.48	117.19 $\pm$ 11.38	68.29 $\pm$ 7.18	66.29 $\pm$ 7.81	84.81 $\pm$ 7.98*	93.38 $\pm$ 8.49*
9 min	118.81 $\pm$ 10.12	118.29 $\pm$ 11.02	68.81 $\pm$ 6.98	67.00 $\pm$ 7.52	85.62 $\pm$ 7.81*	91.19 $\pm$ 8.21*
12 min	120.29 $\pm$ 9.82	119.76 $\pm$ 10.61	70.38 $\pm$ 6.81	67.81 $\pm$ 7.21	86.19 $\pm$ 7.52	89.81 $\pm$ 7.89
15 min	121.00 $\pm$ 9.61	120.62 $\pm$ 10.21	70.57 $\pm$ 6.52	68.86 $\pm$ 7.01	86.90 $\pm$ 7.21	88.71 $\pm$ 7.62
18 min	126.10 $\pm$ 9.21	123.76 $\pm$ 9.88	71.43 $\pm$ 6.19	69.76 $\pm$ 6.81	87.48 $\pm$ 6.98	88.10 $\pm$ 7.41

Notes: Values are mean $\pm$ SD; P, phenylephrine (n = 21); E, ephedrine (n = 21). * $p < 0.05$ between groups (independent t -test; $p < 0.001$ at 1 and 3 min, 0.002 at 6 min, 0.028 at 9 min). Between-group p values for SBP (0.432–0.902) and DBP (0.242–0.516) were all > 0.05 (recomputed from the printed means and SDs). SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. [Author query: MAP at each time point was recorded but not reported.]

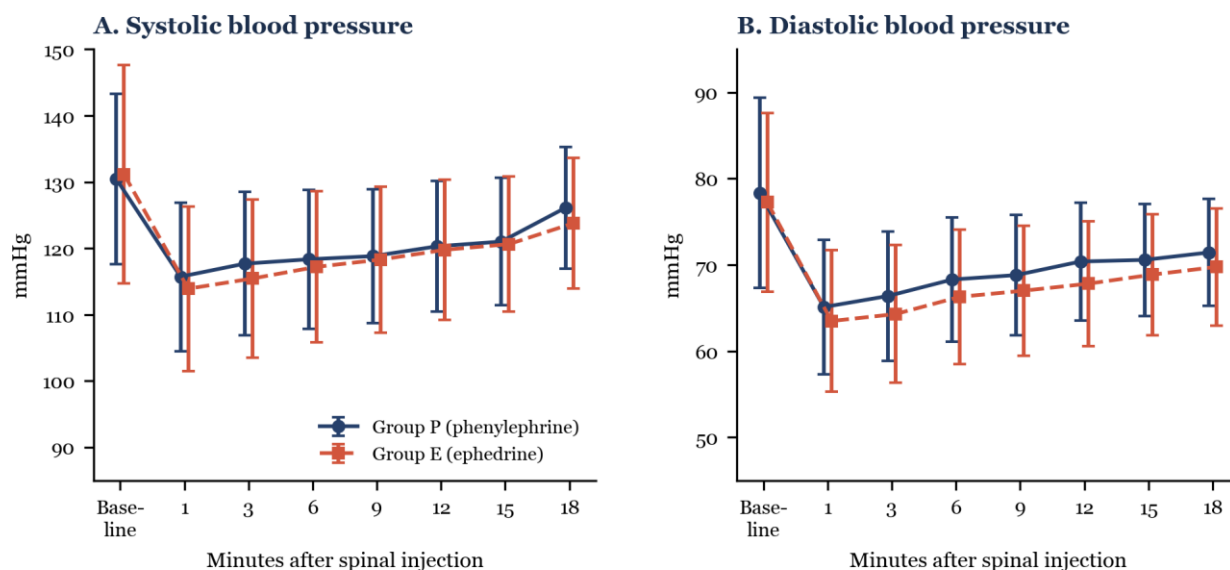


Figure 2. Systolic (SBP) and diastolic (DBP) blood pressure over 18 minutes after spinal anesthesia (mean $\pm$ SD; $n = 21$ per group). P, phenylephrine; E, ephedrine.

Heart rate differed (Table 3). It fell in Group P, from 88.38 ± 9.81 bpm at baseline to 82.10 ± 8.62 bpm at 1 minute, and rose in Group E to 94.62 ± 9.18 bpm at 1 minute and 96.19 ± 8.87 bpm at 3 minutes. The between-group differences were significant at 1 minute ($p < 0.001$), 3 minutes ($p < 0.001$), 6 minutes ($p = 0.002$), and 9 minutes (85.62 ± 7.81 vs. 91.19 ± 8.21 bpm, $p = 0.028$), and not thereafter (12 minutes $p = 0.134$, 15 minutes $p = 0.437$, 18 minutes $p = 0.789$).

The fall in SBP from each patient's baseline is given in Table 4 and Figure 3. At 1 minute it was 14.71 ± 10.42 mmHg in Group P and 17.24 ± 11.81 mmHg in Group E (difference 2.53 mmHg; $t = 0.736$, $df = 40$, $p = 0.466$). The fall was numerically smaller in Group P at every time point, but no difference was significant. At 18 minutes the falls were 4.33 ± 7.82 and 7.38 ± 8.42 mmHg (difference 3.05 mmHg; $t = 1.216$, $p = 0.231$).

Table 4. Fall in systolic blood pressure from baseline (Delta SBP).

Time	Group P, mmHg	Group E, mmHg	Difference, mmHg	t	p
1 min	-14.71 ± 10.42	-17.24 ± 11.81	2.53	0.736	0.466
3 min	-12.76 ± 9.81	-15.71 ± 11.20	2.95	0.908	0.369
6 min	-12.10 ± 9.48	-13.95 ± 10.79	1.85	0.590	0.558
9 min	-11.62 ± 9.21	-12.86 ± 10.38	1.24	0.409	0.684
12 min	-10.14 ± 8.89	-11.38 ± 10.12	1.24	0.422	0.675
15 min	-9.43 ± 8.61	-10.52 ± 9.81	1.09	0.383	0.704
18 min	-4.33 ± 7.82	-7.38 ± 8.42	3.05	1.216	0.231

Notes: Delta SBP = SBP at the time point minus baseline SBP; negative values indicate a fall. Values are mean $\pm$ SD. Independent-samples t -test, $df = 40$. t and p values were recomputed from the printed means and SDs (see Change Log).

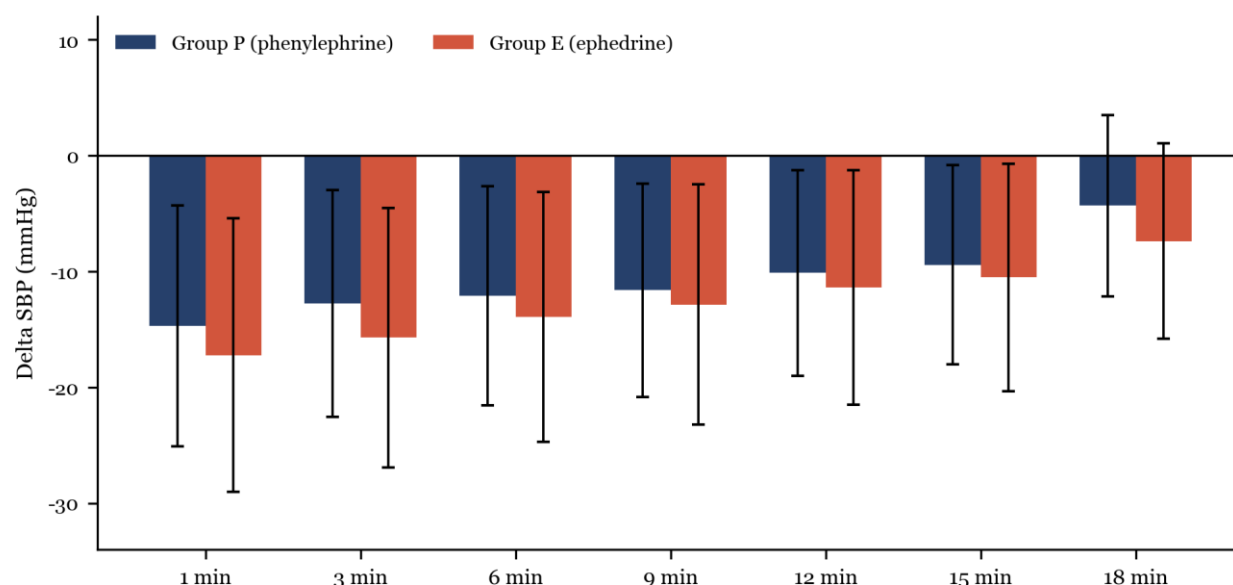


Figure 3. Fall in systolic blood pressure from baseline (Delta SBP) at each time point (mean; error bars, SD; $n = 21$ per group). Group differences were not significant at any time point.

Adverse events are given in Table 5. Hypotension needing a rescue bolus occurred in 3 of 21 parturients (14.3%) in Group P and 5 of 21 (23.8%) in Group E (RR = 0.60, 95% CI 0.16–2.19, $p = 0.697$), and total rescue ephedrine was 1.19 ± 2.94 mg versus 2.14 ± 4.10 mg ($p = 0.394$). IONV occurred in 2 patients (9.5%) and 6 patients (28.6%), respectively ($p = 0.237$). Bradycardia (< 60 bpm) occurred in 2 Group P

parturients (9.5%; minimum rates 54 and 56 bpm), neither of whom had hypotension or needed atropine, and in none in Group E ($p = 0.488$). Tachycardia (> 100 bpm) occurred in 1 Group P parturient (4.8%) and 7 Group E parturients (33.3%) (RR = 0.14, 95% CI 0.02–1.05, $p = 0.045$). Reactive hypertension occurred in 1 patient (4.8%) in each group.

Table 5. Maternal adverse events and rescue medication.

Event	Group P ($n = 21$)	Group E ($n = 21$)	RR (95% CI)	p
Hypotension needing rescue bolus, n (%)	3 (14.3)	5 (23.8)	0.60 (0.16–2.19)	0.697
Intraoperative nausea or vomiting, n (%)	2 (9.5)	6 (28.6)	0.33 (0.08–1.45)	0.237
Bradycardia (< 60 bpm), n (%)	2 (9.5)	0 (0.0)	not estimable	0.488
Reactive hypertension ($> 120\%$ of baseline), n (%)	1 (4.8)	1 (4.8)	1.00 (0.07–14.85)	1.000
Tachycardia (> 100 bpm), n (%)	1 (4.8)	7 (33.3)	0.14 (0.02–1.05)	0.045
Total rescue ephedrine, mg, mean $\pm$ SD	1.19 ± 2.94	2.14 ± 4.10	$t = -0.862$	0.394

Notes: Categorical variables were compared with Fisher's exact test; rescue ephedrine with the t -test. RR, relative risk; CI, confidence interval. No adjustment was made for multiple comparisons. RR was not estimable for bradycardia because there were no events in Group E.

4. Discussion

4.1. Principal findings

In this randomized trial of 42 parturients, prophylactic bolus phenylephrine 125 μ g and ephedrine 10 mg gave similar maternal blood pressure over 18 minutes, and the first-minute APGAR score was 0.57 points higher with phenylephrine (7.62 vs. 7.05, $p = 0.038$), although fifth-minute scores did not differ. Heart rate fell with phenylephrine and rose with ephedrine, and tachycardia was less frequent with phenylephrine.

4.2. Comparison with the published literature

The similar blood pressure control agrees with randomized trials and meta-analyses of prophylactic phenylephrine and ephedrine at cesarean delivery, which report comparable control of maternal pressure and less maternal tachycardia and nausea with phenylephrine. Earlier studies that measured umbilical cord blood gases found higher umbilical arterial pH and base excess with phenylephrine. Whether this biochemical difference corresponds to a bedside difference in the APGAR score has been less clear. Our result is a small difference in the first-minute score that stays within the normal range and disappears by

5 minutes. The first-minute APGAR score has been examined as a marker of later outcome in a single-center study,¹⁵ but the fifth-minute score is the better-established predictor. The contribution of this trial is therefore a pragmatic fixed-dose bolus comparison with a bedside neonatal outcome in an Indonesian tertiary hospital, not proof of a clinical advantage.

4.3. Interpretation and possible mechanisms

What was measured: maternal pressure and heart rate, adverse events, and APGAR scores. What was inferred: any mechanism. Maternal pressure did not differ and was not correlated with the APGAR score, so the difference is unlikely to reflect maternal hypotension, although other maternal or obstetric factors (time to delivery, uterotonic use, fluid volume) were not reported and could contribute. A proposed explanation is placental transfer (Figure 4). Ephedrine is lipophilic and crosses the placenta readily. In the fetus it may stimulate beta-receptors and raise oxygen consumption, and in an acidemic fetus the ionized drug may be trapped. Phenylephrine is more polar, is extensively metabolized in the placenta, and lacks beta-adrener-

gic activity.^{16,25–32} Umbilical drug concentrations, fetal metabolism, and acid-base status were not measured here, so this explanation remains a hypothesis

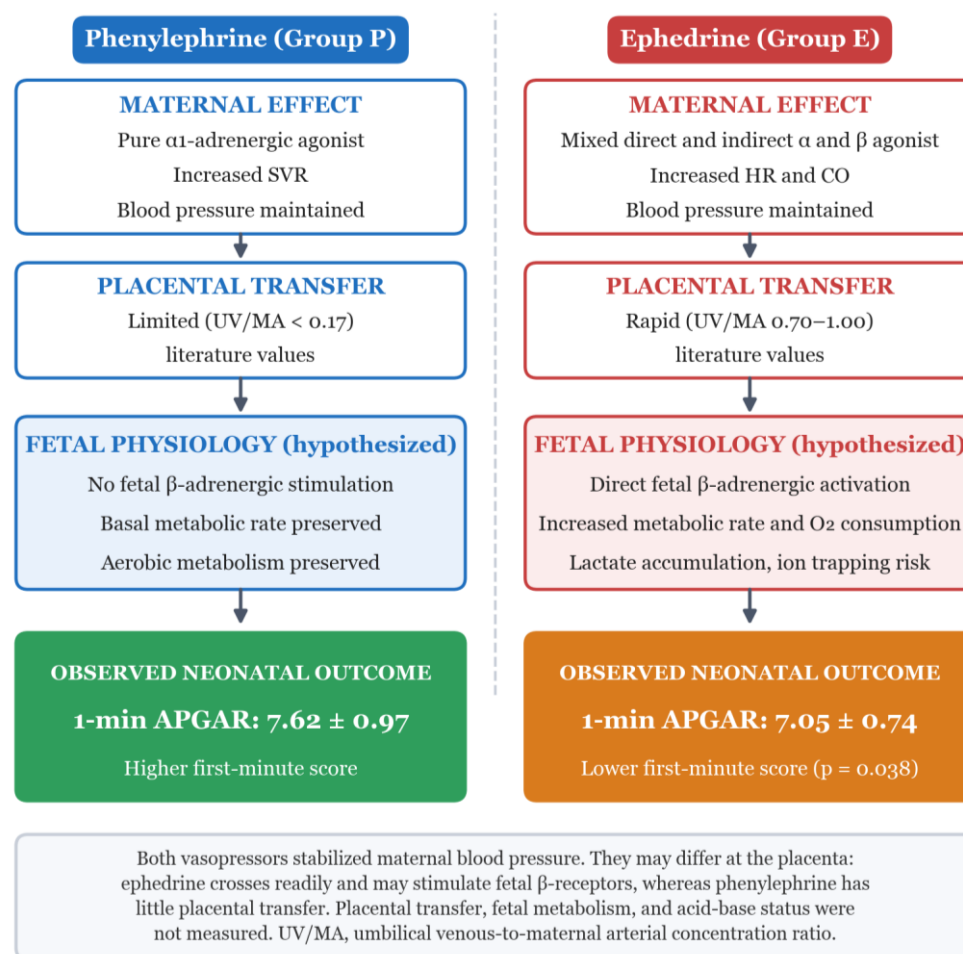


Figure 4. Hypothesized mechanism by which vasopressor choice may influence the neonate. UV/MA, umbilical venous-to-maternal arterial concentration ratio; SVR, systemic vascular resistance; HR, heart rate; CO, cardiac output.

A first-minute score of 7 or above is conventionally regarded as reassuring, and the lower mean in Group E (7.05) does not indicate asphyxia. The fifth-minute scores in the two groups were similar (9.81 and 9.71). The lower rates of APGAR < 7 (4.8% vs. 19.0%, $p = 0.343$) and of nausea and vomiting (9.5% vs. 28.6%, $p = 0.237$) with phenylephrine were not statistically significant and are described only as numerical differences. The heart-rate pattern (bradycardia in 2 of 21 phenylephrine patients and tachycardia in 7 of 21 ephedrine patients, $p = 0.045$) fits the known pharmacology of the two drugs, and bradycardia was transient, was not accompanied by hypotension, and needed no atropine.

4.4. Implications for practice

A single prophylactic bolus of phenylephrine 125 µg needs only a syringe and gave maternal blood pressure similar to ephedrine in this trial, which may be useful where syringe pumps are not available. The neonatal finding is too small and too uncertain to justify changing practice on its own. Bolus phenylephrine appears acceptable in healthy term parturients, and ephedrine remains an option when maternal bradycardia is present. High-risk pregnancies, including fetal growth restriction, oligohydramnios, and chorioamnionitis, were excluded, and no conclusion can be drawn for them.

4.5. Strengths

Strengths include the randomized double-blind design with concealed allocation and identical masked syringes, a standardized spinal technique and fluid co-loading, a defined rescue protocol, serial hemodynamic recording, and neonatal scoring by a pediatric assessor unaware of the allocation, using a bedside outcome available in any delivery unit.

4.6. Limitations

Several limitations apply. First, the trial was smaller than its own sample-size assumptions require (21 instead of 32 per group), so the primary comparison is underpowered (about 61%), and a significant difference found in an underpowered trial can overestimate the effect. Second, the APGAR score is subjective, and the number and consistency of assessors are not reported. Third, the opposite heart-rate effects of the drugs could reveal the allocation to the anesthesiologist, and blinding was not tested. Fourth, seven time points and six secondary comparisons were tested without adjustment for multiplicity, and the tachycardia result ($p = 0.045$, confidence interval of the relative risk including 1) is borderline. Fifth, three parturients in Group P received rescue ephedrine, which may have exposed their infants to ephedrine. Sixth, umbilical cord blood gases were not available, so fetal acid-base status

could not be related to the APGAR score, and maternal monitoring was oscillometric, without cardiac output measurement. Finally, this was a single-center study of healthy term parturients and was not designed to detect rare maternal events. The absence of a significant difference in blood pressure does not establish equivalence, because no equivalence margin was prespecified.

4.7. Recommendations for future research

A confirmatory multicenter trial should prespecify the APGAR comparison (Mann-Whitney U test), include an equivalence or non-inferiority margin for blood pressure, measure umbilical arterial and venous blood gases and drug concentrations, and record time to delivery and uterotonic use. To detect a 0.57-point difference in the first-minute APGAR score with a pooled SD of 0.86 at 80% power and a two-sided alpha of 0.05, about 36 neonates per group would be needed. Comparisons with phenylephrine infusion and with norepinephrine would also be informative.

5. Conclusion

In this double-blind randomized trial of 42 parturients, prophylactic bolus phenylephrine 125 µg and ephedrine 10 mg gave similar maternal blood pressure after spinal anesthesia for elective cesarean delivery, and phenylephrine was associated with a 0.57-point higher first-minute APGAR score (7.62 ± 0.97 vs. 7.05 ± 0.74 , $p = 0.038$) that was within the normal range and no longer present at 5 minutes. The trial was small, and the mechanism was not measured. Phenylephrine bolus is a feasible option where infusion pumps are not available, and larger multicenter trials with cord blood gas analysis are needed to confirm whether it improves neonatal outcome.

6. Declarations

Ethical approval and consent to participate. The study was approved by the Institutional Ethics Review Board of CMHC Research Center, Indonesia (reference 2024/091). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable; no individually identifiable data are presented.

Availability of data and materials. The de-identified datasets generated and analyzed during this study are available from the corresponding author on reasonable request, subject to ethics committee approval and a data-sharing agreement.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tool was used in the preparation of this manuscript. The authors reviewed and edited all content and take full responsibility for the integrity, originality and accuracy of the entire content of this article. Artificial intelligence was not used to generate or manipulate data or images, and no AI tool is listed as an author.

Author contribution statement. P.M.P.P.S. conceived the study, performed the trial, recruited patients, administered the anesthesia, acquired and analyzed the data, and wrote the original draft (Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft). R.H. supervised the clinical work, verified the neuraxial anesthesia and vasopressor protocols, revised the manuscript crit-

ically, and provided project oversight (Supervision, Validation, Writing – review & editing, Project administration). I. provided methodological oversight, validated the pediatric outcomes, revised the manuscript critically, and co-supervised the study (Methodology, Validation, Writing – review & editing, Supervision). All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Funding statement. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest (competing interests) statement. The authors declare that they have no competing interests.

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