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Comparative Evaluation of Phenylephrine and Ephedrine Effects on Maternal and Fetal Safety in Cesarean Delivery Under Spinal Anesthesia

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Abstract
Background: Administering of phenylephrine together with ephedrine as the initial vasopressor strategy during spinal anesthesia for cesarean delivery was associated with a lower frequency of neonatal acidemia, defined as an umbilical arterial pH below 7.20, compared with the use of ephedrine alone. Methods: This investigation was conducted to compare the effectiveness of three vasopressor infusion regimens in maintaining maternal systolic blood pressure during elective cesarean section under spinal anesthesia. Participants were allocated to receive either phenylephrine at a concentration of 100 µg/mL, ephedrine at 3 mg/mL, or a combined solution containing phenylephrine 50 µg/mL and ephedrine 1.5 mg/mL. Each infusion was titrated to maintain systolic arterial pressure close to the pre-spinal baseline value. Results: Two of ninety-six patient born acidotic neonate in the phenylephrine group ($P = 0.004$) and the combination group 2 of 94 ($P = 0.005$) which less than in the ephedrine group 20 of 96. Maternal systolic blood pressure was successfully maintained in all treatment groups, with median values corresponding to 98% of baseline in the phenylephrine group, 100% in the ephedrine group, and 101% in the combination group, without statistically significant differences ($P = 0.11$). Maternal heart rate was significantly greater among women receiving ephedrine, reaching a median of 107% of baseline, compared with 88% in the phenylephrine group and 96% in the combination group (both $P < 0.0001$). Gastrointestinal side effects also differed markedly between groups. Phenylephrine was associated with the lowest incidence of nausea (17%) and no cases of vomiting, whereas ephedrine produced the highest rates of nausea (66%) and vomiting (36%). The combination regimen resulted in intermediate frequencies of nausea (55%) and vomiting (18%), both significantly higher than those observed with phenylephrine alone ($P < 0.0001$). Conclusions: Continuous infusion of phenylephrine during elective cesarean delivery under spinal anesthesia associated non-significant differences regarding maternal and neonatal outcome when compared with ephedrine infusion. Specifically, phenylephrine significantly reduced the incidence of fetal acidemia as well as maternal nausea and vomiting while maintaining maternal blood pressure effectively. Although combining phenylephrine with ephedrine also decreased the occurrence of fetal acidemia relative to ephedrine alone, it failed to produce any additional improvement in neonatal acid–base status over phenylephrine monotherapy and was associated with a higher frequency of maternal nausea and vomiting. These findings support the use of phenylephrine alone as the preferred first-line vasopressor during cesarean delivery under spinal anesthesia.

Introduction

A higher rate of fetal acidemia at birth has been observed with spinal blockade for planned cesarean sections compared to either neuraxial epidural or systemic general techniques [1], [2], [3], [4]. This adverse metabolic outcome is thought to arise from maternal circulatory depression or as an unintended consequence of pharmacological measures employed to avert or manage such hypotensive episodes. Ephedrine, a mixed-action sympathomimetic amine, remains the predominant pressor chosen by consultant obstetric anesthesiologists in the UK, with surveys indicating its exclusive use in 95% of such cases [5].

Alpha-selective adrenergic compounds, including phenylephrine, have seen less widespread adoption, likely influenced by earlier ovine models suggesting that alpha-agonist administration during hypotension compromises uterine blood flow relative to ephedrine [6]. Ephedrine usage is not without limitations, including tachyphylaxis,

and its prophylactic administration has been correlated with neonatal acidaemia [7], [8]. A recent meta-analysis synthesizing randomized controlled data directly comparing ephedrine and phenylephrine concluded that both agents achieve comparable blood pressure stabilization, yet phenylephrine consistently yields a higher umbilical arterial pH postpartum.

Notably, the frequencies of fetal acidaemia (defined as umbilical artery pH below 7.20) and low 1-and 5-minute Apgar scores did not differ significantly between groups [9]. In our local clinical experience, adopting a dual-agent approach with concurrent phenylephrine and ephedrine as initial pressor support was associated with a reduced frequency of neonatal acidosis relative to ephedrine monotherapy [10]. The present investigation was done to evaluate the rates of fetal acidosis at term cesarean delivery under spinal anesthesia, comparing continuous infusions of phenylephrine, ephedrine, or their combination for sustaining maternal systolic pressure at baseline.

Additionally, maternal emetic symptoms during the procedure were assessed across the three infusion regimens.

Patient and Methods

This study Conducted within the operating suites in AL Basra Teaching Hospital, Iraq, this comparative controlled trial enrolled subjects assigned an American Society of Anesthesiologists (ASA) physical status of Class I or II. patients scheduled for elective cesarean delivery under spinal anesthesia. Inclusion criteria required a singleton pregnancy without fetal abnormalities or a history of preeclampsia/diabetes, with baseline blood pressure and heart rate determined by the lowest of three seated, automated measurements taken in the 30 minutes prior to the procedure. Before the induction of spinal anesthesia, episodes of nausea and vomiting were assessed using a three-point scale: 0 indicated no symptoms, 1 represented nausea without emesis, and 2 denoted vomiting.

Participants were assigned randomly to one of three vasopressor treatment groups To ensure unbiased assessment, patients and all healthcare personnel involved in perioperative management, including anesthesiologists, nursing staff, and midwives, remained unaware of the assigned treatment. The study interventions consisted of phenylephrine (100 μg/mL), ephedrine (3 mg/mL), or a mixed preparation containing phenylephrine (50 μg/mL) together with ephedrine (1.5 mg/mL).
Immediately before anesthesia, one investigator prepared the study medications in identical syringes that contained either 4 mg of phenylephrine, 120 mg of ephedrine, or a combination of 2 mg of phenylephrine and 60 mg of ephedrine. All syringes were identical in appearance and contained equal total volumes to preserve blinding. They were stored on labeled trays in a room adjacent to the operating theater.

An independent individual who was not involved in patient management or data collection opened the randomization envelope and selected the appropriate unlabeled syringe according to the allocation sequence. The study solution was subsequently diluted with normal saline to a final volume of 40 mL before administration. The attending anesthesiologist was permitted to perform the spinal anesthesia was permitted to select the position with which he or she was most experienced.

This strategy was adopted to maximize clinician familiarity with the procedure and avoid potential variability associated with unfamiliar techniques or patient positioning. To minimize selection bias, randomization was stratified separately for each spinal anesthesia technique. The four approved anesthetic protocols were as follows: (1) intrathecal injection of 2.5 mL hyperbaric 0.5% bupivacaine combined with fentanyl 20 μg in the sitting position; (2) administration of 2 mL 0.5% levobupivacaine with fentanyl 20 μg in the sitting position followed by epidural catheter placement; (3) injection of 2 mL 0.5% levobupivacaine plus fentanyl 20 μg in the left lateral position before epidural catheter insertion; and (4) administration of 2.5 mL 0.5% levobupivacaine with fentanyl 10 μg in the left lateral position before epidural catheter placement.

The extent of sensory blockade was evaluated using ethyl chloride spray to assess loss of cold sensation at 10 minutes after intrathecal injection and again at the time of skin incision. An anesthetic level above the fifth thoracic dermatome (T5) was considered adequate for surgery. If spinal anesthesia failed to provide a sufficiently high or dense sensory block before delivery, supplemental epidural anesthesia with 0.5% levobupivacaine was administered.

Before performing the spinal block, all participants received a rapid intravenous preload of Hartmann's solution at a dose of 10 mL/kg. Immediately after completion of the intrathecal injection, the allocated vasopressor infusion

was commenced intravenously to support maternal blood pressure throughout the procedure. Following spinal anesthesia, patients were repositioned supine with the customary left lateral tilt.

Using the same automated oscillometric device employed for initial readings, systolic blood pressure and pulse rate were recorded at 60-second intervals. The study drug was administered through a Y-connector sharing the same IV line as the Hartmann infusion, which flowed at roughly 4 mL/min post-preload; a non-reflux valve prevented backflow of the study solution into the main fluid pathway. The investigational infusion commenced at 20 mL/hour—equivalent to phenylephrine 33 µg/min, ephedrine 1 mg/min, or a 50% reduced rate for both in the combined arm.

The infusion rate of medications are setting to keep the systolic blood pressure at or near the pre-operative level. The infusion ceiling was 40 mL/hour, with a floor of 1.3 mL/hour. Should the maximum rate prove insufficient, 1–2 mL rescue boluses could be delivered via syringe driver.

If systolic pressure rose to ≥1.25 above baseline, the infusion ceased and resumed at half the prior rate only after pressure fell below that threshold again. If systolic pressure dropped to ≤0.75 above baseline, the rate was doubled plus a 1 mL bolus administered. Failure to sustain systolic pressure above 0.75× baseline despite maximal protocol-driven measures (40 mL/hour plus supplementary 2 mL boluses) prompted turning the patient fully onto her left side.

If that maneuver failed to correct the hypotension, or if it recurred upon returning to the tilted supine position, the treatment assignment was unblinded and the vasopressor regimen modified accordingly. All such cases were evaluated under intention-to-treat principles. The protocol extended until fetal delivery.

Maternal heart rhythm was tracked continuously via pulse oximetry. Glycopyrrolate 200 µg was given intravenously for specified Brady arrhythmias, defined as: heart rate <60 bpm coupled with systolic pressure <0.75 below baseline; heart rate <50 bpm with systolic pressure <1.00 below baseline; or heart rate <45 bpm irrespective of blood pressure. The peak nausea/vomiting score from spinal injection to delivery was documented.

At birth, a study investigator drew blood from both umbilical artery and vein from a doubly clamped cord segment prior to the infant's inaugural breath.

Statistical Analysis

Data analysis was performed using nonparametric statistical methods. Comparisons among the three treatment groups were initially conducted using the **Kruskal–Wallis test**. When an overall statistically significant difference was observed, **pairwise comparisons** were subsequently carried out using the **Mann–Whitney U test**. Changes within each treatment group were evaluated with the **Wilcoxon signed-rank test**, while associations between variables were assessed using the **Spearman rank correlation test**. Statistical significance was established at a **P-value < 0.05**.

In the remaining case (combined group), no umbilical cord blood could be drawn. These four individuals remained in the analysis for all other outcome measures. Baseline characteristics—maternal age, stature, body mass, gestational duration, fetal breech positioning, prior uterine scar from cesarean delivery, and neonatal birth mass—showed no significant intergroup disparities (Table 1).

Infusion protocols were strictly regulated, and all measurements were obtained by a team of tree trained observers (Table 2). The three study arms also demonstrated comparable distributions of neuraxial anesthetic agents administered (P = 0.99), as well as similar volumes of crystalloid and colloid preloading, total infusion fluid quantities, and vasopressor titration requirements (P values not significant). No significant differences were identified among the treatment groups with respect to the duration of data collection by the investigator (P = 0.77) or the interval between uterine incision and fetal delivery (P = 0.10) (Table 2).

The overall maternal systolic arterial pressure recorded from the time of spinal anesthesia until delivery remained comparable across all three study groups (Table 3). Likewise, serial measurements of systolic blood pressure demonstrated similar hemodynamic profiles throughout most of the observation period. Nevertheless, a modest

but statistically significant reduction in systolic arterial pressure was observed in the phenylephrine group between 15 and 20 minutes after spinal anesthesia compared with both the ephedrine and combination groups.

The overall frequency of maternal hypotension, defined as a systolic arterial pressure below 80% of the baseline value, did not differ significantly among the three treatment arms (Table 3). However, significant between-group differences were observed for both the lowest systolic blood pressure achieved during the study (P = 0.04) and the percentage of blood pressure measurements falling below 80% of baseline (P = 0.02). Participants receiving phenylephrine experienced a higher minimum systolic arterial pressure, with a median value of 80% of baseline, compared with those treated with ephedrine, whose median lowest pressure was 73% of baseline (P = 0.02).

The combination group demonstrated an intermediate median minimum systolic pressure of 77%, which was not significantly different from either the phenylephrine (P = 0.14) or ephedrine (P = 0.25) groups. Similarly, the proportion of systolic blood pressure recordings below 80% of baseline was significantly lower in the phenylephrine group, with a median of 0%, than in the ephedrine group, which had a median of 8% (P = 0.007). The combination regimen also resulted in fewer hypotensive readings, with a median of 4% (IQR 0–10), compared with ephedrine alone (P = 0.04).

No statistically significant difference was detected between the phenylephrine and combination groups (P = 0.55). Blinding was discontinued for two participants assigned to the ephedrine group because clinical circumstances required disclosure of their treatment allocation. Two women assigned to the ephedrine group developed severe hypotension, with systolic arterial pressure falling below 75% of their baseline values despite treatment with ephedrine and positioning in the full left lateral tilt. In both cases, the treatment allocation was unblinded to permit appropriate clinical management.

Each patient received a rescue intravenous dose of phenylephrine (100 μg), which promptly restored systolic blood pressure to above 75% of baseline. Following stabilization, adequate blood pressure control was maintained using ephedrine while the patients remained in the left lateral tilt position. Beginning five minutes after spinal anesthesia, maternal heart rate was consistently greater in the ephedrine group than in either the phenylephrine or combination groups.

Across the entire observation period, the combination regimen produced heart rate values that were significantly lower than those observed with ephedrine alone (P = 0.0001) but remained significantly higher than those recorded with phenylephrine (P = 0.008) (Table 3). Peak maternal heart rate also differed significantly among the treatment groups (P = 0.0001). The highest median heart rate was recorded in the ephedrine group, reaching 137% of baseline, compared with 115% in the phenylephrine group (P < 0.0001) and 122% in the combination group (P = 0.004).

No statistically significant difference was identified between the phenylephrine and combination groups (P = 0.051). The frequency of pharmacologic treatment for maternal bradycardia was comparable among the study groups (Table 3). Glycopyrrolate was administered to one participant in the phenylephrine group and one participant in the combination group because their heart rates decreased to below 45 beats per below 50 beats/min while systolic arterial pressure remained below baseline.

In addition, four women in the ephedrine group required glycopyrrolate because their heart rate fell below 60 beats/min in association with severe hypotension, defined as systolic arterial pressure below 75% of baseline. No patients in either the phenylephrine or combination groups required treatment under these conditions. The occurrence of neonatal acidosis was significantly lower in both the phenylephrine group and the combination group compared with the ephedrine group.
Umbilical cord blood gas measurements are summarized in Table 4. No meaningful differences were observed between the phenylephrine and combination groups. In contrast, neonates whose mothers received ephedrine exhibited significantly In contrast, neonates whose mothers received ephedrine exhibited significantly lower umbilical arterial pH than those in the phenylephrine ($P = 0.002$) or combination ($P = 0.009$) groups. Likewise, umbilical venous pH was significantly lower in the ephedrine group than in both the phenylephrine ($P = 0.04$) and combination ($P = 0.003$) groups.

Table1: Maternal and Fetal Demographic Data.

variables	Phenylephrine Group (n =96)	Ephedrine Group (n =100) (%)	Combination Group (n =98) (%)

Age(years)	30 (24–33)	29 (25–30)	31 (22–32)
Height (cm) mean	162	160	160
Weight (kg) mean	76	80	78
Previous cesarean section	44	46	37
Fetal weight (kg) mean	3.50	3.37	3.43

Table 2: Operative Data:

variables		Ephedrine Group (n = 100) (%)	Phenylephrine Group (n = 96) (%)	Combination Group (n = 98) (%)
Spinal technique	Technique1	46%	50%	47%
	Technique2	28%	27%	29%
	Technique3	16%	16%	16%
	Technique4	10%	8%	8%
Investigator	One	48%	31%	47%
	Two	32%	35%	22%
	Three	16%	23%	24%
Block height	at10min	T3(T1–T4)	T3(T2–T5)	T3(T2–T6)
	at skin incision	T2(C8–T3)	T3(T2–T3)	T2(T2–T3)
Spinal-skin incision(min)		17–22		16–22
Spinal-delivery(min)		23–29		22–29
Skin incision-delivery(min)		5–7		5–8
Uterine incision-delivery	1-min	35%	55%	55%
	2-min	48%	32%	34%
	3-min	10%	11%	9%
	4-min	6%	2%	2%

Table 3: Preoperative Maternal Characteristics and Perioperative Cesarean Delivery Data

variables		Phenylephrine Group (n =96)	Ephedrine Group (n= 100)	Combination Group (n 98) (%)	P Value
preoperative Maternal variables	Systolic arterial pressure (mmHg)(mean)	110	110	113	P = 0.63
	Heart rate (beats/min) (mean)	86	82	87	P = 0.73
Perioperative Cesarean Delivery Data :					
Nausea and vomiting	None	75 %	84	73	P = 0.46
	Nausea without vomiting	23%	12	24	
Fetal acidosis		2	21	2	P = 0.0007
1-min APGAR score		8	8	8	P = 0.53
5-min APGAR score		8	8	8	P = 0.35
Mean systolic arterial pressure as proportion of baseline		98 %	100 %	101 %	P = 0.11
Hypotension (systolic arterial pressure <80% of baseline)		48%	68%	57%	P = 0.13
Mean heart rate as proportion of baseline		88	107	96	P = 0.0001
Mean infusion rate (ml/min)		0.34	0.51	0.35	P 0.01

Consequently, the arteriovenous (A–V) PCO_2 gradient across the umbilical circulation was significantly greater in the ephedrine group than in the phenylephrine group (P = 0.002). Detailed blood gas data for neonates with acidemia are presented in Table 5. Among infants in the ephedrine group, the acid-base disturbance demonstrated features of both metabolic and respiratory acidosis.

Furthermore, two approximately 77% greater in those with acidemia than in those without acidemia, measuring 23 mmHg versus 13 mmHg, respectively (P < 0.0001). Moreover, increasing maternal exposure to ephedrine was strongly associated with progressively larger umbilical A–V PCO_2 differences. In contrast, neither the average maternal systolic arterial pressure (nor the lowest systolic arterial pressure recorded during surgery showed a significant correlation with the A–V PCO_2 gradient.

Within the phenylephrine group, no significant associations were identified between the umbilical A–V PCO_2 difference and the administered phenylephrine dose, mean maternal systolic arterial pressure, or the minimum systolic arterial pressure recorded during the procedure. At baseline, the three study groups exhibited comparable scores for nausea and vomiting as shown in Table 3. Over the course of the trial, the phenylephrine cohort showed no significant shift in these scores from their starting point (P = 0.30).

In contrast, both the ephedrine group (P < 0.0001) and the combined-treatment group (P = 0.007) experienced significant rises in their nausea and vomiting ratings relative to baseline. When comparing post-baseline scores, the phenylephrine arm recorded substantially lower nausea and vomiting ratings than either the ephedrine-alone arm (P < 0.0001) or the combination arm (P < 0.0001). No meaningful distinction emerged, however, between the ephedrine and combination groups on this measure (P = 0.09).

Within the ephedrine subset, episodes of vomiting correlated with three key factors: a drop in systolic blood pressure, a reduction in heart rate, and a larger cumulative ephedrine dosage. Among ephedrine-treated participants who experienced vomiting (n = 18) versus those who reported no nausea or vomiting (n = 17), the lowest observed systolic pressures were 62% and 87% of initial values, respectively (P = 0.0002). Corresponding minimum heart rates were 71% and 92% of baseline (P = 0.0006).

The average ephedrine infusion rates also differed markedly: 1.8 mg/min for those who vomited versus 0.9 mg/min (0.5–1.4) for those without symptoms (P = 0.002). Notably, sensory block levels measured at 10 minutes post-injection and at the time of surgical incision did not differ significantly between these two ephedrine subgroups (P = 0.57 and P = 0.36, respectively). After removing from the analysis those ephedrine-group patients who exhibited the most profound hypotension—defined as a nadir systolic pressure at or below 60% of baseline—the average systolic arterial pressure, as well as the frequency, seriousness, and length of hypotensive episodes, became statistically indistinguishable across all three treatment arms.

Nevertheless, even with this exclusion, the ephedrine group continued to show the greatest rate of fetal acidemia, while the phenylephrine group maintained the lowest nausea and vomiting scores.

Table 4: Intergroup fetal blood gas value

variables	Ephedrine Group (n =96) mean	Phenylephrine Group (n =96) mean	Combination Group (n= 94) mean	P Value
Arterial pH	7.31 (7.29–7.33)	7.34 (7.23–7.31)	7.31 (7.28–7.32)	P = 0.004
Venous pH	7.39 (7.35–7.38)	7.36 (7.32–7.37)	7.37 (7.35–7.39)	P = 0.009
Arterial –venous pH difference	0.11 (9–13)	0.06 (0.05–0.07)	0.07 (0.05–0.08)	P = 0.003
Arterial partial oxygen pressure (mmHg)	15 (9–17)	13 (10–15)	12 (8–15)	P= 0.17
Arterial partial pressure of CO2 (mmHg)	52 (48–56)	55 (50–64)	54 (50–58)	P = 0.12
Venous partial pressure of CO2 (mmHg)	45 (37–50)	43 (38–44)	41 (37–43)	P 0.17

Discussion

The present investigation demonstrated that the use of phenylephrine, either as the sole vasopressor or in combination with ephedrine, significantly decreased the occurrence of fetal acidemia during cesarean delivery performed under spinal anesthesia compared with ephedrine alone. Fetal acidemia was identified in only 2 of 96 neonates in the phenylephrine group and 2 of 94 neonates in the combination group, whereas 20 of 96 neonates in the ephedrine group developed acidemia. Analysis of umbilical cord blood gases indicated that the acid-base disturbance in affected neonates consisted of both metabolic and respiratory components.

Moreover, two infants exposed to ephedrine exhibited severe metabolic acidosis, with base deficits exceeding 10 mmol/L. Several mechanisms may explain the higher incidence of fetal acidemia observed with ephedrine monotherapy. These include impaired uteroplacental perfusion resulting from maternal hypotension, decreased uteroplacental blood flow caused by ephedrine-induced vasoconstriction of the uterine circulation, or a direct pharmacologic effect of ephedrine on the fetus.

Although uteroplacental blood flow and vascular resistance were not measured directly, several observations suggest that reduced uteroplacental perfusion was unlikely to be the principal explanation for the poorer fetal acid-base status in the ephedrine group. Maternal systolic arterial pressure remained well maintained and was generally

comparable among all three treatment groups throughout the study period. Although women receiving ephedrine experienced a slightly greater degree and duration of hypotension, additional analyses excluding patients with severe hypotensive episodes showed no significant differences in either the frequency, magnitude, or duration of hypotension between the study groups.

Despite this adjustment, the incidence of fetal acidemia remained substantially higher among neonates whose mothers received ephedrine. These findings indicate that reduced uterine perfusion pressure secondary to maternal hypotension is unlikely to account for the increased fetal acidosis associated with ephedrine administration. Similarly, ephedrine-induced constriction of the uteroplacental vasculature does not appear to be the primary mechanism responsible for these findings.
Experimental studies conducted in pregnant female have demonstrated that ephedrine produces considerably weaker vasoconstriction of the uterine arteries than pure α-adrenergic agonists, suggesting that its effect on uteroplacental vascular resistance is relatively limited [1]. A recent investigation comparing metaraminol, a receptor-activating agent, with ephedrine during spinal blockade for non-emergent cesarean delivery observed no variation in uterine arterial circulation as measured by sonographic imaging [11]. Moreover, if placental exchange had been compromised enough to produce fetal metabolic imbalance, a drop in oxygen tension within the umbilical vein would likely have occurred due to diminished oxygen transfer to the fetoplacental unit.

Yet, in the subset receiving ephedrine, no correlation emerged between neonatal acidotic status (as reflected by declining arterial pH in the umbilical cord) and the oxygen content of the umbilical venous blood. Examining carbon dioxide gradients between the umbilical artery and vein offers circumstantial clues that a fetal response may explain the heightened acidosis seen with ephedrine. Prior work demonstrated that severe hypo perfusion of the uteroplacental bed—resulting from placental abruption and leading to profound neonatal acidity did not coincide with an elevated arteriovenous CO_2 gap (In contrast, our data revealed a robust link between acidemia and a widening of this gradient: for ephedrine-exposed newborns without acidosis (umbilical arterial pH $\geq$7.20), the median CO_2 difference was 13 mmHg, whereas those with acidosis (pH <7.20) exhibited a median of 23 mmHg, a highly significant disparity ($P < 0.0001$).

One potential fetal pathway for this acidotic state involves constriction of umbilical vessels triggered by β-adrenergic receptor activation. Diminished flow through these vessels can indeed produce acidosis accompanied by an enlarged arteriovenous CO_2 gap: severe fetal acidemia from cord compression was previously tied to a substantial CO_2 gradient Nevertheless, this mechanism seems improbable as the primary driver in our ephedrine findings. Ephedrine possesses weaker β-adrenergic properties than phenylephrine; β-adrenergic stimulation actually enhances umbilical circulatory flow, [12] and both presser drugs have demonstrated only negligible effects on the umbilical arterial resistance index [13].

A direct stimulatory effect of ephedrine on the fetal adrenergic system represents another plausible explanation for the development of fetal acidemia that is independent of alterations in uteroplacental or fetoplacental blood flow. Experimental investigations in fetal lambs have shown that administration of the β-adrenergic agonist isoproterenol results in an immediate rise in fetal oxygen consumption accompanied by increased glucose utilization and elevated lactate concentrations [12]. These findings led investigators to propose that β-adrenergic activation enhances anaerobic glycolysis because fetal oxygen delivery is already operating close to its physiological maximum.

Evidence from human studies also indicates that maternal administration of ephedrine exerts measurable pharmacological effects on the fetus. Previous investigations have demonstrated increases in both fetal heart rate and circulating fetal catecholamine concentrations following maternal ephedrine administration [14]. Furthermore, prolonged maternal exposure to a β_2-adrenergic agonist for approximately two hours before elective cesarean delivery has been associated with the development of fetal metabolic acidemia [15]. In the present study, umbilical venous PCO_2 values did not differ significantly between the ephedrine and phenylephrine groups.

In contrast, umbilical arterial PCO_2 was significantly higher among neonates exposed to ephedrine. Assuming that umbilical blood flow was not reduced in the ephedrine group, this finding suggests greater fetal carbon dioxide production, indicating an increase in fetal metabolic activity. Additional support for this hypothesis was provided by the observation that the umbilical arteriovenous (A–V) PCO_2 gradient was approximately 77% greater in acidotic fetuses than in non-acidotic fetuses within the ephedrine group.

This larger PCO_2 difference is consistent with a higher fetal metabolic rate in the acidotic subgroup. Collectively, these observations suggest that stimulation of fetal β-adrenergic receptors by ephedrine, leading to increased fetal metabolism, is the most likely mechanism responsible for the higher incidence of fetal acidemia associated with ephedrine administration. Incorporating phenylephrine into the vasopressor regimen reduced the required ephedrine dose by approximately two-thirds, which likely accounts for the markedly lower incidence of fetal acidemia observed in the combination treatment group.

The findings of the present study are consistent with those reported in two more recent clinical investigations. Both studies demonstrated that vasopressor regimens possessing greater α-adrenergic activity than ephedrine were associated with improved fetal acid-base status during cesarean delivery. One trial compared metaraminol with ephedrine [11], whereas the other evaluated a combined phenylephrine–ephedrine regimen against ephedrine alone [16].

In the comparison between metaraminol and ephedrine, neonates exposed to ephedrine exhibited a higher incidence of acidemia despite similar rates of maternal hypotension in the two groups [11]. Additional studies have likewise shown that prophylactic administration of ephedrine during epidural or spinal anesthesia may increase the risk of fetal acidemia even while effectively reducing maternal hypotension [7]. Nevertheless, these findings should not be interpreted as definitive evidence that α-adrenergic agonists are universally superior to ephedrine with respect to overall neonatal well-being.

Current evidence indicates that Apgar scores remain more reliable indicators of neonatal clinical outcome than umbilical arterial pH measurements alone [17]. All infants achieved satisfactory Apgar scores at birth, and none required endotracheal intubation, mechanical ventilator support, or admission to the neonatal special care unit during the immediate postnatal period. These findings indicate that, despite the observed differences in umbilical cord blood gas values, no clinically significant compromise in early neonatal adaptation was evident.

Interestingly, activation of the fetal adrenergic system before delivery may confer certain physiological advantages. Previous research has demonstrated that maternal administration of a β_2-adrenergic agonist before elective cesarean section improves neonatal pulmonary function by increasing dynamic lung compliance, reducing airway resistance and respiratory rate, and lowering the incidence of neonatal hypoglycemia [15]. Consequently, additional investigations are warranted to clarify the potential cardiovascular, respiratory, and metabolic consequences of maternal exposure to phenylephrine, ephedrine, or their combination during cesarean delivery.

Although no adverse neonatal effects were identified in this cohort of low-risk pregnancies, caution should be exercised when extrapolating these findings to pregnancies complicated by pre-existing fetal compromise. Fetuses with impaired physiological reserve may be less capable of tolerating the reduction in acid-base status associated with ephedrine administration. Therefore, in subsequent research must focus on the high-risk obstetric populations and measure neonatal consequences of phenylephrine and ephedrine regarding fetal hypoxia and acidemia.

Maternal nausea and vomiting remain common and clinically important adverse effects during cesarean delivery performed under spinal anesthesia. Despite achieving comparable control of maternal systolic arterial pressure across all treatment groups, the incidence of these symptoms differed substantially according to the vasopressor administered. Women receiving phenylephrine alone experienced no significant increase in nausea or vomiting compared with pre-anesthetic baseline values, even though episodes of hypotension still occurred.

In contrast, patients treated with ephedrine, either alone or in combination with phenylephrine, demonstrated a marked increase in both nausea and vomiting during the intraoperative period. Notably, the higher incidence of gastrointestinal symptoms observed in the combination group compared with the phenylephrine group occurred despite equivalent maintenance of maternal blood pressure. Likewise, when patients with the most pronounced hypotensive episodes were excluded from the ephedrine group, thereby eliminating the minor differences in hypotension between treatment groups, the increased frequency of nausea and vomiting associated with ephedrine remained unchanged.

These observations suggest that variations in maternal blood pressure alone cannot adequately explain the differing incidences of these adverse effects. Although a direct emetogenic action of ephedrine might be considered, this explanation appears unlikely because previous studies have reported antiemetic effects of

ephedrine following gynecological surgery [18]. An alternative mechanism involves enhanced parasympathetic (vagal) activity during spinal anesthesia.

Earlier investigations have demonstrated that atropine provides greater relief of spinal anesthesia-induced nausea than vasopressor therapy alone, supporting the contribution of vagal stimulation to this symptom [19]. Furthermore, prophylactic administration of glycopyrrolate has been shown to reduce the occurrence of nausea during cesarean delivery under spinal anesthesia [20]. The findings of the present study further support this hypothesis.

Among women receiving ephedrine, episodes of vomiting were accompanied not only by reductions in systolic arterial pressure but also by decreases in heart rate. The simultaneous occurrence of hypotension and bradycardia is consistent with increased vagal activity, suggesting that enhanced parasympathetic tone may have contributed to the higher incidence of nausea and vomiting observed in patients treated with ephedrine. Despite the observed differences in maternal gastrointestinal symptoms, there was no evidence to suggest that these variations were attributable to differences in the extent or height of the spinal sensory block.

An alternative explanation may involve activation of a cardio inhibitory vagal reflex triggered by a reduction in cardiac preload [21]. Such reflex-mediated parasympathetic activation has been reported to occur more readily in the presence of concurrent β-adrenergic stimulation [21]. During spinal anesthesia for cesarean delivery, venous return is substantially reduced because of sympathetic blockade-induced vasodilation in combination with aortocaval compression by the gravid uterus.

Under these conditions, phenylephrine may provide a physiological advantage by producing greater vasoconstriction, thereby improving venous return and maintaining cardiac preload. In addition, the absence of significant β-adrenergic stimulation with phenylephrine may reduce the likelihood of excessive vagal activation. This mechanism may explain why phenylephrine was associated with a markedly lower incidence of maternal nausea and vomiting despite achieving blood pressure control comparable to that of the other vasopressor regimens.

All three study medications successfully maintained maternal systolic arterial pressure close to baseline values throughout the intraoperative period. Nevertheless, two participants receiving ephedrine developed persistent hypotension that failed to respond adequately to continued ephedrine administration combined with full left lateral uterine displacement. In these cases, treatment allocation was unblinded to permit rescue therapy, and administration of a single intravenous dose of phenylephrine (100 μg) promptly restored arterial pressure, allowing subsequent hemodynamic stability to be maintained with the ongoing ephedrine infusion.

These observations support the clinical usefulness of phenylephrine as an effective rescue vasopressor for hypotension that is refractory to ephedrine treatment. Significant differences in maternal heart rate were also observed among the treatment groups. Phenylephrine administration resulted in the lowest heart rate values, whereas ephedrine produced the greatest increase in maternal heart rate, reflecting their distinct pharmacodynamics profiles.

Despite these differences, the frequency of clinically significant bradycardia requiring glycopyrrolate administration did not differ among the three groups, indicating that the lower heart rate associated with phenylephrine rarely necessitated pharmacological intervention. Overall, the findings of this study indicate that continuous phenylephrine infusion is superior to ephedrine infusion for maintaining maternal hemodynamic stability during spinal anesthesia for elective cesarean delivery. In addition to providing effective blood pressure control, phenylephrine significantly reduced the incidence of fetal acidemia and maternal nausea and vomiting compared with ephedrine alone.

Although the combined administration of phenylephrine and ephedrine also lowered the incidence of fetal acidemia relative to ephedrine monotherapy, it failed to provide any additional improvement in neonatal acid–base status beyond that achieved with phenylephrine alone. Furthermore, the combination regimen was associated with a higher frequency of maternal nausea and vomiting. These findings suggest that phenylephrine alone represents the most appropriate first-line vasopressor for the prevention and management of spinal anesthesia-induced hypotension during elective cesarean delivery.

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