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Ephedrine Versus Norepinephrine in Prophylaxis Against Post-Spinal Hypotension During Elective Cesarean Section: A Randomized Clinical Study

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ABSTRACT

Background: Spinal anesthesia is endorsed anesthetic strategy in elective cesarean sections. CS requires analgesic block at T4, wherefore post-spinal hypotension is observed peaking at 85% of CS under spinal anesthesia. Countless schemes got employed to mitigate post-spinal hypotension. Fluid loading, vasopressors, or both. Norepinephrine just got defined as a potentially effective and risk free to ephedrine.
Objective: This prospective, randomized, double blind study attempted to juxtaposed ephedrine intermittent IV boluses administration as well as norepinephrine to prophylaxis against postspinal hypotension throughout elective cesarean section.
Methods: 80 parturient were recruited and stochastically apportioned into two arms. Group E (n=40) received ephedrine a prophylactic bolus of 6 mg (2 ml) intravenously while Group NE (n=40) received norepinephrine a prophylactic bolus of 5 µg (2 ml) intravenously. Mean arterial blood pressure alongside heart rate (HR) changes were documented thru surgery. MAP, HR, total vasopressor bolus requirements, maternal complications, alongside neonatal Apgar score at 1 and 5 min were documented.
Results: NE group displayed notable elevation MAP versus E group from 4 min till study termination. E group displayed notable surpassing HR thru procedure versus norepinephrine counterpart. Norepinephrine arm warranted fewer vasopressor boluses versus its ephedrine counterpart to preserve arterial pressure. Neonatal Apgar scores at 1 as well as 5 minutes alongside maternal complications were comparable.
Conclusion: Both norepinephrine and ephedrine can be utilized to preclude spinal hypotension in elective cesarean parturient without adverse events on the mother and baby with superiority of noradrenaline on ephedrine.

Keywords: Ephedrine, Noradrenaline, Cesarean section, hypotension, spinal anesthesia.

INTRODUCTION

Hypotension is the predominant adverse effect associated with spinal anesthesia in obstetrics **(1).** Most significant hypotension cause is abrupt sympatholysis onset ascribable to raised nerve fibers sensitivity to local anesthetics during pregnancy (2). Pregnant uterus aortocaval compression aggravates incidence as well as severity of hypotension in pregnant women, relative to non-obstetric patients (3).

Heretofore, phenylephrine as well as ephedrine are handpicked obstetric vasopressors for maternal hypotension; yet, phenylephrine- interrelated myocardial suppression limits its applicability in maternal cardiopathy (4), whereas ephedrine provokes maternal tachycardia and fetal acidemia (5).

Norepinephrine is both a potent α-adrenergic agonist and a slow β-adrenergic. Therefore, it may be a better option for regulating maternal blood pressure with less harmful effects on heart rate and cardiac activity (6). Reduced uteroplacental blood flow is one of the most dangerous adverse effects of taking agonists. According to Minzter et al. (7), norepinephrine has minimal effect on foetal arterial perfusion pressure and has little effect on fetoplacental microcirculation.

This study attempted to juxtaposed ephedrine versus norepinephrine in mitigation of post-spinal hypotension for parturient underwent elective CS.

PATIENTS AND METHODS

This prospective randomized double blinded study took place at Al-Azhar university hospitals (Assiut) at the Department of Anesthesia, Intensive Care as well as pain management, Egypt in a period from April 2022 to September 2022 after approval from the ethics as well as research committee of Al-Azhar University Hospitals. An informed written consent got acquired from each parturient. We included non-complicated pregnant women aged between 21 and 39 years, classified as ASA I, II with a full-term single tone pregnancy with a gestational age exceeding 37 weeks, proposed for elective caesarean under spinal anesthesia.

We excluded parturient of ASA class > II, body mass index > 30 kg/m^2, women on serotonin reuptake inhibitors, with multiple pregnancies history, pre-eclampsia/eclampsia history, abnormal placental insertion, fetal pathologies, chorioamnionitis or restrictions to spinal anesthesia. Parturients withholding consent were ineligible.

Criteria for ineligibility comprised failed spinal anesthesia, excessive neuraxial block necessitating intubation and mechanical ventilation, hypersensitivity to administered anesthetics, intraoperative complications warranting further surgery, or unanticipated recourse to general anesthesia.

Sample size

This study drew upon antecedent research (8), sample size was computed using Epi Info STATCALC, assuming 95% confidence, 80% power, 5% α error, equal group allocation (1:1), and anticipated between-group differences in hypotensive episodes; Epi Info estimated a sample of 65, expanded to 80 to account for prospective attrition.

Randomization via randomization table created by a computer software program was used to allocate patients into 2 equal parallel groups based to the type of vasopressor drug. Ephedrine (E) group: 40 patients received ephedrine (Ephedrine® 30mg/1ml, CID, Egypt) IV Ephedrine prophylactic bolus 6 mg (2 ml) Norepinephrine (N) group: 40 patients received norepinephrine (Levophrine® 4mg/4ml, EgyPharma, Egypt) prophylactic bolus 5 μg (2 ml) intravenously. All drugs were received at the time of subarachnoid block.

Pre-cesarean evaluation encompassed anamnesis, clinical examination, routine laboratory screening, and baseline noninvasive blood pressure alongside oximetry-derived heart rate measurements. Upon operating room admission, bilateral forearm venous access was established using two 20-G cannulae. IV ondansetron (8 mg) got administered, followed by preloading with 0.9% saline (10 mL/kg) 20 minutes preceding spinal blockade.

The medicine was produced in a syringe with the specified amount and concentration by an anaesthetist who was not involved in the investigation. The medication in the syringe was hidden from both the parturient and the case's anaesthetist.

Under complete aseptic condition, spinal anesthesia was done in sitting position at L3/L4 level with 12.5 mg hyperbaric bupivacaine 0.5% (2.5 ml) + 25 μg fentanyl with a total volume (3 ml) via a 25G spinal needle. Then, participants got repositioned supine with leftward inclination. Oxygen (4 L/min) by a clear face mask was given. Sensory and motor blocks got appraised via cold discrimination and the Modified Bromage Scale within 5 min post-spinal (0 = intact mobility, 1 = impaired straight-leg elevation, 2 = abolished knee flexion, and 3 = abolished ankle–foot flexion). Immediately after spinal anesthesia, prophylactic boluses of ephedrine (6 mg/2 mL) or norepinephrine (5 μg/2 mL) got dispensed according to predefined allocation by a study-masked anesthesiologist.

Mean arterial blood pressure (MAP), HR, vasopressor boluses number and ephedrine utilized per group got quantified. Nausea and vomiting incidence were recorded as well as treated with ondansetron 8 mg IV. and attacks of bradycardia (defined as HR<50 b/m) were recorded as well as treated with Atropine 0.01 mg/ Kg IV or hypotension attacks (operationalized as SBP decrement>20% from baseline) were measured and administered boluses (2 ml volume); 6 mg ephedrine or 5 μg norepinephrine. MAP and HR got documented at 2-min intervals until 10 minutes, at 5-min intervals through surgery. Postdelivery, oxytocin (20 IU) got delivered via slow intravenous infusion. Apgar score of newborn **(9)** was assessed at 1 and 5 min.

Statistical analysis of the data

Data were aggregated, codified, scrutinized, alongside uploaded into Statistical Package for Social Science (IBM SPSS) version 27. Qualitative data got displayed as number as well as percentages, whereas quantitative data got summarized as mean±SD and range for parametric distributions or median and interquartile range (IQR) for nonparametric distributions. Chi-square test was employed in comparison among two groups with qualitative data as well as Fisher's exact test supplanted the chi-square test when any expected cell frequency fell below five. Multigroup comparisons of normally distributed quantitative variables employed one-way analysis of variance (ANOVA), whereas nonparametric observations were interrogated using the Kruskal–Wallis test, followed by Student–Newman–Keuls post hoc comparisons. Statistical significance got stipulated at $P<0.05$.

RESULTS

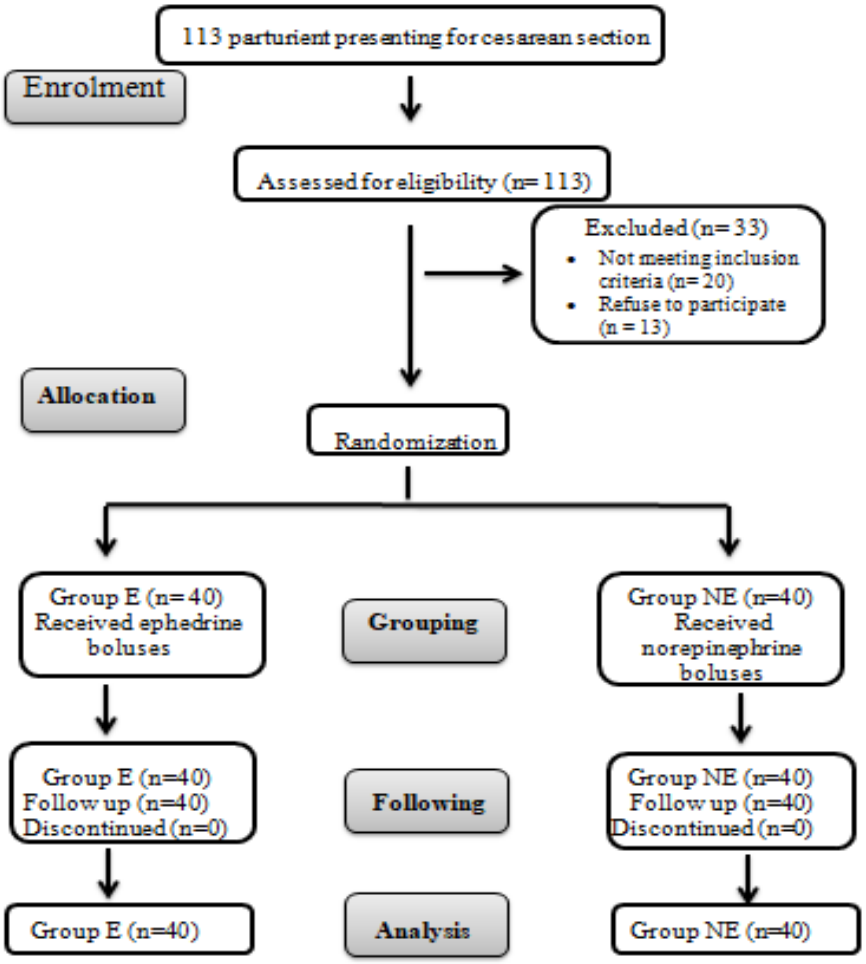

Figure 1. Consort flow chart of the study

From 113 parturient who were eligible for the study, 33 parturient were excluded as 20 were not meeting the inclusion criteria as well as 13 refused to engage; 80 pregnant women were divided into two equal groups (40 parturient each).

There was no markedly variation in the studied groups according to demographic characteristics as well as duration of surgery (table. 1).

Table 1. Demographic characteristics and duration of surgery among groups

Variables	Group E (n=40)	Group NE (n=40)	p-value
	Mean ± SD	Mean ± SD	
Age (years)	27.71±3.49	27.53±3.89	0.187
Weight (Kg)	78.13±11.37	81.67±11.07	0.573

Height (Cm)	161.81±7.24	165.41±8.31	0.078
BMI (Kg/m^2)	27.84±5.10	27.92±5.03	0.993
Surgery duration (min)	47.39±3.92	44.81±8.01	0.087

BMI = body mass index;; independent sample t-test; p value >0.05.

Haemodynamic Variables. There was no marked variations among the two groups in basal mean blood pressure and 2 min (P=0.567, 0.992) respectively. However, maternal mean blood pressure significantly increases in ephedrine in comparison with norepinephrine starting from min 4 till the end of surgery (P= 0.001). **(Table 2).**

Table 2. Maternal mean arterial blood pressure among groups

	Group E (n=40)	**Group NE (n=40)**	**p-value**
	Mean ± SD	**Mean ± SD**	
Baseline	77.06±5.11	76.39±5.31	0.567
2 min	76.11±4.89	76.10±3.82	0.992
4 min	67.81±4.01	64.01±5.27	0.001*
6 min	67.12±3.71	63.87±4.17	0.001*
8 min	66.18±1.22	63.16±3.82	0.001*
10 min	66.39±4.21	62.81±4.06	0.001*
15 min	69.41±2.89	65.79±3.17	0.001*
20 min	73.69±2.71	69.0±3.83	0.001*
25 min	75.41±2.59	72.21±3.62	0.001*
30 min	80.11±3.17	71.0±3.31	0.001*
35 min	81.52±3.52	67.42±4.31	0.001*
40 min	81.13±4.62	71.18±3.72	0.001*
45 min	81.67±4.51	75.13±2.92	0.001*
50 min	81.91±4.32	75.14±3.92	0.001*

Significance between the groups P-value<0.05.

Regarding the HR, there was no marked variations among studied drugs in baseline values of maternal HR and at 2 min (P=0.551, 0.954) respectively. Maternal HR increased significantly in ephedrine group (P< 0.001). (Table 3).

Table 3. Maternal heart rate among groups

	Group E (n=40)	**Group NE (n=40)**	**p-value**
	Mean ± SD	**Mean ± SD**	
Baseline	90.26±6.35	91.17±7.23	0.551
2 min	90.31±5.31	90.22±8.21	0.954
4 min	94.51±8.72	86.32±8.91	0.001*
6 min	94.17±8.32	85.11±7.92	0.001*
8 min	94.0±7.82	86.17±8.21	0.001*
10 min	94.23±9.42	87.37±8.17	0.001*
15 min	88.76±9.82	81.20±10.22	0.001*

20 min	89.96±10.27	80.58±9.21	0.001*
25 min	89.74±11.32	77.12±8.57	0.001*
30 min	88.62±10.92	72.81±8.71	0.001*
35 min	89.11±10.71	74.32±6.81	0.001*
40 min	86.37±7.01	75.11±7.32	0.001*
45 min	89.02±7.42	75.71±6.21	0.001*
50 min	89.43±6.71	75.11±5.79	0.001*

Significance between the groups P-value<0.05.

Vasopressor alongside Atropine Bolus Necessities. Norepinephrine arm exhibited diminished vasopressor bolus demand for arterial pressure stabilization (P = 0.001), albeit with augmented atropine dosing to counteract bradycardia versus the ephedrine cohort (P = 0.012) (Table 4).

Table 4. Number of boluses of vasopressor and atropine used in groups

	Group E (n=40)	**Group NE (n=40)**	**p-value**
	Median (IQR)	**Median (IQR)**	
No. of vasopressor boluses	4 (2 – 6)	2 (1 – 3)	0.001*
No. of atropine boluses	3 (2 – 4)	4 (2 – 6)	0.012*

Significance between the groups P-value<0.05.

Neonatal Apgar Scores. All neonates attained Apgar scores >7 at 1 and 5 minutes, without appreciable intergroup disparities at either interval (Table 5).

Table 5. Apgar score at 1 and 5 min among studied groups

	Group E (n=40)	**Group NE (n=40)**	**p-value**
	Median (IQR)	**Median (IQR)**	
Apgar score at 1 minute	8 (7 – 10)	9 (7 – 10)	0.386
Apgar score at 5 minue	9 (7 – 10)	9 (8 – 10)	0.512

Significance between the groups P-value<0.05.

Intraoperative maternal complications, Group E displayed accentuated incidences of hypertension (P = 0.241) and tachycardia (P = 0.153) versus Group NE, without statistical significance. Although, three patients experienced maternal bradycardia in group NE, while no case in ephedrine group, there was no marked variation among groups (P=0.241). Vomiting predominated in group E versus group NE, without marked variation among groups (P=0.494). The same was reported for the need for anti-emetic drug (ondansetron) (Table 6).

Table 6. Maternal complications among studied groups

	Group E (n=40)		**Group NE (n=40)**		**Chi square test**	
	n	**%**	**n**	**%**	**X2**	**p-value**
Hypertension	3	7.5%	0	0%	3.117	0.241
Tachycardia	5	12.5%	0	0%	5.333	0.153
Bradycardia	0	0%	3	7.5%	3.117	0.241
Vomiting	2	5%	0	0%	2.051	0.494
Ondansetron	2	5%	0	0%	2.051	0.494

Significance between the groups P-value<0.05.

DISCUSSION

Although ephedrine and phenylephrine are the preferred medications, vasopressor medicines are helpful in the prevention and treatment of postspinal hypotension. Traditionally used as a yardstick vasopressor, ephedrine is readily accessible, safe, and well-known to the majority of anaesthesiologists **(10)**. Systolic and diastolic pressures are increased by phenylephrine, a quick but temporary pressor. Although some anaesthesiologists employ it as a first-line vasopressor, particularly in caesarean births, it is often used as a backup option (11).

Many research juxtaposed ephedrine or norepinephrine effectuality in different doses and routes of administration.

Our findings evinced ephedrine alongside Noradrenaline forestalled cesarean postspinal hypotension, ephedrine entailed augmented bolus demand and tachychronotropy, whereas noradrenaline induced transient postbolus negative chronotropy.

Ephedrine entailed superior bolus demand versus noradrenaline, corroborating Elnabtity and Selim (10), documented three versus two boluses for normotensive maintenance.

Conversely, Shah et al. (12) documented greater norepinephrine bolus requisites than mephentermine (3 vs. 1), ascribed to its brisk onset and curtailed half-life of norepinephrine.

Hassani et al. (13) identified preserved arterial pressure but attenuated HR with norepinephrine (10 μg) versus ephedrine (5 mg), corroborating our findings despite dosing disparities.

Concordantly, Elagamy et al. (8) found that norepinephrine preserved arterial pressure beyond 80% of baseline in 120 cesarean parturients, outperforming ephedrine nonetheless eliciting more frequent bradycardia.

In contrast, Awad (14) observed comparable vasopressor redosing requirements, with 16 ephedrine alongside 21 norepinephrine-treated patients requiring no supplementary boluses. This discordance may stem from disparate vasopressor bolus dosages and the lower-limb orthopedic cohort undergoing spinal anesthesia.

Amira (15) juxtaposed norepinephrine (5 μg/mL) alongside ephedrine (5 mg/mL) for postspinal hypotension throughout lower-limb orthopedic surgery, observing a nonsignificant diminution in norepinephrine bolus demand. Unlike our significant findings, this discrepancy may reflect cohort heterogeneity.

Xu et al. (16) associated norepinephrine infusion with attenuated tachycardia, diminished hemodynamic fluctuations, and superior neonatal base excess versus ephedrine, whereas our cohorts exhibited comparable neonatal outcomes.

Wang et al. (17) identified attenuated bradycardic and tachycardic episodes and augmented neonatal base excess with norepinephrine (4 μg) versus ephedrine (4 mg) boluses in preeclamptic parturients. Both agents afforded satisfactory prophylaxis in our cohort, with discrepancies potentially attributable to preeclampsia exclusion.

Neonatal Apgar indices alognside maternal complications showed negligible intergroup divergence, potentially owing to norepinephrine-mediated cardiac output augmentation and enhanced uteroplacental perfusion.

CONCLUSION

Both norepinephrine and ephedrine forestalled cesarean postspinal hypotension without appreciable maternofetal sequelae with superiority of noradrenaline on ephedrine.

Data Availability: Study datasets are accessible through the corresponding author upon justified request.

Conflicts of Interest: Not applicable

REFERENCES

1- Ngan Kee WD. (2010): Prevention of maternal hypotension after regional anaesthesia for caesarean section. Curr Opin Anesthesiol;23(3):304–309.

2- Salinas FV, Sueda LA, Liu SS, et al. (2003): Physiology of spinal anaesthesia and practical suggestions for successful spinal anaesthesia. Best Pract Res Clin Anaesthesiol; 17(3):289–303.

3- Neal JM. (2000): Hypotension and bradycardia during spinal anesthesia: significance, prevention, and treatment. Tech Reg Anesth Pain Manage;4(4):148–154.
4- Hasanin, A., Mokhtar, A. M., Badawy, A. A., & Fouad, R. (2017): Post-spinal anesthesia hypotension during cesarean delivery, a review article. Egyptian Journal of Anaesthesia, 33(2), 189-193
5- Dyer, R. A., Reed, A. R., van Dyk, D., Arcache, M. J., Hodges, O., Lombard, C. J., ... & James, M. F. (2009): Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. The Journal of the American Society of Anesthesiologists, 111(4), 753-765.
6- Hoyme M, Scheungraber C, Reinhart K, Schummer W (2015): Comparison of norepinephrine and cafedrine/theodrenaline regimens for maintaining maternal blood pressure during spinal anaesthesia for caesarean section. ObstetGynecol Int J, 2015: 714966.
7- Minzter BH, Johnson RF, Paschall RL, Ramasubramanian R, Ayers GD, Downing JW (2010): The diverse effects of vasopressors on the fetoplacental circulation of the dual perfused human placenta. Anesthesia & Analgesia, 110 (3): 857-862.
8- A. E. Elagamy, A. M. Kamaly, M. I. Shahin, and M. Saleh, (2021): "Norepinephrine versus ephedrine for hypotension prophylaxis during cesarean section under spinal anesthesia," Ain-Shams Journal of Anaesthesiology, vol. 13, no. 1, pp. 3–6.
9- Persson M, Razaz N, Tedroff K, et al. (2018): Five and 10 minute apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden. BMJ;360:k207.
10- Ali Elnabtity AM, Selim MF. (2018): Norepinephrine versus Ephedrine to Maintain Arterial Blood Pressure during Spinal Anesthesia for Cesarean Delivery: A Prospective Double-blinded Trial. Anesth Essays Res; 12(1):92-97.
11- Ngan Kee WD, Lee SW, Ng FF, et al. (2015): Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology; 122(4):736-45.
12- Shah PJ, Agrawal P, Beldar RK. (2020): Intravenous norepinephrine and mephentermine for maintenance of blood pressure during spinal anaesthesia for caesarean section: An interventional double-blinded randomised trial. Indian J Anaesth; 64(Suppl 4):235-41.
13- V. Hassani, G. Movaseghi, R. Safaeeyan, S. Masghati, B. Ghorbani Yekta, and R. Farahmand Rad, (2018): "Comparison of ephedrine vs. norepinephrine in treating anesthesia-induced hypotension in hypertensive patients: randomized double blinded study," Anesthesiology and Pain Medicine, vol. 8, no. 4, Article ID e79626.
14- Awad, A. A. E. (2019): "Administration of ephedrine versus norepinephrine for management of post-spinal hypotension during lower limb orthopedic surgery," Clinical Practice, vol. 8, pp. 1–9.
15- Amira AE (2019): Admiistration of ephedrine versus norepinephrine for management of post-spinal hypotesion in lower limb orthopedic surgery. Clin Practice 8(1):1–9
16- Xu S, Mao M, Zhang S, Qian R, Shen X, Shen J et al (2019): A randomized doubleblind study comparing prophylactic norepinephrine and ephedrine infusion for preventing maternal spinal hypotension during elective cesarean section under spinal anesthesia: a CONSORT-compliant article. Medicine (Baltimore), 98(51):e18311
17- Wang X, Mao M, Liu S, Xu S, Yang J (2019): A comparative study of bolus norepinephrine, phenylephrine, and ephedrine for the treatment of maternal hypotension in parturients with preeclampsia during Cesarean delivery under spinal anesthesia. Med Sci Monit, 25:1093–1101