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ORIGINAL ARTICLE

Epinephrine vs. phenylephrine infusion for prophylaxis against maternal hypotension after spinal anesthesia for cesarean delivery: a randomized controlled trial

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Abstract

Background The hemodynamic effects of relatively low-dose epinephrine and phenylephrine infusions during cesarean delivery under spinal anesthesia were compared.

Methods This randomized controlled trial included full-term pregnant women who underwent elective cesarean delivery. After spinal anesthesia, participants received either epinephrine (0.03 mcg/kg/min) or phenylephrine (0.4 mcg/kg/min) infusion that continued until 5 min after delivery. The primary outcome was a composite outcome of the occurrence of any of hypotension, hypertension, bradycardia, and/or tachycardia. Neonatal outcomes, including umbilical artery blood gas and Apgar scores, were assessed.

Results In total, 98 patients in each group were analyzed, and the number of patients with the composite outcome was comparable between the epinephrine and phenylephrine groups (30/98 [31%] vs. 31/98 [32%], respectively; $P=0.877$). However, the incidence of hypotension was likely lower in the epinephrine group than in the phenylephrine group ($P=0.066$), and the number of hypotensive episodes per patient was lower in the epinephrine group than in the phenylephrine group. On the other hand, the incidence of tachycardia was higher in the epinephrine group than that in the phenylephrine group. The incidence of hypertension was comparable between the two groups and none of the participants developed bradycardia. Neonatal outcomes were comparable between the two groups.

Conclusions Epinephrine and phenylephrine infusion produced comparable maternal hemodynamics and neonatal outcomes. Epinephrine was associated with a higher incidence of maternal tachycardia and likely lower incidence of maternal hypotension than phenylephrine.

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Clinical trial registration: This study was registered on May 31, 2023 at clinicaltrials.gov registry, NCT05881915, URL: https://classic.clinicaltrials.gov/ct2/show/NCT05881915term=NCT05881915&draw=2&rank=1

Keywords Epinephrine · Phenylephrine · Spinal anesthesia · Hypotension · Cesarean delivery

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Introduction

Cesarean delivery is one of the most common medical interventions worldwide. Despite several maternal and fetal advantages of spinal anesthesia for cesarean delivery, maternal hypotension remains a frequent and serious complication despite extensive measures for its prevention [1]. Due to deleterious effects of hypotension on the mother and fetus, it is well established that prophylaxis against maternal hypotension should be routinely initiated after spinal block in all mothers unless baseline hypertension is present [2].

Several interventions to maintain maternal blood pressure have been described, with pharmacological methods being the most effective. The ideal prophylactic drug should yield the lowest possible incidence of hypotension; however, it is desirable to also minimize other cardiac adverse events, such as tachycardia, bradycardia, and hypertension. Phenylephrine is still considered the gold-standard vasopressor in obstetric practice [2]. However, reflex bradycardia is an important limitation of the use of phenylephrine, especially in mothers with low baseline heart rate or reduced systolic cardiac function. The availability of the drug in low-resource settings is another limitation.

Epinephrine is a commonly-used vasoactive drug with beta-adrenoreceptor activity; thus, its use during cesarean delivery may maintain maternal blood pressure with a better-preserved heart rate. The use of epinephrine in obstetric practice has recently been investigated in few trials. Wang et al. [3] compared epinephrine and phenylephrine in 80 mothers and found that epinephrine yielded a lower incidence of bradycardia than phenylephrine. More recently, a large randomized clinical trial [4] evaluated 3 doses of epinephrine during cesarean delivery and suggested that 0.03 mcg/kg/min was a suitable starting dose, a dose much less than that reported in the trial by Wang et al. [3] (0.1 mcg/kg/min). The present study aimed to compare epinephrine and phenylephrine infusions during cesarean delivery in terms of overall maternal hemodynamic profile using a composite outcome of hypotension, hypertension, bradycardia, and tachycardia.

Methods

This randomized controlled study was conducted at Cairo University Hospital (Cairo, Egypt) between June and October 2023, after Institutional Ethics Committee approval (MD-245-2022). Clinical trial registration was performed before patient enrollment (NCT05881915, PI: Yasmin S Hassabelnaby, May 31, 2023). Written informed consent was obtained from all patients before enrolment. The present study adhered to the CONSORT guidelines.

Participants included full-term, singleton, pregnant women 18–40 years of age who underwent elective cesarean delivery. Individuals with uncontrolled cardiac morbidities, hypertensive disorders of pregnancy, abnormal placentation, coagulation disorders, and baseline systolic blood pressure < 100 mmHg were excluded.

Randomization was performed using an online random numbers generator. The patients were randomly allocated to the study groups in a 1:1 ratio. Group assignments, according to the randomization number and drug preparation instructions, were placed inside sequentially numbered opaque envelopes. A research assistant was responsible for opening the envelopes, preparing the drug, and setting the infusion rate without further involvement in the study. The patient, attending anesthetist, and data collector were blinded to the vasopressor type.

Drug preparation

Phenylephrine (10,000 mcg) was diluted in 500 mL of saline, and the infusion rate was set at 1.2 mL/kg/h (equivalent to 0.4 mcg/kg/min); epinephrine (1000 mcg) was diluted in 500 mL of saline (2 mcg/mL), and the infusion rate was set at 0.9 mL/kg/h (equivalent to 0.03 mcg/kg/min). The doses of the 2 drugs were selected at a ratio of 13:1 according to available data regarding the relative potency of the 2 vasopressors [5, 6].

Anesthetic management

All patients were monitored using 5-lead electrocardiography, pulse oximetry, and noninvasive blood pressure monitor. An 18-gauge (G) cannula was inserted, and 10 mg of metoclopramide was administered, followed by a co-load infusion of 15 mL/kg of lactated Ringer's solution. Baseline systolic blood pressure reading was recorded as the average of 3 readings with < 10% variability.

Spinal anesthesia was administered with patients in the sitting position at the level of the L3–4 or L4–5 intervertebral space using a 25G spinal needle. The local anesthetic solution was 10 mg hyperbaric bupivacaine in addition to 20 mcg fentanyl. After injection of the local anesthetic solution, participants were positioned supine with a left-lateral tilt, and vasopressor infusion was started. Vasopressor infusion was continued for 5 min after delivery. Spinal block was assessed using a pinprick, and block success was confirmed if the sensory blockade was at the level of T4.

Hemodynamic management

Spinal hypotension was defined as systolic blood pressure < 80% of the baseline reading during the period from intrathecal injection until delivery and was managed using either a 9 mg bolus of ephedrine (if the heart rate was < 75 beats/min) or a 50 mg bolus of phenylephrine (if heart rate was > 75 beats/min). Severe spinal hypotension was defined as systolic blood pressure < 60% of the baseline reading, which was managed by the administration of either 15 mg ephedrine (if heart rate was < 75 beats/min) or a 100 mg bolus of phenylephrine (if heart rate > 75 beats/min). Excessive hypertension was defined as systolic blood pressure > 120% of the baseline reading. Excessive hypertension was managed by stopping the infusion if it persisted for > 1 reading and was restarted at 50% of the initial rate when systolic blood pressure decreased to within 20% of the baseline reading.

Intraoperative bradycardia (heart rate < 55 beats/min) was managed by stopping the vasopressor infusion if it was not associated with hypotension. When heart rate increased to > 55 beats/min, the infusion was restarted at 50% of the initial rate. In addition to ephedrine, a bolus of atropine (0.5 mg) was administered if bradycardia was accompanied by hypotension. Excessive tachycardia was defined as a heart rate > 100 beats/min or > 120% of the baseline in the absence of hypotension.

Intraoperative fluid administration was continued to a maximum of 1.5 L. After delivery, a 0.5 IU oxytocin bolus was administered over 5 s, followed by an infusion rate of 2.5 IU/h.

Outcomes

The primary outcome was hemodynamic instability, which was defined as the occurrence of hypotension, hypertension, bradycardia, and/or tachycardia. Secondary outcomes included the following: incidence of spinal and severe spinal hypotension; number of hypotensive episodes per patient; time to first hypotensive episode; incidence of bradycardia, hypertension, and tachycardia; total dose of phenylephrine, epinephrine, and ephedrine; and incidence of intraoperative nausea and vomiting. Patient demographic information and surgical data were also recorded. Neonatal outcomes, namely umbilical artery blood gases and Apgar scores, were recorded 5 min after delivery.

Sample size calculation

The primary outcome was the incidence of hemodynamic instability. In a pilot study, the incidence of hemodynamic instability, including any event of hemodynamic derangement with prophylactic phenylephrine infusion was 45%. The sample size required to detect an absolute risk reduction of 20% was estimated; accordingly, the number of participants was calculated to be 196 (98 in each group) for a study power of 80% and an alpha error of 0.05. The number of envelopes was increased to 226 to compensate for dropouts (113 women per group). The sample size was calculated using MedCalc version 14 (MedCalc Software bvba, Ostend, Belgium).

Statistical analysis

Data analysis was performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA USA). Categorical data are reported as frequency and percentage and were analyzed using the Chi-squared test. Data distribution was assessed using the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± standard deviation and were analyzed using the unpaired Student's *t* test, while skewed data are expressed as median (quartiles) and compared using the Mann–Whitney *U* test. The log-rank test was used to compare the time to hypotensive episodes between groups. Repeated measures data were assessed using analysis of variance for repeated measures to evaluate the dose (between-group factor) and time (repeated measures) effects. The Bonferroni test was used to adjust for multiple comparisons. Differences with $P < 0.05$ were considered to be statistically significant.

Results

Of 235 mothers assessed for eligibility, 9 were excluded, leaving 226 for data analysis, with 30 patients excluded (15 from each group), and 196 patients were analyzed (Fig. 1).

Demographic data and baseline hemodynamic characteristics were comparable between the 2 groups (Table 1). The mean (± SD) total phenylephrine consumption in the phenylephrine group was 719 ± 164 mcg and mean total epinephrine consumption in the epinephrine group was 51 ± 11 mcg.

The number of patients with hypotension, hypertension, bradycardia, and/or tachycardia was comparable between the epinephrine and phenylephrine groups (30/98 [31%] vs. [vs.] 31/98 [32%], respectively; $P = 0.877$).

Systolic blood pressure decreased in both groups compared with baseline and was generally comparable between the two groups (Fig. 2). However, the number of patients with spinal hypotension was likely to be less in the epinephrine group than in the phenylephrine group (18/96 [18%] vs. 29/96 [30%], respectively; $P = 0.066$), and the number of hypotensive episodes per patient was lower in the epinephrine group than in the phenylephrine group.

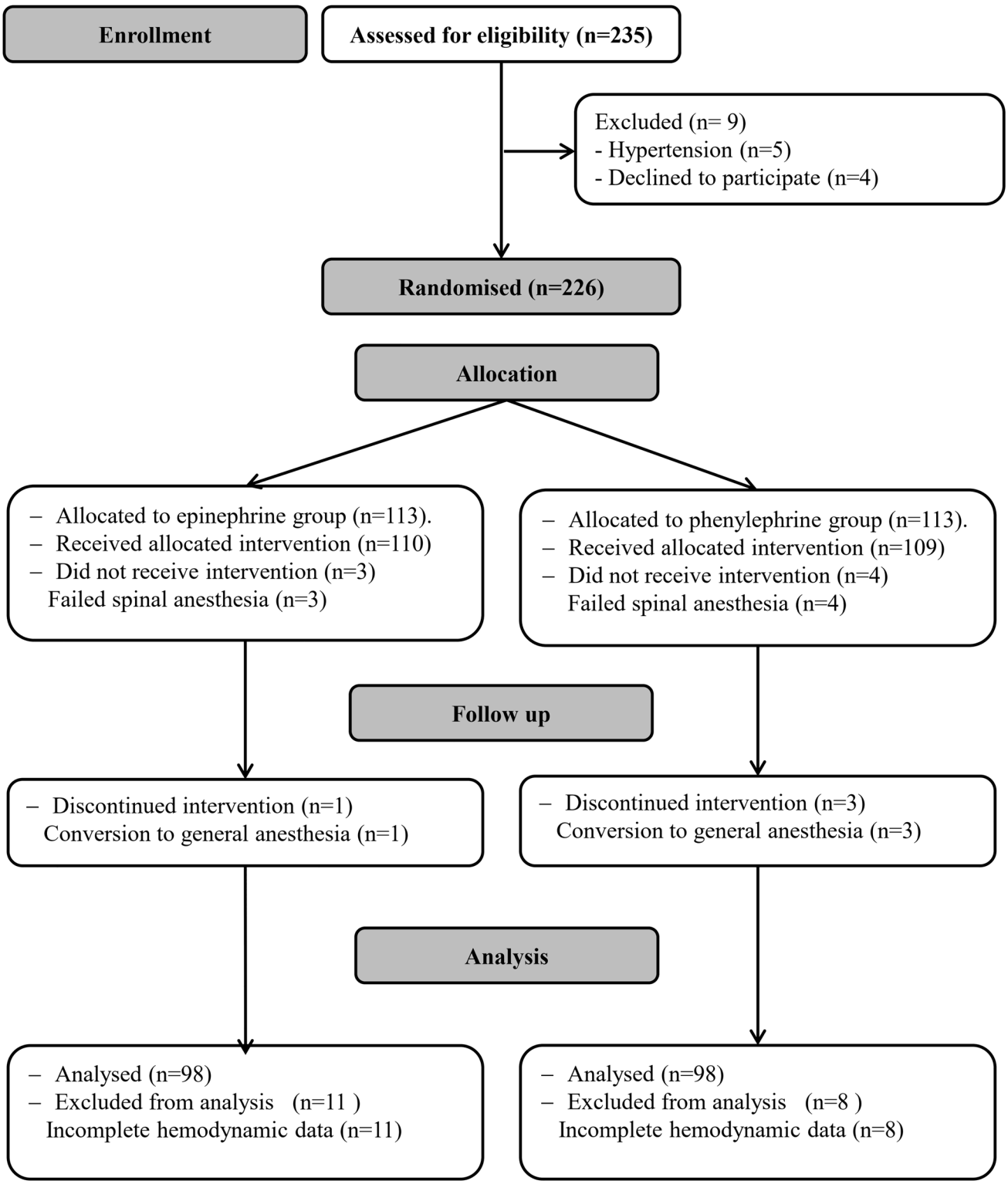

Fig. 1 CONSORT's flow chart

Table 1 Demographic data and baseline hemodynamic characteristics. Data are presented as median (quartiles) and mean ± standard deviation

	Epinephrine group ($n=98$)	Phenylephrine group ($n=98$)	P value
Age (years)	27 (23, 32)	28 (23, 32)	0.253
Weight (kg)	89 ± 13	89 ± 13	0.996
Baseline systolic blood pressure (mmHg)	123 ± 9	122 ± 10	0.380
Baseline heart rate (bpm)	97 ± 13	100 ± 14	0.080
Time to delivery (min)	14 (12, 16)	14 (11, 17)	0.913

The incidence of hypertension was comparable between the two groups (Table 2).

Heart rate was generally comparable between the two groups. Heart rate generally increased in the epinephrine group and decreased in the phenylephrine group compared with baseline reading (Fig. 3). The number of patients with tachycardia was higher in the epinephrine group than in the phenylephrine group (13/96 [13%] vs. 4/96 [4%], respectively; $P=0.022$). No patients developed bradycardia (Table 2).

Other maternal outcomes, namely the incidence of nausea, vomiting, and neonatal outcomes, were comparable between the two groups (Tables 2 and 3).

Discussion

We compared relatively low-dose epinephrine and phenylephrine infusions to maintain maternal hemodynamic profile during cesarean delivery using a composite outcome that included all undesirable cardiovascular events (hypotension, hypertension, tachycardia, and bradycardia). Our results revealed that the 2 drugs demonstrated comparable performances in terms of the primary outcome, with a relatively lower incidence of hypotension ($P=0.06$) in the epinephrine group and a lower incidence of tachycardia in the phenylephrine group ($P=0.02$).

We selected the epinephrine dose according to our recent randomized controlled dose-finding trial, which found that 0.03 mcg/kg/min could be the appropriate starting infusion rate during cesarean delivery. There is no available data regarding the relative potency of epinephrine and phenylephrine; thus, we referred to a study by Ngan Kee [6], which reported that the relative potency of norepinephrine and phenylephrine was 13:1. Epinephrine and norepinephrine have the same relative potency [5]; thus, we hypothesized that epinephrine and phenylephrine should have the same ratio, as previously described by Ngan Kee. However, this should be confirmed in future studies.

Post-spinal hypotension during cesarean delivery is a common event, and the prophylactic use of vasopressors is now established as the standard approach for decreasing its

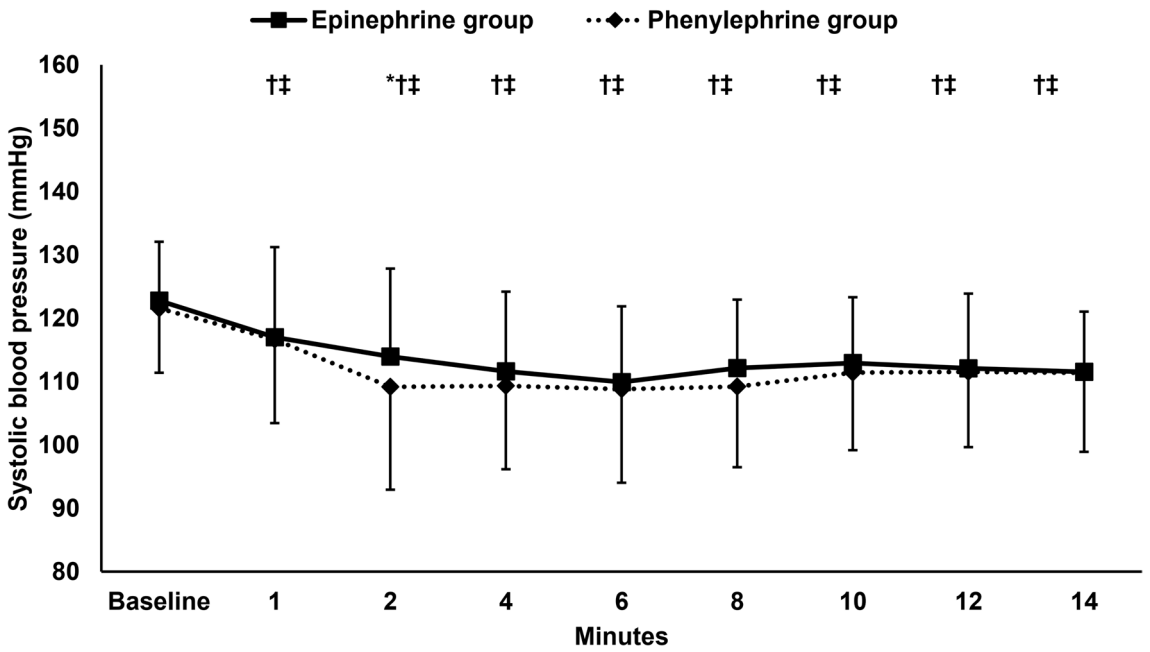

Fig. 2 Systolic blood pressure. Markers are means and error bars are their standard deviation. *Denotes significance between the groups, †denotes significance in relation to the baseline reading in the epinephrine group, and ‡denotes significance in relation to the baseline reading in the epinephrine group

Table 2 Maternal outcomes. Data are presented as median (quartiles) and frequency (%)

	Epinephrine group ($n=98$)	Phenylephrine group ($n=98$)	*P* value
Composite outcome	30/98 (31%)	31/98 (32%)	0.877
Incidence of spinal hypotension	18/98 (18%)	29/98 (30%)	0.066
No. of hypotensive episodes per patient	0 (0, 0)*	0 (0, 1)	0.019
Incidence of severe spinal hypotension	2/98 (2%)	3/98 (3%)	1.000
Time to first hypotensive episode (min)	6 (4, 12)	4 (2, 8)	0.070
Incidence of postdelivery hypotension	5/98 (5%)	2/98 (2%)	0.248
Incidence of excessive hypertension	1/98 (1%)	1/98 (1%)	1.000
Incidence of excessive tachycardia	13/98 (13%)*	4/98 (4%)	0.022
Total Phenylephrine boluses (mcg)	0 (0, 0)	0 (0, 50)	0.056
Total Ephedrine boluses (mg)	0 (0,0)	0 (0,0)	0.311
Incidence of nausea	16/98 (16%)	22/98 (22%)	0.278
Incidence of vomiting	4/98 (4%)	10/98 (10%)	0.096

*Denotes statistical significance between the groups

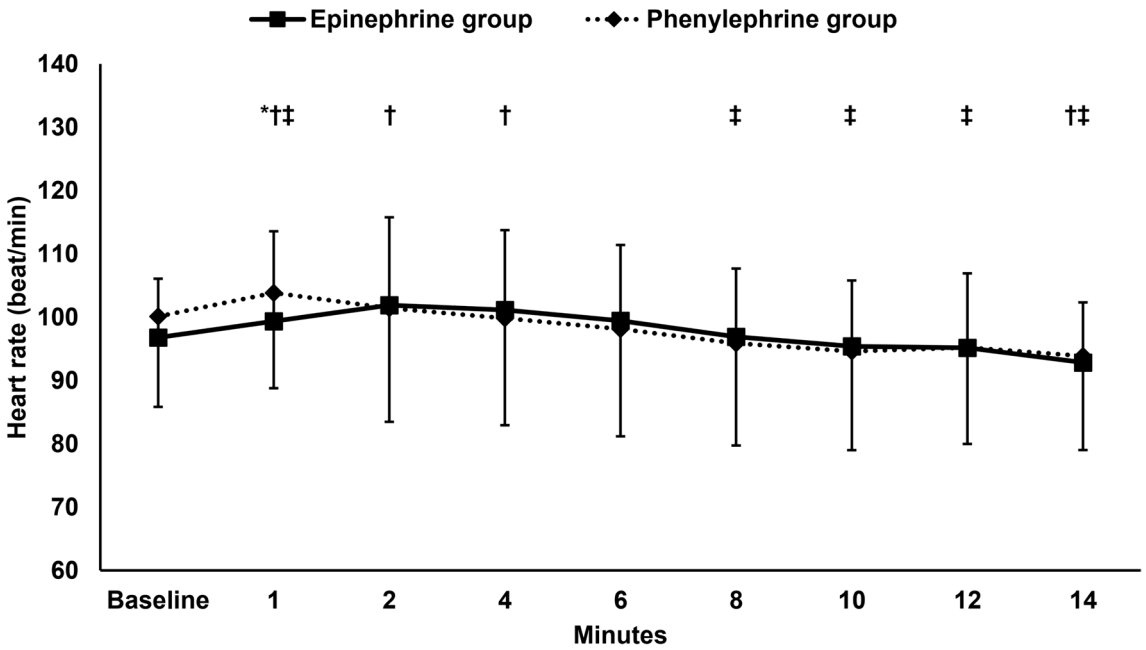

Fig. 3 Heart rate. Markers are means and error bars are their standard deviation. *Denotes significance between the groups, †denotes significance in relation to the baseline reading in the epinephrine group, and ‡denotes significance in relation to the baseline reading in the epinephrine group

incidence and severity [2]. Vasopressors have the advantage of maintaining blood pressure through their direct action on blood vessels as well as increasing the mean systemic filling pressure, which subsequently increases venous return and cardiac output [7]. However, selection of the optimum prophylactic drug should consider the balance between all hemodynamic events, not only hypotension. Several drugs are used to prevent hypotension, including phenylephrine (the standard drug to date), ephedrine, and norepinephrine [2]. The most common drawback of phenylephrine is reflex bradycardia, which is undesirable in mothers with low baseline heart rate or pathologies associated with low cardiac output [8, 9]. A recent systematic review reported that phenylephrine decreases cardiac output due to a consistent decrease in heart rate and a modest decrease in stroke volume [9]. Furthermore, phenylephrine is relatively expensive compared with other vasopressors and is not readily available in several countries, including our country. Norepinephrine is a vasopressor that has attracted considerable attention in recent years. However, it may also be associated with

Table 3 Neonatal outcomes

	Epinephrine group ($n=98$)	Phenylephrine group ($n=98$)	P value
Apgar score at 1 min	5 (5, 7)	6 (4, 7)	0.873
Apgar score at 5 min	9 (8, 10)	9 (8, 10)	0.948
*p*H	7.28 (7.24, 7.31)	7.28 (7.23, 7.30)	0.630
PO_2 (mmHg)	26 ± 8	27 ± 0	0.269
PCO_2 (mmHg)	52 ± 8	52 ± 7	0.794
HCO_3 (mmol/L)	20 ± 2	20 ± 2	0.390
Lactate (mmol/L)	2.4 (1.9, 3.0)	2.4 (2.0, 3.0)	0.807

Data are presented as median (quartiles) and mean ± standard deviations

bradycardia (less than phenylephrine) [10] and is sometimes not available, even in developed countries [11]. The United States previously experienced a shortage of norepinephrine, which was responsible for increased mortality [11]. The main advantage of using epinephrine during cesarean delivery is the avoidance of the side effects of other vasopressors, especially reflex bradycardia. Furthermore, epinephrine has another important advantage because it is economical and available in all hospitals worldwide. Thus, the feasibility of epinephrine in obstetric anesthesia, if confirmed, would improve patient safety by providing more choices for prophylaxis.

Epinephrine is a classic sympathomimetic drug with α- and β-adrenoceptor agonistic activities that produce both vasopressor and inotropic effects. Very few recent studies have evaluated epinephrine in obstetric anesthesia; and the largest (including 271 mothers) suggested that 0.03 mcg/kg/min was a reasonable starting dose after spinal block [4]. Data regarding the use of epinephrine during cesarean delivery are limited. A previous study compared epinephrine (0.1 mcg/kg/min) and phenylephrine (1 mcg/kg/min) in mothers receiving combined spinal–epidural anesthesia during cesarean delivery using maternal bradycardia as the primary outcome [3]. The authors concluded that epinephrine was associated with a lower incidence of bradycardia and a better neonatal acid–base balance [3]. Our study differed from the above study in several respects including larger sample size (196 vs. 80) and the lower and relatively equipotent doses of the 2 vasopressor drugs (i.e., 0.03 mcg/kg/min epinephrine and 0.4 mcg/kg/min phenylephrine). Our study also had the advantage of using a composite outcome that included all adverse cardiovascular events.

To link our findings with future research and practices. We believe that, despite the lack of superiority of either of the two drugs in the general maternal hemodynamic profile (the primary outcome), our results suggest that epinephrine could be a better choice in patients with a low baseline heart rate and borderline baseline blood pressure (likely superior in terms of hypotension), whereas phenylephrine appears to be more appropriate in patients with a high baseline heart rate and normal baseline blood pressure (superior in terms of tachycardia). The choice of vasopressor should be individualized according to patient type, anesthetist experience, and hospital resources. Our results support the feasibility of using epinephrine when other vasopressors are unavailable.

The present trial, however, had some limitations, including its single-center design, which did not include mothers with major cardiovascular disease. Further studies assessing epinephrine in different patient subgroups and those evaluating the efficacy of epinephrine boluses with and without infusion are warranted.

In conclusion, epinephrine and phenylephrine infusions yielded comparable maternal hemodynamic and neonatal outcomes. Epinephrine was associated with a higher incidence of maternal tachycardia and likely lower incidence of maternal hypotension than phenylephrine. Our results support the feasibility of using epinephrine in obstetric practice when confirmed in additional clinical trials.

Author contributions Yasmin S Hassabelnaby: this author helped in data collection, shared in analysis, writing and revision. Ahmed Hasanin: this author helped in conception of the idea, supervision, senior author, and writing the first draft. Mohamed Shamardal: this author helped in data collection, shared in analysis, writing and revision. Maha Mostafa: this author helped in data collection, shared in analysis, writing and revision. Rana M. Zaki: this author helped in data collection, shared in analysis, writing and revision. Mona Elsherbiny: this author helped in data collection, shared in analysis, writing and revision. Sherin Refaat: this author helped in data collection, shared in analysis, writing and revision. All authors approved the manuscript and agreed to be accountable for all aspects of the work.

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Data availability The data are available upon reasonable request to the corresponding author.

Declarations

Conflict of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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