

Phenylephrine and Ephedrine for Prevention of Hypotension in Women during Lower Segment Caesarean Section under Spinal Anaesthesia: A Randomised Clinical Study

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ABSTRACT

Introduction: Hypotension is the most common serious adverse event associated with Spinal Anaesthesia (SA) and is associated with nausea and vomiting leading to pulmonary aspiration, respiratory depression and cardiac arrest. Phenylephrine (PE) and Ephedrine (EP) are vasopressors commonly used for prevention of hypotension associated with SA.

Aim: To compare the efficacy and safety of PE and EP in prevention of hypotension induced by SA in women during Lower Segment Caesarean Section (LSCS) surgery.

Materials and Methods: The present randomised clinical study was conducted on 60 women, between 18-36 years of age and a Heart Rate (HR) of 60-100 per minute randomised to receive either 100 mcg Intravenous (i.v.) bolus of PE, or 12 mg i.v. of EP during intrathecal block. Women having intraoperative hypotension were injected additional doses of vasopressor. Cardiovascular parameters were recorded at baseline (before block) and then at 1, 5, 10, 15, 30, 40 and 60 minutes. Further, safety was also assessed based on hypotension events and adverse events reported during immediate postoperative period. Data analysis was done using IBM SPSS 17 and a p-value <0.05 was considered statistically significant.

Results: The mean age of the study participants in PE and EP group was 26.67±5.40 and 26.23±4.59 years, respectively. Significant differences were observed between PE and EP groups for change in Systolic Blood Pressure (SBP) after 1, 10, 30, 40 and 60 minutes. Overall, there was a slight fall in SBP with PE, whereas, with EP there was a slight rise in SBP. Also, the Diastolic Blood Pressure (DBP) was maintained with EP throughout the 60 minute period, whereas with PE there was an initial rise in DBP followed by a slight fall in DBP. The Mean Arterial Pressure (MAP) was well-maintained with PE throughout, whereas with EP there was a fall in MAP after 15 minutes. However, these changes were not clinically significant. The Pulse Rate (PR) was lower with PE compared to EP group at time points of 1, 5, 15 and 20 minutes. The mean respiratory rates and blood oxygen saturation were similar with PE and EP administration (p>0.05). A total of 13 (43.3%) patients in the PE group and 14 (46%) in the EP group had adverse events excluding hypotensive patients.

Conclusion: According to the findings of the present study, the i.v. bolus of 100 mcg PE and 12 mg EP administered immediately after SA are equally effective in prevention of maternal hypotension and do not cause any significant cardiovascular and respiratory effects.

Keywords: Analgesia, Blood pressure, Haemodynamic, Perfusion index, Side-effects

INTRODUCTION

Spinal Anaesthesia (SA) is the preferred anaesthetic procedure used in women posted for LSCS, and single shot SA is the most commonly used technique because of its distinct advantages [1]. During SA, the mother does not lose consciousness, which decreases the issues related to airway management, and avoids potentially harmful effects of general anaesthesia on the foetus. SA is a reliable method and provides fast and profound symmetrical sensory and motor block and uses lower doses of local anaesthetics compared to epidural anaesthesia [2].

However, it also causes hypotension as the most common serious adverse event with a reported incidence of more than 80% [3]. Hypotension with SA is especially associated with nausea, vomiting, and in more severe cases there may be risks of decreased consciousness, pulmonary aspiration, respiratory depression, and cardiac arrest. Maternal hypotension can have detrimental effects on the neonate due to reduced uteroplacental flow, foetal hypoxia, asphyxia and acidosis [4,5]. Also, spinal block is associated with precipitous hypotension and poor extent of analgesia.

Several strategies for preventing and treating hypotension are investigated, like the use of lateral uterine displacement [6], i.v. fluid preloading [7], gravity [8], compression devices on legs

and prophylactic vasopressors, but none of them are proven to be satisfactory [9]. Preloading or co-loading is commonly administered, but it has controversial results [10]. Most often, the non pharmacological techniques fail to manage hypotension, and a vasopressor is usually required during SA. Vasopressors like EP, PE and metaraminol are commonly used for preventing hypotension during SA. However, selection of appropriate vasopressor in obstetrics depends on several factors like efficacy, non cardiovascular maternal effects, ease of use, foetal effects, cost and availability. PE is a potent directly acting adrenergic alpha receptor agonist used in hypotensive states. However, high doses of PE may be required in pregnancy, because of physiological changes in pregnancy [11]. Also, foetal complications like acidosis have not been reported, even with the high dose PE use in obstetric practice [12].

Ephedrine, a sympathomimetic amine is the most used vasopressor which acts indirectly by increasing the release of noradrenaline at the postsynaptic α and β receptors [13]. It also has a direct agonistic action on both α and β receptors. It increases the blood pressure by β_1 adrenergic receptor stimulation with increased HR and cardiac contractility, whereas the α adrenergic receptor agonist action causes peripheral vasoconstriction. EP is administered as 6-12 mg i.v. bolus for the treatment of hypotension following SA.

The drug not only has a delayed onset of action, but also has a longer duration of action upto 60 minutes [14]. Repeated use of EP is associated with depletion of endogenous norepinephrine stores leading to rapid tolerance (tachyphylaxis) [15].

Studies have compared maternal and foetal effects of i.v. PE and EP administration during spinal anaesthesia for caesarean delivery in high-risk pregnancies at various doses of the drugs. These reports suggest that both PE and EP can be safely used to counteract hypotension after spinal anaesthesia in patients with uteroplacental insufficiency, pregnancy-induced hypertension, and in non elective caesarean deliveries [16-20]. Different vasopressors are commonly used at present with varying degrees of success [21]. Despite the use of prophylactic i.v. infusion or bolus EP for the last three decades, a sizeable number of failures have also been reported and a rescue PE bolus dose appears effective when EP alone fails to correct hypotension [22-25].

Prophylactic PE infusion significantly lowers the incidence of SA induced maternal hypotension despite its limitations like bradycardia, hypertension and reduced Cardiac Output (CO) at higher dose [26,27]. Due to this reason, previous researches focused on finding adequate preventive measure for hypotension from LSCS. However, the best prophylaxis of maternal hypotension during caesarean section is still under research. This randomised study compared the efficacy and safety of 100 mcg PE versus 12 mg EP dose that remains unexplored in preventing SA induced hypotension during LSCS. The primary efficacy outcome was the incidence of hypotension during the period of 60 minutes after administration of SA. The secondary outcomes were repercussion on SBP, DBP, MAP, HR, Perfusion Index (PI), Respiratory Rate (RR) and blood oxygen saturation (SpO₂).

MATERIALS AND METHODS

This randomised clinical study was conducted during August 2018 to March 2019 in the Department of Anaesthesia, Dr. D.Y. Patil Hospital, Dr. D.Y. Patil Deemed University, School of Medicine, Navi Mumbai, Maharashtra, India. The study documents were reviewed and approved by the Institutional Ethics Committee (PDDYPMC/Ethic/PG Dissert/2017, Dated 10.10.2017). Informed written consent was obtained from all participating women prior to any study related procedure.

Sample size calculation: A sample size of 60 was decided for the study purpose on the basis of calculation using Medcalc version 12.0.3 software, with error of 5%, and a confidence level at 95%.

Inclusion criteria: Full-term pregnant women between 18-36 years of age, who were scheduled for elective LSCS under SA, with physical status ASA-II were screened for study eligibility. All women with a basal HR of between 60-100 beats per minute were enrolled in the study.

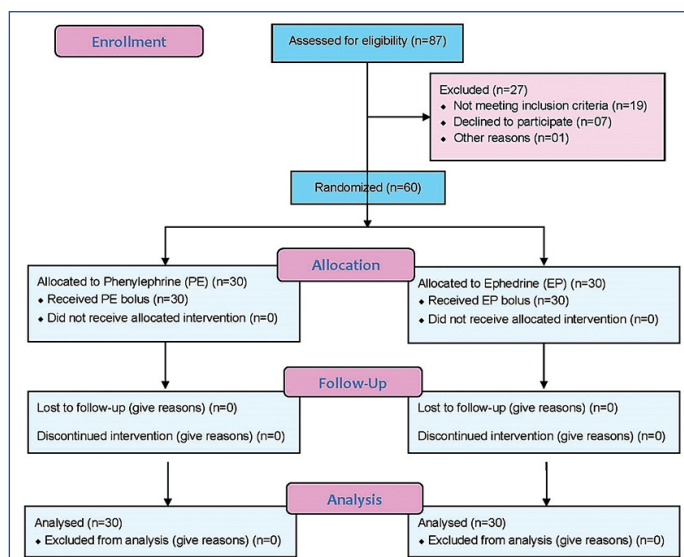
Exclusion criteria: Women with use of any opioids or sedatives, or a history of alcoholism were not included. Also, women having any abnormalities of thyroid, cardiopulmonary, liver, kidney, those with neurological conditions, or having tremors or fever or any active infection were also excluded.

Eligible women were randomised in a 1:1 ratio to receive either PE or EP based on a predetermined computer-based randomisation (Rando V 1.2, © R. Raveendran 2004). The study team received the randomisation codes in separate envelopes for each study participant and were instructed to open the envelope only after assigning the study number to the eligible participant. The investigator and study team were blinded to treatment allocation.

There was no data loss, and data of all sixty patients was used for final analysis [Table/Fig-1].

Study Procedure

Detailed preanaesthetic check-up of all the patients posted for LSCS surgery was done a day prior to surgery. All the patients were



[Table/Fig-1]: CONSORT flow diagram.

fasted for more than 8 hours prior to surgery. Vital parameters were measured at baseline before administration of SA. SA (intrathecal) was administered with a 23/25-gauge Quincke spinal needle, in a sitting position, at the L3-4/L4-5 interspace (mid line approach) with 2 mL bupivacaine (0.5%, heavy). Women were continuously monitored for occurrence of any hypotensive events (a decrease below 80% baseline and the combined definition of a blood pressure below 100 mmHg or a decrease below 80% baseline was defined as hypotension). After one minute of SA, 30 random women received 100 mcg i.v. bolus of PE and the other 30 women received 12 mg i.v. bolus of EP. Only in case of further rescue management if required, a rescue bolus dose of 50 mcg of PE and rescue dose of 6 mg EP was given to their respective groups. SBP, DBP, MAP, and PR were recorded at 0 (baseline), 1, 5, 10, 15, 20, 30, 40, 50 and 60 minutes.

Outcome measures: The primary efficacy outcome was the incidence of hypotension during the period of 60 minutes after administration of SA. Secondary efficacy outcomes were SBP, DBP, MAP, HR, PI, RR and SpO₂. Safety outcomes were the adverse events recorded during intraoperative period and upto 24-hrs postoperative period.

STATISTICAL ANALYSIS

Measurement data for the SBP, DBP, MAP, PI, PR, RR and SpO₂ are expressed as means± SD. Similarly, change from the baseline was computed for all measurement variables at each time point and expressed as mean±standard deviation (Mean±SD). A repeat-measures Analysis of Variance (ANOVA) was used to analyse the difference between the two groups for all cardiovascular parameters. Differences between the two groups (PE and EP) are computed for each variable at each time point and presented as means with 95% Confidence Intervals (CI). Categorical data and discrete data are expressed as numbers with percentages (proportions). Data analysis was done using a windows based statistical program IBM SPSS 17 (IBM Corporation, Armonk, New York, US). All measurement data was compared between the two groups using an unpaired t-test. Categorical data is compared between the two groups using an Chi-square test. All testing was done using two-sided tests at alpha 0.05. A p-value of <0.05 was considered significant.

RESULTS

The two groups were similar with respect to the demography, level of anaesthesia and baseline values for vital parameters [Table/Fig-2]. Hypotension was observed in only 6 (20.0%) patients with PE and 4 (13.3%) patients with EP (OR=1.625; 95% CI=0.408 to 6.469; p=0.488). [Table/Fig-3] presents the adverse events observed during the intraoperative and upto 24 hours postoperative period.

Variables	Phenylephrine (PE) (n=30)	Ephedrine (EP) (n=30)	Difference		t-test	
	Mean±SD	Mean±SD	Mean	95% CI	t	p-value
Age (years)	26.67±5.40	26.23±4.59	0.43	-2.16 to 3.02	0.335	0.739
Pulse (per min)	103.60±12.0	100.23±10.98	3.37	-2.58 to 9.31	1.134	0.261
SBP (mmHg)	117.33±10.8	119.87±8.95	-2.53	-7.68 to 2.61	-0.986	0.328
DBP (mmHg)	75.17±8.88	77.10±6.89	-1.93	-6.04 to 2.18	-0.942	0.350
Perfusion Index (PI)	2.36±0.82	2.61±0.73	-0.25	-0.65 to 0.15	-1.232	0.223
SpO ₂ (%)	99.47±0.57	99.57±0.50	-0.10	-0.38 to 0.18	-0.719	0.475

Level of anaesthesia

Variables	PE, No. (%)	EP, No. (%)	Chi-square	p-value
T4	14 (46.67%)	16 (53.33%)	0.300	0.861
T5	13 (43.33%)	11 (36.67%)		
T6	6 (20%)	3 (10%)		

[Table/Fig-2]: Demography and baseline data.

T4: 4th Thoracic vertebra; T5: 5th Thoracic vertebra; T6: 6th Thoracic vertebra

Variables	Phenylephrine (PE) (n=30)	Ephedrine (EP) (n=30)	Chi-square/p-value
	No. (%)	No. (%)	
Headache	2 (6.7%)	3 (10.0%)	9.915/0.538
Vomiting	7 (23.3%)	5 (16.7%)	
Nausea	3 (10.0%)	4 (13.3%)	
Shivering	1 (3.3%)	1 (3.3%)	
Sweating	0 (0%)	1 (3.3%)	
Hypotension	6 (20%)	4 (13.3%)	
Total events	19 (63.3%)	18 (60.0%)	
Total patients (excluding hypotension)	13 (43.3%)	14 (46.0%)	

[Table/Fig-3]: Adverse events reported by the patients in the two groups.

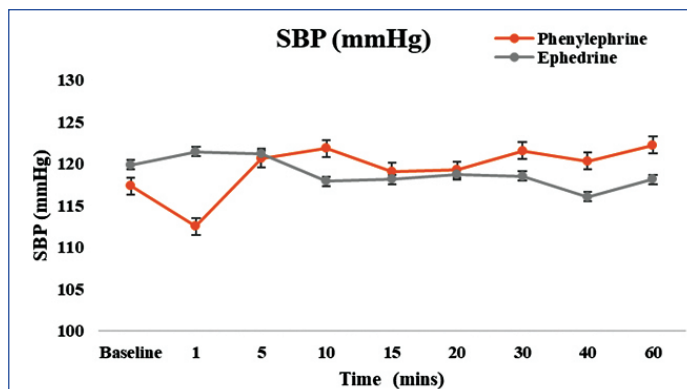
Most common events reported were vomiting and nausea accounting for about 30% events. The profile of adverse events was similar in the two groups (p=0.538). The RR and SpO₂ were maintained in all the patients throughout the study period with no significant difference between the two groups (p>0.05).

Systolic Blood Pressure (SBP)

[Table/Fig-4] presents the SBP at different time intervals in both the groups. The baseline mean SBP was similar to PE and EP (p=0.328). However, at a time interval of one minute, the mean SBP was lower in the PE group compared to the EP group. In both the groups, mean SBP was fluctuating from baseline at different time intervals, but there were significant differences between the two groups (p<0.05). Overall repeat-measures ANOVA showed no differences between the two groups (p>0.05). Significant differences were observed between PE and EP for change in SBP after one minute (p=0.006), 10 minutes (p=0.013), 30 minutes (p=0.031), 40 minutes (p=0.020), and 60 minutes (p=0.033). Thus, overall, there was a slight rise in SBP with PE, whereas with EP there was a slight fall in SBP.

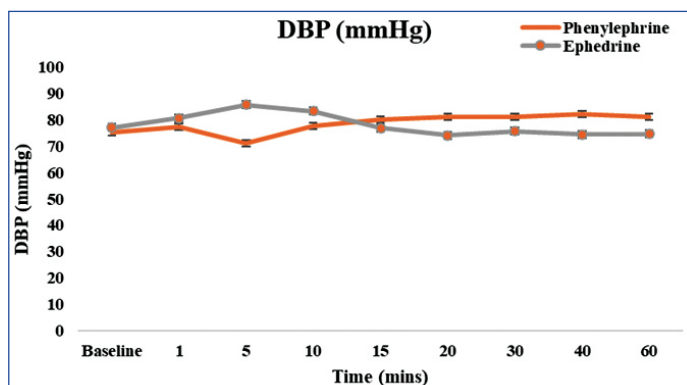
Diastolic Blood Pressure (DBP)

[Table/Fig-5] presents the DBP at different time intervals in both the groups. Baseline mean DBP was similar with PE and EP (p=0.350). However, the mean DBP was lower in the PE group compared to EP group at time intervals of one minute (p=0.105), five-minutes (p=0.006) and 10 minutes (p=0.074). After 15 minutes onwards the



[Table/Fig-4]: The SBP (mmHg) in the patients at different time points in the two groups.

mean DBP was higher in PE group as compared to EP group, and these differences were statistically significant (p<0.05) except for 15 minute time period (p=0.067). However, significant differences were observed between PE and EP for change in DBP from baseline after five minute (p<0.0001), 15 minutes (p=0.002), 20 minutes (p<0.0001), 30 minutes (p<0.0001), 40 minutes (p<0.0001), and 60 minutes (p<0.0001) (Data not shown in table). ANOVA showed no differences between the two groups (p>0.05). Thus, overall, the DBP was maintained with EP throughout the 60-minute period, whereas with PE there was an initial rise in DBP followed by a slight fall in DBP.



[Table/Fig-5]: The DBP (mmHg) in the patients at different time points in the two groups.

Mean Arterial Pressure (MAP)

[Table/Fig-6] presents the MAP at different time intervals in both the groups. The MAP was similar with PE and EP at baseline (p=0.245) and upto 10 minutes (p>0.05). However, from 15 minutes onwards, the MAP was lower with EP than PE (p<0.05). Overall repeat measures ANOVA showed no differences between the two groups (p>0.05). The change in MAP from baseline was similar (p>0.05) with PE and EP at one minute, five minutes and 10 minutes.

Time line	Phenylephrine (PE) (n=30)	Ephedrine (EP) (n=30)	Unpaired t-test			
	Mean±SD	Mean±SD	Difference	95% CI	t	p-value
Baseline	73.77±6.60	75.63±5.67	-1.87	(-5.05 to 1.31)	-1.175	0.245
1 min	73.67±7.35	76.43±6.83	-2.77	(-6.43 to 0.90)	-1.511	0.136
5 min	75.97±7.18	76.93±6.86	-0.97	(-4.60 to 2.66)	-0.533	0.596
10 min	76.30±7.47	76.20±6.49	0.10	(-3.52 to 3.72)	0.055	0.956
15 min	76.90±7.36	73.43±5.05	3.47	(0.20 to 6.73)	2.127	0.038
20 min	76.80±6.79	72.83±4.71	3.97	(0.95 to 6.99)	2.630	0.011
30 min	78.00±7.56	73.03±4.77	4.97	(1.70 to 8.23)	3.042	0.004
40 min	78.80±6.80	73.27±4.50	5.53	(2.55 to 8.52)	3.714	<0.0001
60 min	79.30±6.81	72.37±4.11	6.93	(4.03 to 9.84)	4.774	<0.0001

[Table/Fig-6]: The MAP (mmHg) in the patients at different time points in the two groups.

However, the change in MAP was significantly different ($p < 0.0001$) in PE and EP from 15 minutes onwards. Overall, the MAP was well-maintained with PE throughout the study period, whereas with EP there was a fall in MAP after 15 minutes.

Pulse Rate (PR)

[Table/Fig-7] presents the PR at different time intervals in both the groups. The baseline mean PR was similar to PE and EP ($p = 0.261$). However, at time points of 1, 5, 15, 20 minutes, the mean PR was lower with PE compared to the EP group ($p < 0.05$). However, at all other time points, minor changes were observed in the PR from baseline, which were not significant ($p > 0.05$). Overall, repeat-measures ANOVA showed no differences between the two groups ($p > 0.05$). There was a fall in PR with PE starting at 15 minutes, whereas there was a rise in PR with EP from one minute till 20 minutes. A slight fall in PR was observed with EP after 40 minutes. However, the change in PR from baseline between the groups was not similar at one minute ($p < 0.0001$), 5 minutes ($p = 0.001$), 10 minutes ($p = 0.020$), 15 minutes ($p = 0.001$), 20 minutes ($p = 0.012$), and 60 minutes ($p = 0.035$) (Data not shown in table).

Time line	Phenylephrine (PE) (n=30)	Ephedrine (EP) (n=30)	Unpaired t-test			
	Mean±SD	Mean±SD	Difference	95% CI	t	p-value
Baseline	103.60±12.00	100.23±10.98	3.37	(-2.58 to 9.31)	1.134	0.261
1 min	105.43±10.84	113.90±9.02	-8.47	(-13.62 to -3.31)	-3.288	0.002
5 min	109.97±11.33	117.17±8.72	-7.20	(-12.42 to -1.98)	-2.758	0.008
10 min	107.77±10.70	112.30±8.99	-4.53	(-9.64 to 0.57)	-1.776	0.081
15 min	102.53±9.72	108.30±9.65	-5.77	(-10.77 to -0.76)	-2.307	0.025
20 min	98.83±9.77	103.70±7.48	-4.87	(-9.36 to -0.37)	-2.166	0.034
30 min	98.30±9.54	100.13±6.64	-1.83	(-6.08 to 2.42)	-0.864	0.391
40 min	96.07±6.90	97.93±5.25	-1.87	(-5.04 to 1.30)	-1.179	0.243
60 min	93.30±7.92	96.80±7.60	-3.50	(-7.51 to 0.51)	-1.747	0.086

[Table/Fig-7]: The PR in the patients at different time points in the two groups.

Perfusion Index (PI)

[Table/Fig-8] Baseline mean PI was similar to PE and EP ($p = 0.223$). However, at a time interval of 40 minutes, the mean PI was lower in the EP group compared to the PE group ($p = 0.017$). At all other time-points, minor changes were observed in the PI from baseline, which were not significant ($p > 0.05$). Overall, repeat-measures ANOVA showed no differences between the two groups ($p > 0.05$). The PI increased with both PE and EP at all time points. However, the change (increase) in PI was greater with PE as compared to EP at 5, 10, 30, 40 and 60 minutes ($p < 0.05$).

Time line	Phenylephrine (PE) (n=30)	Ephedrine (EP) (n=30)	Unpaired t-test			
	Mean±SD	Mean±SD	Difference	95% CI	t	p-value
Baseline	2.36±0.82	2.61±0.73	-0.25	(-0.65 to 0.15)	-1.232	0.223
1 min	2.59±0.85	2.81±0.77	-0.22	(-0.64 to 0.20)	-1.065	0.291
5 min	2.89±0.81	2.84±0.63	0.05	(-0.33 to 0.42)	0.249	0.804
10 min	2.91±0.76	2.81±0.57	0.10	(-0.24 to 0.45)	0.594	0.555
15 min	2.88±0.70	2.75±0.54	0.13	(-0.19 to 0.45)	0.808	0.423
20 min	3.00±0.85	2.93±0.63	0.07	(-0.32 to 0.45)	0.346	0.730
30 min	3.12±0.76	2.85±0.62	0.27	(-0.09 to 0.63)	1.504	0.138
40 min	3.28±0.63	2.89±0.58	0.38	(0.07 to 0.70)	2.458	0.017
60 min	3.33±0.71	3.01±0.56	0.32	(-0.01 to 0.65)	1.929	0.059

[Table/Fig-8]: The PI in the patients at different time points in the two groups.

DISCUSSION

The maternal hypotension during LSCS under SA for caesarean section is unacceptably high, despite preloading and lateral uterine displacement [28]. Several mechanisms are proposed to be the

cause of the hypotensive response after SA. First, sympathetic blockage from T1-L2 with subsequent arterial vasodilation leads to a reduction in Systemic Vascular Resistance (SVR), contributing to intraoperative hypotension. This decrease in SVR is often thought to be the main cause of hypotension after SA. Second, a decrease in venous vasomotor tone increases venous pooling and consequently reduces venous return, thereby decreasing CO. Finally, the physiological haemodynamic reserve capacity decreases with age, and limited cardiovascular compensation mechanisms contribute to a decline in CO and blood pressure in response to SA [29]. In addition, use of an opioid like fentanyl to local anaesthetic to improve the quality of intraoperative and postoperative analgesia can also contribute towards increased rate of maternal hypotension, but some believed it to be worth the risk [30].

In this study, the efficacy of prophylactic bolus of two vasopressors, PE and EP to prevent maternal hypotension was compared following SA in caesarean section. In present study, similar hypotension rates were observed with PE and EP ($p = 0.488$), when administered prophylactically with SA. These results corroborate with the findings of other researchers which concluded that PE and EP are both suitable vasopressors for use in non elective caesarean sections [16,18,20]. On the other hand, a randomised comparative study reported a greater effect of EP (1 mg/min. i.v. infusion) than PE (10 mcg/min. i.v. infusion) preventing maternal hypotension in healthy women undergoing elective LSCS under SA [31]. Simon L et al., in their prospective observation real-world study reported that increasing the dose of the prophylactic bolus of EP to 15 or 20 mg significantly reduces the hypotension events without increasing the undesirable tachycardia [32]. Ngan Kee WD et al., reported i.v. 30 mg dose of EP as the smallest effective dose for prophylaxis of hypotension during SA for caesarean delivery [33]. However, Shearer VE et al., reported foetal hypoxia (umbilical artery blood pH <7.20) with 10 mg i.v. EP in women receiving regional anaesthesia [34]. In similar lines, McGrath JM et al., showed that EP was superior to PE in restoring uterine blood flow and foetal oxygenation during ritodrine infusion and epidural anaesthesia-induced hypotension in gravid [35].

Overall, repeat-measures ANOVA, showed no significant difference between the two groups ($p > 0.05$) with respect to PR and BP. However, PE caused a slight increase and EP caused a slight decrease in SBP and DBP, but these changes were not clinically significant to cause any intervention. Similarly, the MAP was also similar with PE and EP at different time-points with minor fluctuations, which were not clinically significant. Similarly, the RR and SpO₂ were similar with PE and EP in our study.

A total of 13 (43.3%) patients with PE and 14 (46%) patients with EP group had experienced adverse events excluding hypotension. In the present study, lesser incidence of adverse events, especially nausea was observed when compared to those reported by Hall PA et al., [31]. Balki M and Carvalho JCA reported that intraoperative nausea and vomiting can be best prevented by controlling hypotension, and antiemetics should be reserved for high-risk patients and for those not responding to routine measures [4].

Limitation(s)

Being a single-centre study, the findings of the study could not be generalised, as there are varied reports of comparative results with PE and EP for prevention of hypotension with SA since last three decades.

CONCLUSION(S)

According to the present study results, the i.v. bolus of PE (100 mcg) and EP (12 mg) administered immediately after SA are equally effective in prevention of maternal hypotension and do not cause any significant cardiovascular and respiratory effects.

REFERENCES

- [1] Yeoh SB, Leong SB, Heng AST. Anaesthesia for lower-segment caesarean section: Changing perspectives. *Indian J Anaesth* [Internet]. 2010 [cited 2022 Oct 14];54(5):409-14.
- [2] Gizzo S, Noventa M, Fagherazzi S, Lamparelli L, Ancona E, Di Gangi S, et al. Update on best available options in obstetric anaesthesia: Perinatal outcomes, side-effects and maternal satisfaction. Fifteen years systematic literature review. *Arch Gynecol Obstet*. 2014;290(1):21-34.
- [3] Prakash S, Pramanik V, Chellani H, Salhan S, Gogia AR. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: A randomised study. *Int J Obstet Anesth*. 2010;19(1):24-30.
- [4] Balki M, Carvalho JCA. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. *Int J Obstet Anesth*. 2005;14(3):230-41.
- [5] Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomised controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg*. 2002;94(4):920-26.
- [6] Kinsella SM. Lateral tilt for pregnant women: Why 15 degrees? *Anaesthesia*. 2003;58(9):835-36.
- [7] Kinsella SM, Pirlot M, Mills MS, Tuckey JP, Thomas TA. Randomised study of intravenous fluid preload before epidural analgesia during labour. *Br J Anaesth*. 2000;85(2):311-13.
- [8] McCrae AF, Wildsmith JA. Prevention and treatment of hypotension during central neural block. *Br J Anaesth*. 1993;70(6):672-80.
- [9] Rout CC, Rocke DA, Gouws E. Leg elevation and wrapping in the prevention of hypotension following spinal anaesthesia for elective caesarean section. *Anaesthesia*. 1993;48(4):304-08.
- [10] Kubli M, Shennan AH, Seed PT, O'Sullivan G. A randomised controlled trial of fluid preloading before low dose epidural analgesia for labour. *Int J Obstet Anesth*. 2003;12(4):256-60.
- [11] Weiner CP, Martinez E, Chestnut DH, Ghodsi A. Effect of pregnancy on uterine and carotid artery response to norepinephrine, epinephrine, and phenylephrine in vessels with documented functional endothelium. *Am J Obstet Gynecol*. 1989;161(6 Pt 1):1605-10.
- [12] Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for caesarean section. *Br J Anaesth*. 2004;92(4):469-74.
- [13] Ralston DH, Shnyder SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. *Anesthesiology*. 1974;40(4):354-70.
- [14] Nazir I, Bhat MA, Qazi S, Buchh VN, Gurcoo SA. Comparison between phenylephrine and ephedrine in preventing hypotension during spinal anesthesia for cesarean section. *Journal of Obstetric Anaesthesia and Critical Care*. 2012;12(2):92.
- [15] Nguyen LP, Gerstein NS. Chapter 11- Cardiovascular Pharmacology in Noncardiac Surgery. In: Kaplan JA, Cronin B, Maus TM, editors. *Essentials of Cardiac Anesthesia for Noncardiac Surgery*. New York: Elsevier; 2019: 247-88.
- [16] Ngan Kee WD, Khaw KS, Lau TK, Ng FF, Chui K, Ng KL. Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non elective caesarean section. *Anaesthesia*. 2008;63(12):1319-26.
- [17] Cooper GM. *Signaling Molecules and Their Receptors*. The Cell: A Molecular Approach 2nd edition. 2000.
- [18] Mohta M, Aggarwal M, Sethi AK, Harisinghani P, Guleria K. Randomised double-blind comparison of ephedrine and phenylephrine for management of post-spinal hypotension in potential fetal compromise. *Int J Obstet Anesth*. 2016;27:32-40.
- [19] Jain K, Makkar JK, Subramani Vp S, Gander S, Kumar P. A randomised trial comparing prophylactic phenylephrine and ephedrine infusion during spinal anesthesia for emergency cesarean delivery in cases of acute fetal compromise. *J Clin Anesth*. 2016;34:208-15.
- [20] Ituk US, Cooter M, Habib AS. Retrospective comparison of ephedrine and phenylephrine for the treatment of spinal anesthesia induced hypotension in pre-clamptic patients. *Curr Med Res Opin*. 2016;32(6):1083-86.
- [21] Connolly NR, Dunn SM, Ingold V, Villa EA. The use of fentanyl added to morphine-lidocaine-epinephrine spinal solution in patients undergoing cesarean section. *Anesth Analg*. 1994;78(5):918-20.
- [22] Ngan Kee WD, Khaw KS, Ng FF, Lee BB. Prophylactic phenylephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg*. 2004;98(3):815-21.
- [23] Kee WDN, Khaw KS, Ng FF. Prevention of hypotension during spinal anesthesia for cesarean delivery: An effective technique using combination phenylephrine infusion and crystalloid cohydration. *Anesthesiology*. 2005;103(4):744-50.
- [24] Mercier FJ, Riley ET, Frederickson WL, Roger-Christoph S, Benhamou D, Cohen SE. Phenylephrine added to prophylactic ephedrine infusion during spinal anesthesia for elective cesarean section. *Anesthesiology*. 2001;95(3):668-74.
- [25] Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. *Anesth Analg*. 2010;111(5):1230-37.
- [26] Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2002;97(6):1582-90.
- [27] Dyer RA, Reed AR. Spinal hypotension during elective cesarean delivery: Closer to a solution. *Anesth Analg*. 2010;111(5):1093-95.
- [28] Cooper DW, Sharma S, Orakkan P, Gurung S. Retrospective study of association between choice of vasopressor given during spinal anaesthesia for high-risk caesarean delivery and fetal pH. *Int J Obstet Anesth*. 2010;19(1):44-49.
- [29] Ogawa T, Spina RJ, Martin WH, Kohrt WM, Schechtman KB, Holloszy JO, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation*. 1992;86(2):494-503.
- [30] Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. *BMC Anesthesiol*. 2005;14(5):5.
- [31] Hall PA, Bennett A, Wilkes MP, Lewis M. Spinal anaesthesia for caesarean section: Comparison of infusions of phenylephrine and ephedrine. *Br J Anaesth*. 1994;73(4):471-74.
- [32] Simon L, Provenchère S, de Saint Blanquat L, Boulay G, Hamza J. Dose of prophylactic intravenous ephedrine during spinal anesthesia for cesarean section. *J Clin Anesth*. 2001;13(5):366-69.
- [33] Ngan Kee WD, Khaw KS, Lee BB, Lau TK, Gin T. A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg*. 2000;90(6):1390-95.
- [34] Shearer VE, Ramin SM, Wallace DH, Dax JS, Gilstrap LC. Fetal effects of prophylactic ephedrine and maternal hypotension during regional anesthesia for cesarean section. *J Matern Fetal Med*. 1996;5(2):79-84.
- [35] McGrath JM, Chestnut DH, Vincent RD, DeBruyn CS, Atkins BL, Poduska DJ, et al. Ephedrine remains the vasopressor of choice for treatment of hypotension during ritodrine infusion and epidural anesthesia. *Anesthesiology*. 1994;80(5):1073-81; discussion 28A.

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