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Comparative Study Among Ephedrine, Norepinephrine and Phenylephrine Infusions to Prevent Spinal Hypotension During Cesarean Section. A Randomized Controlled Double-Blind Study

Ashraf M Eskandr [a], Ali M Ahmed[b] and Nadia Mohee Eldin Bahgat [c]

aAssistant Professor in Anesthesiology and Intensive Care Department, Faculty of Medicine, Menoufia University, Quisna, Egypt; bSenior Registrar in Anesthesiology, and Intensive Care Department, General Sohag Health Hospital, Sohag, Egypt; cLecturer in Anesthesiology and Intensive Care Department, Faculty of Medicine, Menoufia University, Shebin El-Kom, Egypt

ABSTRACT

Background: Spinal anesthesia is the recommended technique in elective cesarean sections. Usage of vasopressors is more widely accepted as an effective method for decreasing post-spinal hypotension than fluid loading. However, the ideal vasopressor to prevent spinal hypotension during cesarean section has been a subject of much debate. It should maintain maternal blood pressure and placental perfusion, with minimal adverse effect on fetus and mother.

Aim: The primary aim was to compare the effect of prophylactic infusion of phenylephrine versus norepinephrine versus ephedrine in the prevention of postspinal hypotension in elective cesarean section. The secondary aim was to assess their effects on neonate.

Methods: Seventy-five patients were enrolled in this study and randomly divided into three groups. Group P received phenylephrine infusion and group N received norepinephrine infusion, while group E received ephedrine infusion. The changes in mean arterial blood pressure and heart rate were recorded throughout the surgery. Maternal and neonatal perioperative complications were controlled and recorded.

Results: MAP were higher in the ephedrine group than the phenylephrine and norepinephrine groups. Maternal tachycardia was significantly more common in ephedrine, and bradycardia was more common in phenylephrine group without significant difference. Nausea and vomiting were more common in ephedrine group. Neonatal acidosis was lesser in phenylephrine and norepinephrine groups than in the ephedrine group.

Conclusion: Prophylactic infusion of phenylephrine and norepinephrine can be successfully used to prevent postspinal hypotension in parturient undergoing cesarean section with less drawbacks and fetal well-being than ephedrine.

1. Introduction

For a safe elective cesarean delivery, the updated obstetric anesthesia guidelines recommend the administration of neuraxial anesthesia, whenever feasible [1]

Hypotension is the most common side effect associated with spinal anesthesia in obstetrics [2]. The reported incidences of hypotension varied between 1.9% and 71% [3]. The most significant cause of hypotension is rapid onset of sympatholysis due to increased sensitivity of nerve fibres to local anesthetics during pregnancy [4]. Aortocaval compression of the pregnant uterus aggravates incidence and severity of hypotension in pregnant women, compared to non-obstetric patients [5]. Pregnant women also exhibit an increased level of sympathetic activity compared to parasympathetic activity [4]. Higher sympathetic block reduces the occurrence of compensatory mechanisms and increases the risk of cardio-inhibitory reflexes [5]. Hypotension leads to adverse maternal outcomes such as nausea, vomiting, and dizziness [6]. Decrease in systolic pressure can compromise uterine blood flow and foetal circulation, and thus cause foetal hypoxia and acidosis. Furthermore, hypotension leads to a significant fetal ischemia and reperfusion injury [7]. Prolonged hypotension may also affect the neurobehavioral outcome of the newborn [8].

One of the main challenges in obstetric anesthesia is to find efficient treatment for hypotension of spinal block. Many interventions were tried like the administration of crystalloids and/or colloids before and during anesthesia [9], and administration of smaller doses of local anesthetics combined with opioid analgesics but not provide a satisfactory efficiency [10]. Vasopressor's administration was proven to be essential to manage hypotension in obstetric patients [11].

Ephedrine, phenylephrine, and norepinephrine are the three commonly used vasopressors for managing spinal hypotension [11,12]. Ephedrine is a long-

CONTACT Nadia Mohee Eldin Bahgat ✉ dr_nmbahgat@med.menofia.edu.eg;dr_nmbahgat@yahoo.com 🖂 Lecturer in Anesthesiology and Intensive Care Department, Faculty of Medicine, Menoufia University, Shebin El-Kom, Egypt

established and readily available familiar drug to most anesthetists for treatment and prophylaxis against spinal anesthesia-induced hypotension. Ephedrine is sympathomimetic amine that acts directly as alpha- and beta-adrenergic agonist and indirectly through release of norepinephrine from sympathetic neurons. Recently, there are some concerns about its use due to the probability of fetal acidosis, maternal supraventricular tachycardia, and tachyphylaxis [13].

Phenylephrine is a pure alpha-adrenergic receptor agonist with no beta-adrenergic receptor activity. It can effectively prevent or treat postspinal hypotension. Despite it could decrease utero-placental perfusion, recent studies have proven that it can improve neonatal outcome by maintaining maternal mean arterial blood pressure and organs perfusion pressure [14].

Norepinephrine has weak beta-adrenergic receptor agonistic properties, other than alpha adrenergic receptor agonist property. It has favorable effect on maternal heart rate and CO, rendering it a promising alternative to phenylephrine in obstetric anesthesia [12,15]

To the best of our knowledge, there was no study comparing phenylephrine, norepinephrine, and ephedrine, to select the ideal vasopressor for prevention of postspinal hypotension with least side effects. This research was designed to investigate and compare the efficacy and safety of (phenylephrine, norepinephrine, and ephedrine) constant infusions to prevent postspinal hypotension in elective cesarean sections. Figure 1.

2. Methods

This randomized prospective trial was conducted from October 2018 to October 2019 after approval from the ethics and research committee of Menoufia University Hospitals (IRB 3-2018 ANET4). The trial was registered at www.pactr.org (PACTR 201810518426098). An informed written consent was obtained from each parturient. We studied 75 parturient, ASA physical status I or II, aged 18-40 years, 37 week or more normal singleton pregnancy, scheduled for elective cesarean section under spinal anesthesia block.

We excluded patients if they refused to participate or had pre-eclampsia, eclampsia, cardiac disorders, asthmatic patients, Known fetal abnormality, coagulations defect or any contraindication to spinal anesthesia.

Simple randomization using a randomization table created by a computer software program was used to allocate patients into 3 equal parallel groups according to the type of vasopressor drug. Phenylephrine (P) group: 25 patients received phenylephrine (Phenylephrine HCL® 10mg/1ml STEROP, Belgium) infused at 0.1 ug/kg/min I.V. Norepinephrine (N) group: 25 patients received norepinephrine (Levophrine® 4mg/4ml, EgyPharma, Egypt) infused at 0.05 ug/kg/min I.V. Ephedrine group: 25 patients received ephedrine (Ephedrine® 30mg/1ml, CID, Egypt) 1 mg/min I.V infusion. All infusions started just after receiving spinal anesthesia using syringe pump.

Three measurements of noninvasive blood pressure (at 1-min interval) were recorded after the parturient were allowed a 5-min rest period in the supine position with left lateral tilt. The average of the three readings of mean arterial blood pressure (MAP) was used as a baseline.

An anesthetist, who was not involved in the case management, prepared a syringe for the drug infusions with the designated concentration. Both the parturient and the anesthetist in charge of the case were blinded to the drug in the syringe.

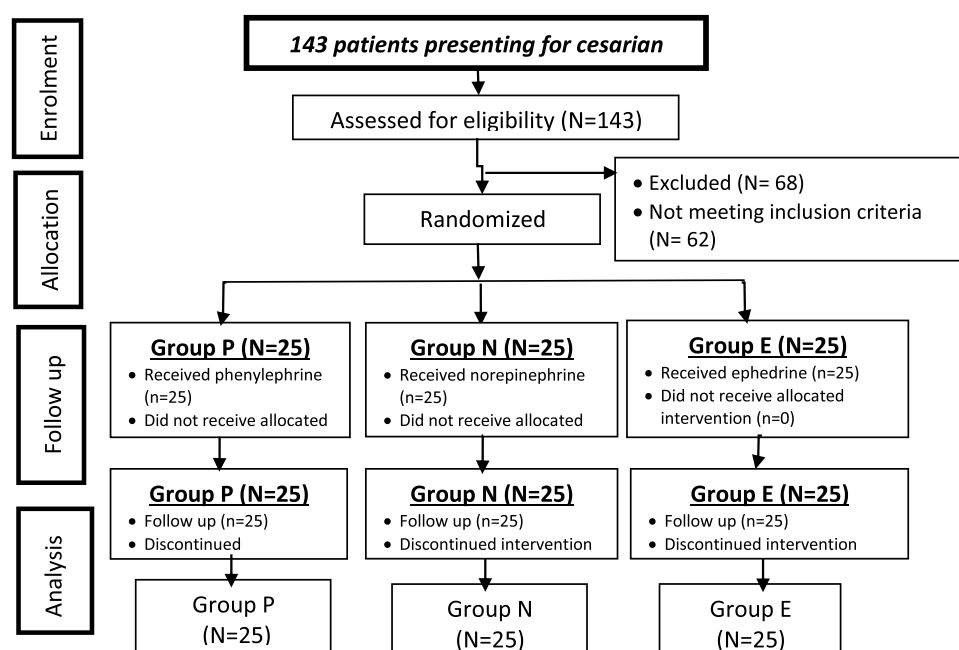On arrival to operating room, patients were monitored using: electrocardiogram, noninvasive arterial

Figure 1. Flow diagram of the study.

blood pressure, and pulse oximeter. Intravenous cannula 16 gauge was inserted and ringer solution (10 ml/kg/hr) was started. An arterial cannula was inserted for continuous maternal blood pressure monitoring.

The parturient was adjusted in the sitting position. The head was tilted anteriorly, and the shoulders were relaxed.

The skin was prepared with povidone iodine. After 3 min, the injection area was cleared using sterile gauze. After the skin was infiltrated with 2% lidocaine. A 25 G spinal needle was inserted at the L2-3 or L3-4 interspace. Subarachnoid injection of 0.5% hyperbaric bupivacaine with 25 μg fentanyl. The injected volume was chosen according to parturient height. If she was < 155, 155–170, >and 170 cm, we gave 1.8, 2.2, and 2.6 ml of hyperbaric bupivacaine, respectively. Then, parturient were positioned supine with left lateral tilt and two pillows supporting the head and shoulders. Oxygen (4 L/min) by a clear face mask was given.

Immediately after spinal anesthesia, a vasopressor infusion pump started according to type of the group. The infusion rate was constant, and boluses of phenylephrine (0.2 ug/kg), norepinephrine (0.1ug/kg), and ephedrine (5 mg) were given if the MAP decreased to more than 20% of baseline.

The upper sensory level of anesthesia was assessed. Heart rate and mean arterial blood pressure of parturient recorded immediately from the time of receiving spinal anesthesia then every 5 min until skin closure. If bradycardia (heart rate <50 beats/min) developed, intravenous atropine (0.01 mg/kg) was used. Incidence of maternal complication as nausea and vomiting was recorded and treated with metoclopramide (10 mg IV).

After delivery, an intravenous infusion of oxytocin (20 IU) was slowly administered. Apgar score of fetuses [16] (appendix- 1) was assessed at 1 and 5 min after delivery, and cord blood sample was taken for pH, PO2, PCO2, and HCO3 measurement. After the end of surgery, the mother was transported to the recovery room with routine monitoring.

2.1. Sample size calculation

During the study design, depending on our primary outcome (maternal MAP) and according to previous clinical studies [17,18], we assumed the differences in MAP means and SDs would be 10%. By setting level of significance (α) to 5% and a power to 80% using G Power program version 3.1.9.2, Franz Faul, Universitat Kiel, Germany, we calculated that appropriate group size would require 22 patients. We planned to include 25 patients per group to allow for potential dropouts or protocol violations.

2.2. Statistical design

Data were collected, coded, revised, and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution and median with interquartile range (IQR) for the quantitative data with nonparametric distribution. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the chi-square test when the expected count in any cell found less than 5. The comparison between more than two groups with quantitative data and parametric distribution were done by using one-way analysis of variance (ANOVA) test, and Kruskal-Wallis test was used in the comparison between more than two groups with quantitative data and nonparametric distribution followed by Student–Newman Kaul's post hoc test. P-value was considered significant as the $p < 0.05$.

3. Results

From 143 patients who were eligible for the study, 68 patients were excluded as 62 were not meeting the inclusion criteria and 6 refused to participate in the study; 75 pregnant women were enrolled in this study. There was no significant difference in the studied groups according to demographic data. In addition, variables as time of surgery and number of interventions (number of boluses of studied drugs), there was no significant difference in studied drugs according to these variables although more boluses were given in group E (4 boluses) than in other groups P and N (2 boluses each) (Table 1).

There was no statistically significant difference between studied drugs in baseline values of maternal pulse (p-value = 0.87). Maternal pulse increased significantly in ephedrine group (P value < 0.001). The heart rate slightly decreased in group P than in group N with frequent significance in some points of time measuring (Table 2).

There was no significant difference among the three groups in basal mean BP. However, maternal mean blood pressure significantly increases in ephedrine in comparison with phenylephrine and norepinephrine. MAB was slightly higher in group P than in group N with frequent significance in some point of time measuring (Table 3).

There was no significant difference among groups in terms of the 1st and 5th mints Apgar score, which was better in group P and N than group E. Umbilical arterial blood gas analyses are summarized in table 4. Based on the one-way ANOVA test, there was significant

Table 1. Comparison between studied groups as regards demographic data.

	Group P (n = 25)	Group N (n = 25)	Group E (n = 25)	One-way ANOVA	
	Mean±SD	Mean±SD	Mean±SD	F	P-value
Age (yr)	27.64 ± 4.00	27.40 ± 3.71	28.04 ± 5.35	0.134	0.875
Weight (kg)	77.16 ± 6.39	77.36 ± 6.92	81.52 ± 8.91	2.701	0.074
BMI	28.02 ± 2.31	28.07 ± 2.58	31.07 ± 3.79	8.718	0.061
Time of surgery (min)	46.40 ± 4.9	43.8 ± 6	43.2 ± 5.18	2.499	0.089
Number of interventions (boluses) Phenylephrine (0.2 µg/kg) Norepinephrine(0.1µg/kg) Ephedrine(5 mg)	2	2	4	0.230	0.891

Table 2. Comparison between studied groups as regards maternal heart rate.

	Group P (n = 25)	Group N (n = 25)	Group E (n = 25)	One-way ANOVA	
	Mean±SD	Mean±SD	Mean±SD	F	P-value
Before anesthesia	88.36 ± 3.96	91.04 ± 8.65	91.28 ± 8.13	1.26	0.29
After 5 min	79.72 ± 5.00[#]	87.32 ± 9.01[†]	94.6 ± 9.45[‡]	21.24	0.001*
10 min	76.48 ± 7.85[#]	83.44 ± 10.56[†]	94.24 ± 10.43[‡]	21.3	0.001*
15 min	75.96 ± 5.39[#]	80.20 ± 11.18	87.32 ± 10.42[‡]	9.41	0.001*
20 min	73.76 ± 3.41[#]	79.4 ± 8.58[†]	88.96 ± 12.03[‡]	19.26	0.001*
25 min	70.36 ± 7.74[#]	76.12 ± 7.85[+]	88.64 ± 13.00[‡]	22.55	0.001*
30 min	71.24 ± 6.64[#]	71.88 ± 9.3	87.76 ± 13.52[‡]	20.96	0.001*
35 min	66.64 ± 5.44[#]	73.84 ± 5.85[†]	88.00 ± 11.91[‡]	43.07	0.001*
40 min	67.12 ± 5.67[#]	74.64 ± 7.34[†]	85.96 ± 6.00[‡]	55.28	0.001*
45 min	67.12 ± 5.54[#]	74.88 ± 5.29[†]	88.00 ± 7.86[‡]	69.35	0.001*
50 min	67.52 ± 2.87[#]	74.12 ± 5.41[†]	88.64 ± 6.82[‡]	104.21	0.001*
55 min	68.32 ± 3.7[#]	74.32 ± 4.67[†]	89.44 ± 5.55[‡]	133.98	0.001*

* significance between the groups P-value<0.05. [†] significance between group N and group P, [‡] significance between group E and group N, [#] significance between group P and group E.

Table 3. Comparison between studied groups as regards maternal mean blood pressure.

	Group P (n = 25)	Group N (n = 25)	Group E (n = 25)	One way ANOVA	
	Mean±SD	Mean±SD	Mean±SD	F	P value
Before anesthesia	78.72 ± 5.8	75.48 ± 5.54	77.04 ± 5.14	2.17	0.122
After 5 min	69.24 ± 4.03[†]	64.04 ± 5.53[#]	67.4 ± 4.06	8.24	0.001*
10 min	67.8 ± 4.85[†]	64.4 ± 4.15	66.88 ± 4.06[‡]	4.05	0.021*
15 min	70.24 ± 5.1[†]	66.8 ± 3.21	69.44 ± 3.9[‡]	4.72	0.012*
20 min	70.52 ± 4.1	71.0 ± 3.81[#]	73.88 ± 3.71[‡]	5.49	0.006*
25 min	71.28 ± 4.56	72.32 ± 3.5	74.4 ± 3.59[‡]	4.12	0.02*
30 min	75.36 ± 4.06[†]	70.48 ± 3.68[#]	81.32 ± 3.52[‡]	52.11	0.001*
35 min	74.4 ± 3.06[†]	66.61 ± 4.14[#]	81.96 ± 3.51[‡]	113.8	0.001*
40 min	76.6 ± 3.67[†]	70.64 ± 3.33[#]	81.56 ± 4.26[‡]	52.5	0.001*
45 min	76 ± 3.49	74.28 ± 3.82[#]	81.52 ± 4.58[‡]	22.47	0.001*
50 min	77.08 ± 3.4[†]	74.24 ± 3.81[#]	81.76 ± 4.43[‡]	23.66	0.001*
55 min	78 ± 4.24[†]	75.4 ± 4.5[#]	82.32 ± 4.37[‡]	15.99	0.001*

* significance between the groups P value<0.05. [†] significance between group P and group N, [‡] significance between group P and group E, [#] significance between group N and group E.

difference among groups regarding pH, PO2, HCO3 (P =0.001, 0.012, 0.016 respectively). Two neonates in group E (8.0%) reported to have neonatal acidosis, no one in other groups. Acidosis was significantly

Table 4. Comparison between studied groups as regards Neonatal outcome.

	Group P (n = 25)	Group N (n = 25)	Group E (n = 25)	F	P-value
Apgar score at the first minute	9 (8–10)	9 (7–10)	8 (7–10)	H = 0.424	0.809
Apgar score after 5 min	9 (9–10)	9 (8–10)	9 (7–10)	H = 0.249	0.883
pH	7.38 ± 0.03	7.37 ± 0.03[#]	7.33 ± 0.07[‡]	7.84	0.001*
Fetal acidosis	0(0)	0(0)	2(8)	X^2 =4.11	0.128
PO2	27.47 ± 2.15[†]	25.94 ± 3.07	25.2 ± 2.7[‡]	4.71	0.012*
PCO2	38.5 ± 2.94	39.6 ± 3.4	39.2 ± 6.74	0.35	0.703
HCO3	23.88 ± 1.34	23.15 ± 0.76	22.81 ± 1.66[‡]	4.37	0.016*

* significance between the groups P value<0.05. [†] significance between group P and group N, [‡] significance between group P and group E, [#] significance between group N and group E.

Table 5. Comparison between studied groups as regards maternal complications.

	Group P (n = 25)		Group N (n = 25)		Group E (n = 25)		Chi square test	
	n	%	n	%	n	%	X^2	P value
Nausea	2	8.0%	0	0.0%	2	8.0%	2.113	0.348
Vomiting	1	4.0%	0	0.0%	2	8.0%	2.083	0.353
Metoclopramide	3	12.0%	0	0.0%	4	16.0%	4.097	0.129
Hypertension	0	0.0%	0	0.0%	2	8.0%	4.11	0.128
Tachycardia	0	0.0%	0	0.0%	3	12.0%	6.25	0.044*
Bradycardia	4	16.0%	2	8.0%	0	0.0%	4.348	0.114

* significance between the groups P-value<0.05.

higher in group E than in the other groups (P=0.043). (Table 4)

As regards maternal complications, nausea and vomiting were more reported in group E and group P than in group N, with no significant difference between the groups (p = 0.348, 0.353, respectively). The same was reported for the need for anti-emetic drug (metoclopramide). Tachycardia was significantly higher in group E than others (p = 0.044). Although, four patients experienced maternal bradycardia in group P, while two patients in group N and no case in ephedrine group, there was no significant difference between the groups (p = 0.129) (Table 5).

4. Discussion

The results of this study showed that mean arterial blood pressures were best maintained with a prophylactic fixed dose infusion of either phenylephrine or norepinephrine compared with those who received prophylactic ephedrine infusion with no serious or significant maternal complications except for more bradycardia in phenylephrine group. On the neonatal side, general condition was better in phenylephrine and norepinephrine groups than neonates of the ephedrine group who developed mild acidosis.

The reduction of systematic vascular resistance (SVR) is the main mechanism involved in postspinal hypotension. It is secondary to small artery vasodilatation along with a mild degree of venous vasodilatation [19,20].

Since then, prevailing opinion suggests use of vasopressors, to rescue spinal anesthesia-induced hypotension. The current study designed to compare between ephedrine, phenylephrine, and norepinephrine as three commonly used vasopressors in obstetric patients to detect the ideal one used in fixed rate infusion prophylactically to prevent hypotension without maternal and fetal side effects.

Much research has compared the effectiveness of phenylephrine and ephedrine or norepinephrine in different doses and routes of administration.

The traditional idea that ephedrine is the preferred choice as vasopressor to combat postspinal hypotension for cesarean sections was challenged by many researches comparing between ephedrine and phenylephrine [21,22]. These researches concluded that phenylephrine was associated with better fetal acid–base status, although there was no difference in the clinical outcome based on the Apgar scores between the two drugs.

Our result documented that both phenylephrine and norepinephrine are better choices than ephedrine in controlling maternal MAP, as ephedrine group needed more frequent boluses on top of already infused fixed dose to control hypotension than in phenylephrine and norepinephrine groups. That was in agree with a meta-analysis of four randomized clinical trials by Lee A et al. [22], who noticed that ephedrine cannot prevent hypotension in low doses by infusion, so it failed to be used for prophylaxis against hypotension. In addition, ephedrine may produce hypertension in high doses, which is confirmed by the present study as there was two cases of hypertension and three cases of tachycardia in ephedrine group, which was not reported in the other groups. However, those treated with noradrenaline and phenylephrine needed fewer rescue boluses as compared to ephedrine, which needed more frequent boluses until stability of maternal MAP.

Also, our results were in agree with Sayasach et al. [18] who found that phenylephrine infusion for prophylaxis against maternal hypotension is a better choice than ephedrine or their combination with lower doses. In addition, a combination of the drugs was better than ephedrine alone but had no additional benefit over phenylephrine.

There was moderate increase in MAB and decrease in heart rate in P group in comparison with N and E groups, this is due to increase in blood pressure with an α-agonist (phenylephrine) that may lead to reactive bradycardia (baroreceptor reflex). However, norepinephrine is a potent α-adrenergic receptor agonist and has weak β-adrenergic receptor agonist activity, and therefore, it has neutral and less negative effects on heart, so it is more suitable for maintaining blood pressure without bradycardic effect compared with phenylephrine [23].

In parturient treated with ephedrine, there were decreased pH, base excess, and oxygen tension in umbilical cord arterial blood. Two babies of these patients developed neonatal acidosis in this study. The mechanism of this side effect was explained in old studies by the different action of various vasopressors on uteroplacental circulation [24]. But Ngan Kee et al. [25] explained the depressed fetal acid–base status due to ephedrine crossing the placenta and associated with greater fetal concentrations of

lactate, glucose, and catecholamines because of the metabolic processes in the fetus caused by activation of fetal β-adrenergic receptors [25]. Mercier et al [26] reported that the addition of phenylephrine to ephedrine infusion improve the neonatal pH in comparison with ephedrine infusion alone.

Current study supports the use of either phenylephrine or norepinephrine as the vasopressors of choice than ephedrine because of improved fetal acid–base status [27,28]. With favorable effect of norepinephrine over phenylephrine, the phenylephrine's effect of on feto-maternal physiology due to the possibility of bradycardia decreased cardiac output, which have adverse impact on placental perfusion [23,29]. Furthermore, norepinephrine is not proved to cross the placenta [30] while ephedrine crosses the placenta more than phenylephrine [24]. Ngan Kee et al. [23] suggested that the use of norepinephrine may reduce catecholamine level of the baby compared to phenylephrine, by keeping out the potential stimulation of fetal metabolism and acidemia often observed with ephedrine.

By evaluation of first- and fifth-minute Apgar scores, there were no difference among groups. This agreed with previous studies that used the three vasopressors in management of postspinal hypotension in cesarean section [11,23,31]. Therefore, prophylactic use of vasopressors is very effective for neonatal outcome, due to feasibility to control of maternal blood pressure and utero-placental perfusion [31,32].

Regarding of maternal complications, the most important observation was modest bradycardia related to phenylephrine infusion, which was transient and only in four cases (HR <50 per min) in comparison with two cases in norepinephrine group that managed by 0.01 mg/kg I.V. atropine. These findings were in accordance with other previous studies [2,11,15].

Nausea and vomiting are common complications in obstetric anesthesia. They were higher in ephedrine and phenylephrine groups than norepinephrine in group, which responded rapidly to metoclopramide 10 mg IV. The possible cause of nausea and vomiting may be the increase of vagal tone following the reduction of preload as documented by Cooper et al. [33]. None of the observed complications were severe.

5. Limitation of the study

Our current study included a relatively small number of patients and was done in a single centre, so larger and multi-center studies will be needed to verify the safe and efficient replacement of norepinephrine instead of phenylephrine and ephedrine in the management of postspinal hypotension during cesarean section.

6. Conclusion

In summary, the current study results showed that both norepinephrine and phenylephrine are more effective than ephedrine in preventing postspinal hypotension during cesarean section through their more maternal hemodynamic stability and fetal outcome with a more favorable effect of norepinephrine over phenylephrine on maternal heart rate, nausea, and vomiting.

ORCID

Ashraf M Eskandr iD http://orcid.org/0000-0002-5791-1855
Nadia Mohee Eldin Bahgat iD http://orcid.org/0000-0003-1419-7521

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Appendix

Table A1 Apgar Score.

	0	1	2
Color	Blue or pale all over	Blue at extremities body pink (Acrocyanosis)	No cyanosis body and extremities pink
Pulse rate	Absent	<100	≥100
Reflex	No response to stimulated	stimulation	Grimace/feeble cry when stimulated
Cry or pull away when stimulated			
Muscle tone	Flaccid	Some flexion	Flexed arms and legs that resist extension
Breathing	Apneic	Weak, irregular, gasping	Regular, lusty cry