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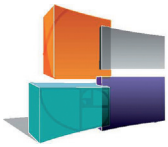

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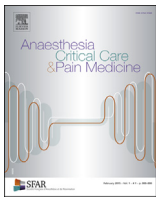

Original Article

Norepinephrine versus phenylephrine infusion for prophylaxis against post-spinal anaesthesia hypotension during elective caesarean delivery: A randomised controlled trial

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ABSTRACT

Background: Prophylactic vasopressors are fundamental during caesarean delivery under spinal anaesthesia. The aim of this work is to compare the efficacy and safety of phenylephrine and norepinephrine when used in variable infusion rate during caesarean delivery.
Methods: A randomised, double-blinded, controlled trial was conducted including mothers scheduled for elective caesarean delivery under spinal anaesthesia. Participants were allocated to two groups norepinephrine group (n = 60), and phenylephrine group (n = 63). Participants received prophylactic vasopressors after spinal block at rate started at 0.05 mcg/kg/min and 0.75 mcg/kg/min respectively. The rate of vasopressor infusion was manually adjusted according to maternal systolic blood pressure. Both groups were compared according to incidence of post-spinal hypotension (the primary outcome), incidence of bradycardia, incidence of reactive hypertension, systolic blood pressure, heart rate, rescue vasopressor consumption, number of physician interventions, and neonatal outcomes.
Results: One hundred and twenty-three mothers were available for final analysis. Both groups were comparable in the incidence of post-spinal hypotension (32% versus 30%, P = 0.8). The number of physician intervention was lower in norepinephrine group. The incidence of bradycardia and the incidence of reactive hypertension were potentially lower in norepinephrine group without reaching statistical significance, (13% vs. 21%, P = 0.3) and (12% vs. 24%, P = 0.1). Rescue vasopressor consumption, and neonatal outcomes were comparable between both groups.
Conclusion: When given in a manually adjusted infusion, norepinephrine effectively maintained maternal SBP during caesarean delivery under spinal anaesthesia with lower number of physician interventions, and likely less incidence of reactive hypertension and bradycardia compared to phenylephrine.

1. Introduction

Maternal hypotension is a frequent complication after subarachnoid block for caesarean delivery. Without prophylactic vasopressors, post-spinal hypotension (PSH) affects nearly 60% of mothers undergoing caesarean delivery [1,2]; thus, the use of prophylactic vasopressors is now fundamental in obstetric population receiving subarachnoid block [3,4]. Many vasopressors are used for prophylaxis against PSH such as phenylephrine (PE), ephedrine, and recently, norepinephrine (NE) [3,5]. PE is still the vasopressor of choice for both prophylaxis and management of PSH [1,5,6]. PE is a potent α adrenergic agonist; thus, it is usually associated with reflex bradycardia, which limits its use in patients with cardiac morbidities, and in patients with low baseline heart rate [5–7].

In addition to its α adrenergic agonistic activity, NE is characterised by weak β adrenergic agonistic activity; thus, it

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had been investigated in obstetric population as an attractive alternative to PE with minimal cardiac depressant effect [8,9]. Until now, the available data for comparison of NE and PE are not enough. Ngan Kee et al. compared both drugs during caesarean delivery in a computer-based infusion protocol [9]. In an open-labelled study, Vallejo et al. compared fixed-infusion of NE and PE during caesarean delivery [10]. No double-blinded studies, to the best of our knowledge, had compared manual, titrated infusions of both drugs in caesarean delivery [7]. The aim of this study was to compare NE and PE variable, manually adjusted infusion for maintenance of maternal blood pressure during caesarean delivery.

2. Patients and methods

A randomised, double-blinded, controlled trial was conducted in obstetric theatre, Cairo University hospital, after being approved by Cairo University research ethics committee (N-82-2017) from November 2017 to April 2018. The study was registered before patient recruitment at clinicaltrial.gov registry system on November 1, 2017 (clinical trial identifier: NCT03328533, principal investigator: Ahmed Hasanin). Written informed consent was obtained from the recruited mothers. A computer-generated sequence was achieved by a statistician using an online random number generator. Patient codes were placed into sequentially numbered sealed opaque envelopes. Each envelope included the instructions of preparing the drug and calculating the starting infusion rate. A research assistant who was not involved in patient management was responsible for opening the envelope, preparing the study drug, and calculation of the starting dose; whilst, the anaesthetist in charge was totally blinded to the infused vasopressor.

Included participants were full-term singleton pregnant women, admitted for elective caesarean delivery, aged between 18 and 40 years. Patients with uncontrolled cardiac morbidities, hypertensive disorders of pregnancy, peripartum bleeding, coagulation disorders, and baseline systolic blood pressure (SBP) $<$ 100 mmHg were excluded from the study.

Upon arrival to the operating room, patients were monitored using electrocardiography, pulse oximetry, and non-invasive blood pressure monitor. An 18G-cannula was inserted, and pre-medication drugs were delivered (metoclopramide 10 mg, and ranitidine 50 mg). Rapid co-load infusion of lactated Ringer's solution was commenced (15 mL/kg over 10 minutes) [11], and subarachnoid block was performed in sitting position. Ten milligrams hyperbaric bupivacaine in addition to 20 mcg fentanyl were injected in L3-L4 or L4-L5 interspace using 25 G spinal needle.

After subarachnoid block, patients received the vasopressor infusion according to the allocated study group:

- NE group (n = 60): received NE infusion with a starting rate of 0.05 mcg/kg/min. Norepinephrine bitartrate (8 mg norepinephrine bitartrate/4 mL, which is equivalent to 4 mg norepinephrine base/4 mL produced by Alexandria Co. for pharmaceuticals and chemical industries, Egypt) was diluted to reach a final concentration of 4 mcg/mL.
- PE group (n = 63): received PE infusion with a starting rate of 0.75 mcg/kg/min. Phenylephrine hydrochloride (10 mg/1 mL ampoule, produced by Sterop Co. Belgium) was diluted to reach a final concentration of 50 mcg/mL.

Block success was assessed after 5 minutes from intrathecal injection using pinprick. Successful block was confirmed if sensory block level was at T4 at least. The vasopressor was infused in the same line with intravenous fluids using a three-way stopcock. Blood pressure was non-invasively monitored using General electric (GE, Solar^{TM} 8000i) monitor. The baseline SBP reading was calculated as the average of 3 readings obtained in the supine position at two-minute intervals with a difference of $<$ 10%.

Haemodynamic management in both groups was performed through manual titration of vasopressor infusion in addition to vasopressor boluses as follows:

2.1. Hypotension

PSH (defined as SBP $\leq$ 80% of the baseline reading during the period from intrathecal injection to delivery of the foetus) was managed by increasing the vasopressor infusion rate by 20% in addition to a vasopressor bolus. The vasopressor bolus was PE 50 mcg (if the heart rate was above 75 bpm), or IV ephedrine 9 mg (if the heart rate was below 75 bpm). Vasopressor infusion was returned to the initial rate if SBP returned within 20% of the baseline reading.

Severe PSH (defined as SBP $\leq$ 60% of the baseline reading) was managed by administration of either IV PE 100 mcg (if the heart rate was above 75 bpm) or IV ephedrine 15 mg (if the heart rate was below 75 bpm) in addition to increasing the vasopressor infusion rate by 20%.

2.2. Hypertension

Reactive hypertension (defined as SBP $\geq$ 120% from the baseline reading) was managed by stoppage of the infusion till the next SBP reading. The infusion was then re-started in a reduced rate (50% of the initial dose) when SBP decreased to be back within 20% of the baseline reading.

2.3. Bradycardia

If not accompanied by hypotension, intraoperative bradycardia (defined as heart rate less than 55 bpm) was managed by stoppage of the vasopressor infusion. The infusion was then re-started in a reduced rate (50%) when the heart rate was more than 55 bpm. IV atropine bolus (0.5 mg) was administered if bradycardia persisted despite stoppage of the infusion. If accompanied with hypotension, bradycardia was managed by IV bolus of ephedrine 9 mg.

SBP was recorded starting from the baseline pre-injection reading at two-minute intervals for 30 minutes after intrathecal injection, followed by five-minute intervals till the end of the operation. Fluid administration continued up to a maximum of 1.5 litres. After subarachnoid block, mothers were placed in supine position with left-lateral tilt. After delivery, an oxytocin bolus (0.5 IU) was delivered over 5 seconds, followed by infusion at a rate of 2.5 IU/hour. The prophylactic vasopressor infusion was maintained until 5 minutes after delivery of the foetus

2.3.1. Primary outcome

Incidence of PSH.

2.3.2. Secondary outcomes

Incidence of severe PSH, incidence of post-delivery hypotension, SBP (baseline reading and the subsequent 12 readings), heart rate (baseline reading and the subsequent 12 readings), incidence of intraoperative nausea and vomiting, incidence of reactive hypertension, intraoperative requirements of phenylephrine, ephedrine and atropine, number of physician interventions per mother (physician intervention was defined as any of the following: vasopressor bolus, atropine bolus, cessation, re-starting, and changing of the vasopressor infusion rate), intraoperative fluid intake, umbilical blood gases (pH, PCO_2, PO_2, and HCO_3), and Apgar score for the neonate at 1 minute and 5 minutes post-delivery.

2.3.3. Statistical analysis and sample size calculation

Our primary outcome was the incidence of PSH. The incidence of PSH was previously reported in parturients receiving the same dose of norepinephrine infusion to be 49% [10]. Using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium), 114 mothers (57 mothers per group) were calculated for an absolute difference of 30% in the incidence of PSH between both groups, with a study power of 90% and an alpha error of 0.05. This number was increased to 126 patients (63 patients per group) to compensate for possible dropouts.

Analysis of data was performed using Statistical package for social science (SPSS) software, version 15 for Microsoft Windows (SPSS Inc., Chicago, iL, USA). Categorical data were reported as numbers and percentages and were analysed using chi-squared test. Continuous data were checked for normality using Kolmogorov-Smirnov test. Normally distributed data were presented as means (standard deviations) and were analysed using unpaired student *t*-test. Skewed data were expressed as medians (quartiles) and were analysed using Mann Whitney U test. For repeated measures, a two-way repeated measures ANOVA was used to evaluate dose (between-groups factor) and time (repeated measures). Post-hoc pairwise comparison was performed using Bonferroni test. *P*-value of 0.05 or less was considered significant.

3. Results

One hundred and forty mothers were screened for eligibility. Eight mothers did not meet our inclusion criteria, 6 mothers declined to participate, and 126 mothers were randomised into our study. Three participants in the NE did not complete the intervention. One hundred and twenty-three mothers were available for final analysis (Fig. 1). Patient characteristics were comparable in the two study groups (Table 1). The incidence of PSH {NE group: 18/60 (30%), PE group: 20/63 (32%), $P = 0.8$}, severe PSH, nausea, vomiting and rescue vasopressor consumption were not statistically different between the two groups (Table 2). Incidence of reactive hypertension was halved, and incidence of bradycardia was also nearly halved in NE group compared to PE group, although these differences did not reach statistical significance (respectively: 12% vs. 24%, $P = 0.1$, and 13% vs. 21%, $P = 0.3$). NE group showed lower number of physician interventions per mother compared to PE group with median (quartiles) number of interventions of 0 (0, 1) and 1(0, 3) respectively ($P = 0.001$). The number of mothers who needed at least one physician intervention was lower in NE group compared to PE group [26 (43%) versus 45 (71%), P = 0.002] (Table 2). The neonatal outcomes (Apgar scores and umbilical blood gases) were

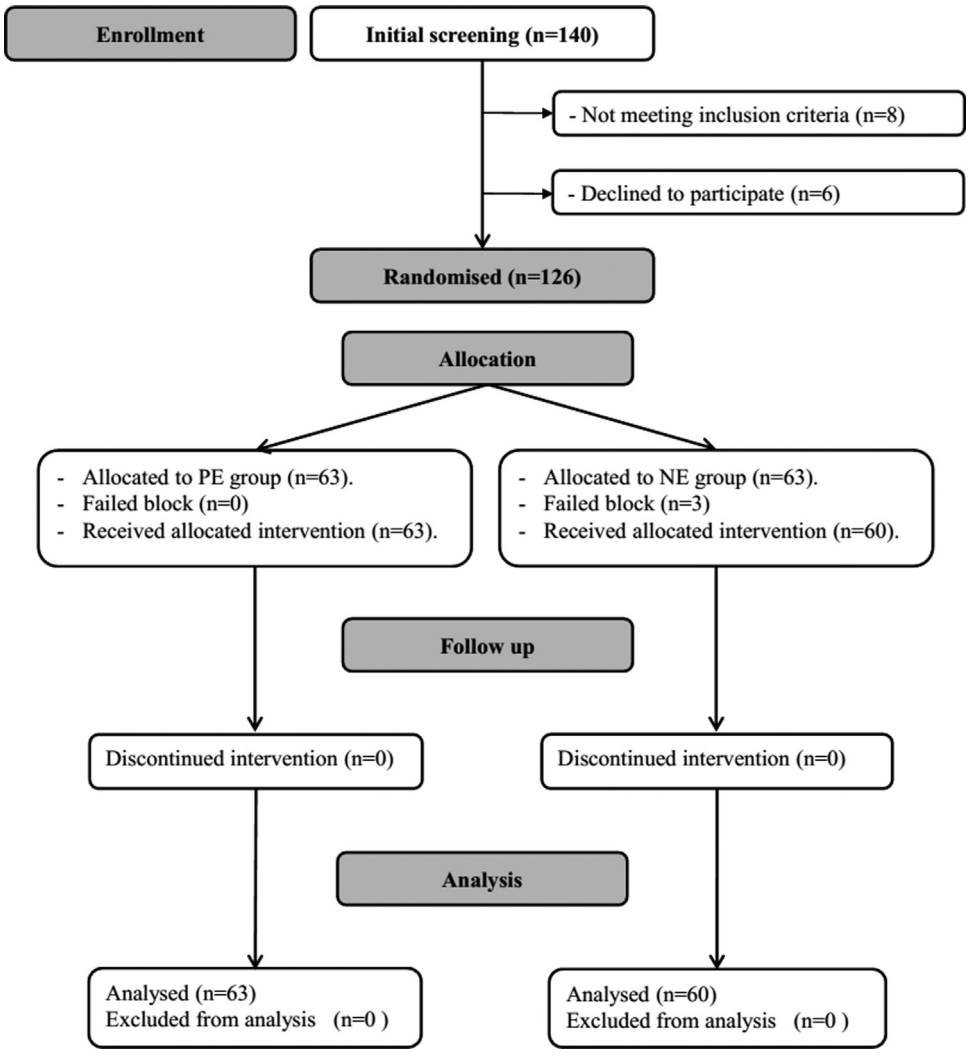

Fig. 1. Consort chart showing patient recruitment. PE: phenylephrine, NE: norepinephrine.

Table 1
Demographic data, operative data, and baseline characteristics. Data are presented as median (quartiles), frequency (%), and mean (standard deviation).

	NE group (n = 60)	PE group (n = 63)	P-value
Age (years)	29 (25.33)	28 (24.31)	0.1
Weight (kg)	76 (61.90)	77 (60.91)	0.6
Time from SAB to delivery of the foetus (minutes)	23 (20.26)	23 (19.25)	0.2
Baseline vital signs			
SBP (mm/Hg)	121 (12)	120 (11)	0.6
Heart rate (bpm)	94 (16)	98 (14)	0.1

NE: norepinephrine; PE: phenylephrine; SAB: subarachnoid block; SBP: Systolic blood pressure.

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

	NE group (n = 60)	PE group (n = 63)	P-value
PSH	18 (30%)	20 (32%)	0.8
Severe PSH	8 (13%)	11 (18%)	0.6
Post-delivery hypotension	2 (3%)	2 (3%)	0.9
Bradycardia	8 (13%)	13 (21%)	0.3
Reactive hypertension	7 (12%)	15 (24%)	0.1
Nausea	9 (15%)	4 (6%)	0.1
Vomiting	3 (5%)	1 (2%)	0.4
Hypotensive episodes (0/1/2/3) (%)	70/25/3/2	68/25/7/0	0.7
Rescue ephedrine requirements (mg)	0 (0.0)	0 (0.0)	0.07
Rescue PE requirements (mg)	0 (0.0)	0 (0.50)	0.3
Atropine requirements (mg)	0 (0.0)	0 (0.0)	0.3
Number of physician interventions per mother	0 (0.1)	1 (0.3)	0.001

NE: norepinephrine; PE: phenylephrine; PSH: post-spinal hypotension.

Table 3
Neonatal outcomes. Data are presented as median (quartiles) and mean (standard deviation).

	NE group (n = 60)	PE group (n = 63)	P-value
Umbilical artery pH	7.31 (7.27, 7.34)	7.3 (7.25, 7.33)	0.2
Umbilical artery PCO_2 (mmHg)	47 (8)	49 (7)	0.1
Umbilical artery PO_2 (mmHg)	23 (26,30)	20 (15, 28)	0.3
Umbilical artery HCO_3 (mEq/dL)	23 (2)	24 (2)	0.1
Apgar score at 1 minute	8 (7, 9)	8 (7, 9)	0.74
Apgar score at 5 minutes	10 (10, 10)	10 (10, 10)	0.3

NE: norepinephrine; PE: phenylephrine.

comparable between both groups (Table 3). The median (quartiles) total vasopressor consumption during infusion was 104 (80, 132) mcg NE and 1600 (1210, 2000) mcg PE.

SBP and heart rate decreased within both groups after subarachnoid block compared to the baseline reading. No significant differences were reported between both groups in neither heart rate nor SBP at most of the time points. NE group showed modestly lower SBP compared to PE group starting from 14-minute reading till delivery of the foetus (Figs. 2,3).

4. Discussion

We reported that NE and PE effectively controlled maternal blood pressure during caesarean delivery; however, NE infusion was associated with less number of physician interventions. The relatively equivalent haemodynamic profile of both study groups is most probably due to the adequately chosen relative potency, which is 15:1. There was a potentially lower incidence of bradycardia and reactive hypertension in NE group compared to PE group without reaching statistical significance; this was not in line with Ngan Kee and colleagues results who reported that NE infusion was associated with lower incidence of bradycardia compared to PE infusion [9]. Ngan Kee et al. used 60 bpm for definition of bradycardia; whilst we used 55 bpm. Ngan Kee et al. used computerised infusion regimen, which might provide more tight control of maternal haemodynamics than our manually-titrated regimen. The non-significant results in our secondary outcomes (bradycardia and reactive hypertension) might also be explained by the lack of adequate power to detect significant difference in these outcomes. The number of physician interventions was lower in NE group, which is most probably because calculation of the number of interventions is based on the sum of episodes of bradycardia, hypotension, and reactive hypertension together.

PE is still considered the vasopressor of choice in obstetric population [5,6]. However, this may change in the next future because PE is not devoid of side effects, the commonest being reflex maternal bradycardia (sometimes severe) and decreased maternal cardiac output [1,2,5,6]. NE was hypothesised to have lower cardiac inhibitory effect because it has a mild beta-adrenergic agonistic activity in addition to alpha-adrenergic agonistic activity [2,9].

Two previous studies compared NE and PE prophylactic infusion regimens during caesarean delivery. Ngan Kee et al. [9] had reported that NE was comparable to PE when used in computer-based protocol during caesarean delivery; however, this computer-based protocol is not applicable in many settings. Caesarean delivery is a procedure, which is performed nearly in every hospital; thus, a simplified protocol for vasopressor infusion during this operation is highly warranted [5]. Vallejo and colleagues compared NE and PE during caesarean delivery in a more simple fixed-infusion protocol, and they reported equivocal

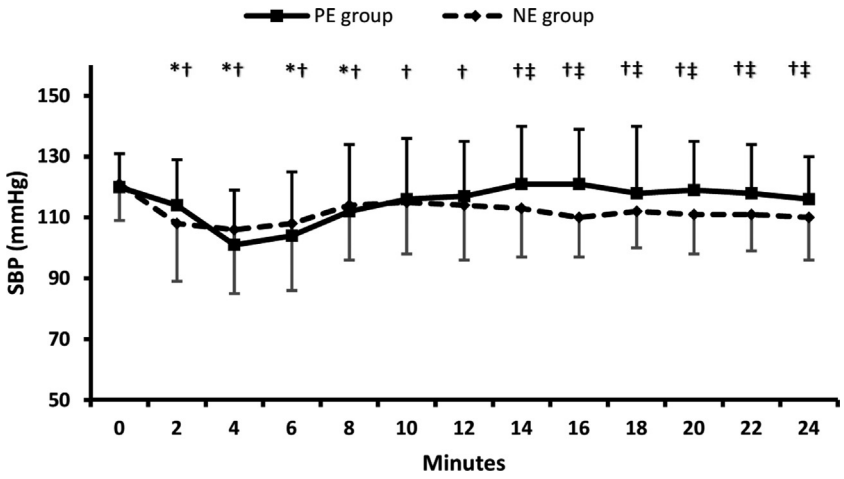

Fig. 2. Systolic blood pressure. NE: norepinephrine; PE: phenylephrine; SBP: systolic blood pressure; *: denotes statistical significance compared to the baseline reading within PE group; †: denotes statistical significance compared to the baseline reading within NE group; ‡: denotes statistical significance between both PE group and NE group.

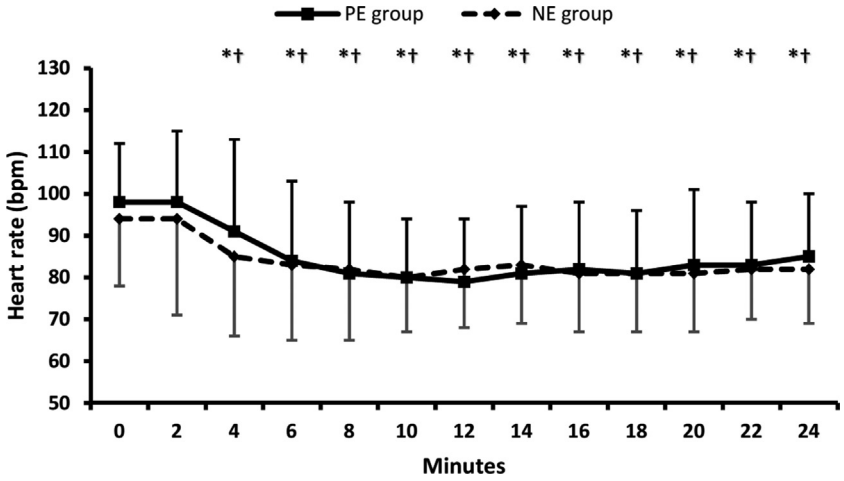

Fig. 3. Heart rate. NE: norepinephrine; PE: phenylephrine; *: denotes statistical significance compared to the baseline reading within PE group; †: denotes statistical significance compared to the baseline reading within NE group.

results between both drugs [10]. Many explanations were suggested by Smiley R. for Vallejo et al. equivocal results such as the use of open-labelled, fixed rate study design, the use of a relatively high dose of bupivacaine (12–15 mg), the use of total number of rescue vasopressor boluses as a primary endpoint instead of the number of mothers who needed a rescue bolus, and mostly, the use of non-equipotent doses at all (PE:NE ratio 2:1) of the two study drugs [12]. The most acceptable relative potency of NE and PE ranges between 16:1 and 13:1 [7,13]. In our study, we tried to provide:

- variable titrated infusion for more haemodynamic stability;
- manually-adjusted rate for more feasibility;
- double-blinded design to overcome any possible bias;
- standard dose of bupivacaine.

Although nine studies had evaluated the use of NE in obstetric population during caesarean delivery, none of them compared manually-titrated NE versus PE prophylactic infusion; thus, two recent systematic reviews had suggested that more high-quality studies are warranted [7,14].

An important barrier for comparing NE and PE prophylactic infusion was the lack of dose-finding studies for NE during caesarean delivery. In a recent dose-finding study on 284 mothers, Hasanin et al. had compared three doses of NE, and reported that a dose of 0.05 mcg/kg/min could be a reasonable starting dose [8]; hence, we used the same dose as an initial dose in the NE group. In our PE group, we used the same starting dose (0.75 mcg/kg/min), which was reported by Siddik-Sayyid and colleagues [15]. In a landmark, dose-finding study, Allen et al. compared four fixed-infusion rates (25 mcg/min, 50 mcg/min, 75 mcg/min, and 100 mcg/min) for PE during caesarean delivery, and they demonstrated that the most suitable PE dose ranges between 25 mcg/min and 50 mcg/min [16]. Referring to the average weight of our patients (76–77 kg), our starting dose would correspond to 0.33 to 0.65 mcg/kg/min, which is close to the recommended dose range by Allen et al. The same dose of PE was recommended by the latest consensus statement for using vasopressors during caesarean delivery [3]. Hence, we tried to compare both drugs using the best available doses in clinical practice. The optimum ratio for comparing different doses of PE and NE is debatable. Ngan Kee et al. had compared both drugs in a 20:1 ratio [9]. Whilst, Vallejo et al. had compared both drugs in 2:1 ratio [10]. Ngan Kee had recently revised the ratio between both drugs to 13:1 [13]. More recently, Mohta et al. had reported that the ratio relative potency between NE and PE is 11:1 [17]. The two later studies had been published

after we started recruiting our participants. The two later studies had different study design from our study:

- the authors of both studies evaluated boluses and not continuous infusion of both drugs;
- the authors of both studies used vasopressor boluses for management and not for prophylaxis against hypotension.

In addition to the prophylactic vasopressor infusion, we used rescue boluses of either ephedrine, or PE, according to the maternal heart rate during the hypotensive episode. This practice had been recently recommended in the latest consensus statement for management of PSH during caesarean delivery using vasopressors [3].

The usual route for infusion of NE is through central veins; however, peripheral administration had shown adequate safety in obstetric anaesthesia with no significant local side effects [8–10]. Cardenas-Garcia et al. had used peripheral NE infusion concentrations up to 32 mcg/mL with local tissue complications less than 2% [18]. In our study, we used NE with some safety precautions such as:

- adequate dilution (4 mcg/mL);
- administration through wide bore cannula;
- infusing the drug in the same line with running fluids.

According to the recent consensus statement for the use of vasopressors during caesarean delivery, prophylactic use of vasopressors after spinal block is preferred to reactive management (after development of hypotension). The use of prophylactic vasopressors provides better haemodynamic profile and lower incidence of nausea and vomiting compared to reactive management [3,4]. The recommended regimen for vasopressor administration is continuous infusion, which is superior to rescue bolus regimen [15]. Delaying the start of vasopressor infusion would impair its efficacy in maintenance of maternal blood pressure. The current gap that had not been resolved yet is the choice of the proper vasopressor [3,5]. PE had been considered the first line vasopressor for prevention and management; however, NE had been recently introduced with very promising results especially in mothers with low baseline heart rate [3,5]. According to our results, we suggest that both drugs, NE and PE, were efficient when used for prophylactic infusion after spinal block. The incidence of PSH was nearly 30% in both groups. This incidence is lower than the incidence of PSH in Vallejo et al. study [10]; this is most probably due to the lower dose of bupivacaine used in our patients (10 mg) compared to Vallejo et al. (12–15 mg). We suggest that NE would be a safe, and efficient alternative for PE in maintenance of maternal SBP, in addition to a potential lower incidence of bradycardia, which makes NE a useful choice in mothers with low baseline heart rate and in mothers with impaired cardiac contractility.

Our study had some limitations:

- it is a single-centred study;
- we did not include mothers with cardiac morbidities;
- all our participants were scheduled to elective caesarean delivery.

Thus, we recommend more studies to compare NE and PE in mothers with cardiac morbidities and in mothers admitted for emergency caesarean delivery.

In conclusion, when given in a variable, manually-adjusted infusion, norepinephrine effectively maintained maternal SBP during elective caesarean delivery under spinal anaesthesia with lower number of physician interventions, and likely less incidence of reactive hypertension and bradycardia compared to phenylephrine when both drugs are infused at 1:15 ratio. NE is a promising alternative for PE during caesarean delivery. More studies are warranted for reaching the optimum protocol for NE infusion in obstetric anaesthesia.

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Availability of data and material

The data that support the findings of this study are available from Cairo university hospitals; however, they are not publicly available. Data are however available from the authors upon reasonable request after permission of Cairo university.

Disclosure of interest

The authors declare that they have no competing interest.

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