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COMPARATIVE STUDY OF PHENYLEPHRINE, EPHEDRINE AND MEPHENTERMINE FOR TREATMENT OF HYPOTENSION DURING SPINAL ANESTHESIA FOR CAESAREAN SECTION

Anaesthesiology

KEYWORDS: Phenylephrine, Ephedrine, Mephentermine, Hypotension, Spinal anesthesia

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ABSTRACT

Background: Hypotension is one of the commonest problems following Spinal anesthesia which may require vasopressors to maintain normal blood pressure. This study compares the efficacy of intravenous bolus Phenylephrine, Ephedrine and Mephentermine for maintenance of blood pressure during Spinal anesthesia for Caesarean section.

Materials & Methods: The study population consisted of 75 patients undergoing elective caesarean section who developed hypotension following subarachnoid block. They were randomly allocated into 3 groups of 25 each to receive Group P-Phenylephrine 100 microgram, Group E- Ephedrine 6 mg, and Group M-Mephentermine 6 mg in 1 ml as bolus intravenously.

Results: It was found that rise of Systolic blood pressure for first 6 minutes after administration of study drugs was significantly higher in group P as compared to group E and group M($p<0.05$). Similarly elevation of Diastolic blood pressure in group P was significantly higher as compared to other two groups for first 2 minutes. No significant differences were observed between changes in systolic and diastolic blood pressure of Ephedrine and Mephentermine group at any time. There was significant reduction in heart rate in Phenylephrine group but there was tachycardia following administration of Ephedrine and Mephentermine. Neonatal APGAR score were similar in all three groups.

Conclusion: All study drugs maintained Blood pressure within 20% of baseline values on intravenous administration however rise in BP within first 6 min after bolus dose was significantly higher in phenylephrine group in comparison to ephedrine and mephentermine group. Correction of hypotension was better sustained in phenylephrine group. Moreover, Phenylephrine group causes significantly lower heart rate. There was no undue effect on the fetus in any group as assessed by neonatal APGAR scores.

Introduction

Spinal anesthesia for caesarean section has several advantages over general anaesthesia like decreased risk of failed intubation, decreased risk of aspiration of gastric contents, avoidance of the depressant effects of general anaesthetics on neonate etc.

Single shot spinal is most commonly performed because it is quicker, has faster onset with superior block and infrequent failure. However, single shot spinal anesthesia has some adverse effects also. The most common adverse effect is hypotension. The incidence of hypotension is as high as 75-85%.[1]

Several pharmacologic and non-pharmacologic methods have been used for management of hypotension, with no single method conclusively superior. Amongst the vasopressors used (ephedrine, phenylephrine, metaraminol, mephentermine) none is conclusively better over the other.[2]

Ephedrine is synthetic noncatecholamine that stimulates alpha and beta adrenergic receptors by indirect action as well as direct stimulating effects,6 it has been used as the agent of choice, but the position has been challenged because of potential to cause tachyphylaxis and fetal acidosis.[3,4]

Recent studies favour Phenylephrine, a α1 agonist which elevates arterial blood pressure by increasing systemic vascular resistance secondary to vasoconstriction. However, it causes bradycardia. It may cause uterine arteriolar constriction and thus diminishing uterine blood flow.[5]

Mephentermine, which has mechanism of action similar to ephedrine, has been used for treatment of hypotension during spinal anaesthesia. Mephentermine is direct and indirect symp athomimetic action and probably the increase in arterial blood pressure is chiefly by increased cardiac output.[6,7]

The present study was conducted to compare three vasopressors: Phenylephrine, Ephedrine and Mephentermine as treatment of hypotension during spinal anaesthesia for caesarean section.

Material and Methods

The present prospective, randomized, double-blinded clinical study was conducted after obtaining permission from institutional ethical committee on 75 American Society of Anesthesiologists grade I-II patients with singleton, full term, uncomplicated pregnancy scheduled for elective caesarean section under spinal anesthesia. Patients with pregnancy-induced hypertension, history of diabetes, cardiovascular and cerebrovascular disease, fetal abnormalities and contraindication to spinal anesthesia were excluded from the study.

Informed written consent was taken from all patients. The patients were allocated to either of the three groups using computer generated random numbers. **Group P**(n=25) received Phenylephrine 100mcg in 1ml as iv bolus. **Group E**(n=25) received Ephedrine 6mg in 1ml as iv bolus. **Group M**(n=25) received Mephentermine 6mg in 1ml as iv bolus.

Participants fasted overnight. On the morning of surgery, after intravenous cannulation with 18 gauge catheter, participant was preloaded with Ringer lactate solution, 10 mL/kg BW rapidly which was continued thereafter at a rate of approximately 15 mL/min throughout the study period. Three readings of systolic blood pressure, diastolic blood pressure and heart rate were obtained at three minutes of interval with patient at supine with a 15 degree wedge under right hip after the preloading. The lowest reading of blood pressure and heart rate was taken as baseline values to minimize influence of anxiety in patients with high initial values. Participants were randomly allocated by sealed envelope method to receive bolus either Phenylephrine 100 µg or Ephedrine 6 mg or Mephentermine 6 mg upon developing hypotension. The preparation of the study drugs for treatment of anticipated hypotension was done by an anesthesiologist blind to the study. The volume of each dose was equaled by adding 0.9% NaCl solution making the concentration of Phenylephrine 100µg/ml, Ephedrine 6mg/ml and Mephentermine 6mg/ml. The identical syringes containing the solution were unlabeled and put in labeled tray.

Pulse oximeter probe, ECG electrodes, automated oscillometric blood pressure cuff were attached. Fetal heart rate was monitored using stethoscope till the painting and draping of the participant.

Spinal anaesthesia was administered with subarachnoid placement of bupivacaine 12.5 mg (2.5 ml of 0.5% bupivacaine with dextrose 8% solution) through the L3-L4 interspinous spaces using 25 G Quinke

needle under complete aseptic condition. The patient was turned to supine position and after 5 min a 15 0 wedge was placed under the right hip. Dermatomal level of anaesthesia was assessed by loss of thermal discrimination to cold using ice cubes along mid-clavicular line 10 minutes after spinal anaesthesia. The target block height equal to or above T6 and the surgeons were asked to proceed.

Oxygen was administered at a rate of 3Lmin by a face mask to all the patients until the umbilical cord was clamped. Inj. oxytocin 10U in 5% saline was given after clamping the cord. Participant was administered i.v. midazolam 0.02 mg/kg BW after the delivery of baby and shivering during the study was treated with i.v. tramadol 0.5mg/kg BW. Episode of nausea and vomiting was treated with i.v. ondansetron 4mg. Bradycardia was defined as fall in heart rate below 50 beats per min and was treated with atropine 0.6 mg i.v.

Systolic blood pressure & diastolic blood pressure were noted every 2 minutes after administration of spinal anaesthesia till next 20 minutes and every 5 minutes thereafter till the completion of surgery or at least 45 minutes and every 30 minutes for rest of study period. Heart rate and any cardiac rhythm disorder was monitored continuously using lead II. Nausea and vomiting and other maternal undesired effects were noted.

The time from spinal anaesthesia to delivery of baby (SAB-Del) and from uterine incision to delivery of baby (UI-Del) were noted.

Hypotension was defined as a decrease in systolic arterial pressure > 20% of baseline values and it was treated by vasopressor. Total number of doses of vasopressor used was also noted.

Apgar score of the neonate for neurobehavioral assessment was noted at 1 and 5 minutes of delivery by attending paediatrician who was unaware of the vasopressor used.

STATISTICAL METHOD

Statistical analysis was done using Graph Pad InStat 3 software. Data were expressed as either mean and standard deviation or numbers and percentages. The means for the continuous variables were compared between the three groups using analysis of variance ANOVA. The $P < 0.05$ was considered statistically significant.

RESULT

All the 75 patients who were enrolled in the study completed the study protocol and included in the data analysis. No spinal analgesia failure was observed. Demographic data & maternal and neonatal characteristics were comparable among all three groups [Table 1].

TABLE 1 Demographic data & maternal and neonatal characteristics

Characteristics	Group P	Group E	Group M	P value
Age (years)	23.84±3.41	23.60±2.50	23.76 ±3.18	0.301
Weight (kg)	54.28±4.18	52.48±3.36	54.76±3.87	0.090
Height (cm)	151.88±2.91	151.56±2.53	151.20±2.47	0.662
Gestational age(wks)	37.64±0.637	37.56±0.583	37.56±0.650	0.872
Weight of neonate(kg)	2.864±0.222	2.86±0.250	2.80±0.232	0.663
SA to delivery(min)	8.12±1.092	8.24±2.026	8.84±1.772	0.272
UI to delivery(sec)	2.08±0.276	2.32±0.556	2.52±0.918	0.057
Block height at skin incision(dermatome)*	T4 (T4,T5)	T4 (T4,T5)	T4 (T4,T5)	

Baseline mean heart rate was statistically comparable in all three groups. Heart rate increased in all three groups during hypotension. On intergroup comparison, post drug administration, heart rate was significantly less in group P as compared to Group E and Group M till 25 min (P>0.05), after that it was not significant (P>0.05). No significant differences were observed between Group E and Group M (P>0.05) [Table 2].

Baseline mean systolic blood pressure was statistically comparable in all three groups. There was fall in systolic blood pressure in all the three groups during hypotension. On intergroup comparison, post drug administration, rise of systolic blood pressure at 2,4 and 6 min were significantly less in Group E and Group M as compared to Group P ($p<0.05$), after 6min it was not significant ($p>0.05$). No significant differences were observed between Group E and Group M ($p>0.05$) [Table 3].

Baseline mean diastolic blood pressure was statistically comparable in all three groups. There was fall in diastolic blood pressure in all the three groups during hypotension. On intergroup comparison, post drug administration, rise of diastolic blood pressure at 2min was significantly less in Group E and Group M as compared to Group P ($p<0.05$) after that it was not significant ($p>0.05$). No significant differences were observed between Group E and Group M ($p>0.05$) [Table 4].

Group P, 72% required single bolus dose while 28% required two bolus doses to maintain systolic blood pressure within 20% limit of basal value. In Group E 56% required single, 40% two and 4% three bolus doses, whereas In Group M 64% required single, 28% two, and 8% three doses to maintain systolic blood pressure within 20% limit of basal value [Table 5].

Apgar score at 1 minute was 6.16, 6.12 and 6.20 in group P, group E and group M respectively. Apgar score at 5 min was 8.04, 8.12 and 8.16 in group P, group E and group M respectively. No significant difference was observed between the three groups ($p>0.05$) [Table 6].

There were 12% cases of nausea and vomiting in group P, 16% cases of nausea and vomiting in group E and 12% cases of nausea and vomiting in group M. In group P 12% of patients developed bradycardia and no patient developed bradycardia in group E and group M [Table 7].

Table 2 Mean Heart Rate (per minute)

	Group P		Group E		Group M		P value		
	Mean	SD	Mean	SD	Mean	SD	P&E	P&M	E&M
Baseline	91.56	9.09	93.24	10.33	95.72	13.26	0.544	0.202	0.464
HP (VP given)	100.12	14.13	103.64	15.71	101.48	15.44	0.409	0.746	0.626
2 min after VP	68.76	11.64	93.36	15.27	90.80	16.04	0.000	0.000	0.566
4 min after VP	81.40	10.47	95.28	13.98	94.80	16.04	0.000	0.001	0.910
6 min after VP	83.40	9.82	96.20	13.97	95.32	15.27	0.000	0.001	0.832
8 min after VP	85.88	7.50	97.32	13.42	97.40	15.91	0.000	0.002	0.984
10 min after VP	88.92	10.21	99.04	14.29	99.04	14.67	0.005	0.006	1.00
12 min after VP	88.16	8.46	99.92	14.52	99.64	12.12	0.001	0.000	0.941
15 min after VP	87.08	7.78	100.4	14.04	97.32	14.15	0.000	0.002	0.443
20 min after VP	88.72	6.81	100.16	14.62	96.72	12.65	0.000	0.007	0.378
25 min after VP	90.04	5.60	98.12	11.76	95.16	12.01	0.003	0.043	0.284

HP- Hypotension, VP – Vasopressor agents

Table 3 Mean Systolic Blood Pressure (mmHg)

	Group P		Group E		Group M		P value		
	Mean	SD	Mean	SD	Mean	SD	P&E	P&M	E&M
Baseline	121.68	5.80	117.08	8.14	118.76	7.40	0.025	0.126	0.448
HP (VP given)	86.12	9.10	84.56	8.74	88.04	6.35	0.539	0.391	0.113

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2 min after VP	123.12	14.81	111.12	11.56	110.40	11.45	0.002	0.001	0.825
4 min after VP	120.24	9.55	110.96	11.82	112.64	10.65	0.003	0.010	0.599
6 min after VP	116.64	9.04	109.72	9.14	110.20	11.27	0.009	0.030	0.673
8 min after VP	113.32	8.72	108.56	10.27	110.32	9.78	0.083	0.257	0.537
10 min after VP	111.68	10.45	106.48	9.81	108.92	12.27	0.075	0.397	0.44
12 min after VP	109.84	10.14	104.76	8.84	105.40	13.98	0.065	0.204	0.847
15 min after VP	109.96	7.09	105.44	11.35	105.56	9.22	0.097	0.064	0.630
20 min after VP	109.76	5.33	106.92	9.13	105.68	9.93	0.185	0.076	0.647
25 min after VP	111.16	4.86	107.52	8.16	107.64	7.80	0.061	0.061	0.957
30 min after VP	113.72	5.15	110.96	6.61	111.16	6.51	0.106	0.129	0.914

HP- Hypotension, VP – Vasopressor agents

Table 4 Mean Diastolic Blood Pressure (mmHg)

	Group P		**Group E**		**Group M**		**P Value**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P&E**	**P&M**	**E&M**
Baseline	78.36	6.01	78.48	6.36	77.60	7.38	0.945	0.691	0.653
HP (VP given)	51.52	6.66	52.00	7.69	51.60	5.61	0.814	0.963	0.834
2 min after VP	76.08	10.71	69.56	10.41	69.48	11.84	0.033	0.044	0.979
4 min after VP	72.60	9.10	69.00	11.45	68.20	12.44	0.224	0.159	0.813
6 min after VP	70.04	8.26	66.32	9.77	66.48	8.45	0.152	0.138	0.950
8 min after VP	68.64	8.79	63.76	9.34	66.52	9.07	0.063	0.405	0.294
10 min after VP	66.36	9.66	62.36	7.59	64.28	10.73	0.110	0.474	0.468
12 min after VP	64.36	8.27	60.96	7.37	62.16	9.83	0.131	0.396	0.627
15 min after VP	64.64	8.30	60.44	7.43	62.76	7.16	0.065	0.395	0.266
20 min after VP	65.68	7.30	63.28	6.16	63.44	6.80	0.267	0.215	0.930
25 min after VP	67.68	7.44	65.88	7.64	64.96	5.27	0.402	0.142	0.622
30 min after VP	70.28	7.24	66.07	7.55	68.24	5.25	0.259	0.062	0.243

HP- Hypotension, VP – Vasopressor agents

Table 5 Number of bolus dose of vasopressor required in various groups

No of bolus	Group P	Group E	Group M
1	18 (72%)	14 (56%)	16 (64%)
2	7 (28%)	10 (40%)	7 (28%)
3	0	1 (4%)	2 (8%)

Table 6 Apgar score

APGAR score	Group P	Group E	Group M	P value
1min	6.16±0.850	6.12±0.725	6.20±0.707	0.933
5min	8.04±0.675	8.12±0.665	8.16±0.624	0.805

Table 7 Incidence of Side Effects

	Group P	Group E	Group M
Nausea & Vomiting	3 (12%)	4 (16%)	3(12%)
Shivering	4(16%)	3(12%)	3(12%)
Bradycardia	3(12%)	0	0

DISCUSSION

The demographic data, baseline parameters were comparable in both groups. The hemodynamic parameters at the development of hypotension were also comparable between the groups. Vasopressor was given at the onset of hypotension in all the three groups. Rise in systolic blood pressure and diastolic blood pressure was found in all the three groups.

On intergroup comparison, post drug administration, rise of systolic blood pressure at 2, 4 and 6 min & rise of diastolic blood pressure at 2min were significantly less in Group E and Group M as compared to Group P ($p<0.05$), after that it was not significant for the rest of the observation period ($p>0.05$). No significant differences were observed between Group E and Group M ($p>0.05$). Our results are comparable with the results of study done by Sahu D et al.6

Hypotension due to spinal anaesthesia is caused due to various factors. Mesenteric vasodilation along with partial caval compression leads to decreased venous return. The decreased cardiac output thus caused is further accentuated by the decreased in heart rate. Ephedrine and Mephentermine has predominant β-agonist activity and hence causes restoration of blood pressure mainly by increase in cardiac output and heart rate. Phenylephrine, on the other hand, has predominant **α**-agonist activity and restores the blood pressure by virtue of peripheral vasoconstriction and increase in venous return to the heart.

The restoration of systolic and diastolic blood pressure in all the three groups demonstrates that all the three drugs are equally effective in restoration of blood pressure. However, significantly high rise in systolic blood pressure for first 6 min in Phenylephrine group might suggest that mesenteric vasodilation is the predominant cause of hypotension due to spinal anaesthesia and inability of Ephedrine and Mephentermine to constrict the vessels.

The baseline mean heart rate was similar in all the three groups. There was rise in mean heart rate from the baseline at the onset of hypotension in all groups. On intergroup comparison, post drug administration, heart rate was significantly less in group P as compared to Group E and Group M till 25 min ($p>0.05$), after that it was not significant ($p>0.05$). No significant differences were observed between Group E and Group M ($p>0.05$). The significant decrease in mean heart rate in Phenylephrine group as compared to Ephedrine and Mephentermine groups in our study is comparable with the results of study done by Sahu D et al.6

The observations made above can be explained on the mechanism of the actions of Phenylephrine, Ephedrine and Mephentermine. Mephentermine and Ephedrine have predominantly β-agonist activity. Therefore, they are expected to cause increase in heart rate. On the other hand, phenylephrine, with predominant α-agonist action, causes a rise in the arterial blood pressure without any direct effect on the heart rate. This leads to activation of baroreceptor reflex and subsequent decrease in heart rate indirectly.

There were 12 % cases of bradycardia required atropine in Phenylephrine group as compared to no case of bradycardia in Ephedrine and Mephentermine. Our results are similar with the study done by Thomas DG et al.8 More than 50% of women given Phenylephrine in their study developed significant bradycardia.

Bradycardia could be caused by cardiac sympathetic denervation associated with high spinal block or a secondary baroreflex response to vasopressor induced hypertension. As Ephedrine and Mephentermine are associated with **β**-agonist activity, bradycardia may be masked by the tachycardia induced by Ephedrine. Phenylephrine, on the other hand, is devoid of any **β**-agonist activity and can be associated with bradycardia.

Apgar score at 1min and 5 minute did not show any difference between the groups ($p>0.05$). Apgar score was normal in all the

neonates in all three groups and there was no case of neonatal depression.

The incidence of nausea and vomiting and other effects was comparable between the two groups. The current study was limited in not being able to assess umbilical artery pH. However this limitation was tried to overcome with assessment of Apgar score of the neonates.

Conclusion

We conclude from the above study that all the three drugs maintained arterial blood pressure within 20% limit of baseline values on intravenous bolus administration without any undue effect on mother and fetus, although rise in BP within first 6 min after bolus dose was significantly higher in Phenylephrine group in comparison to Ephedrine and Mephentermine group. Correction of hypotension was better sustained in Phenylephrine group and it also causes reduction in heart rate, which may be advantageous in cardiac patients and patients in whom tachycardia is undesirable. Hence, it may be inferred that bolus Phenylephrine may be better alternative to Ephedrine and Mephentermine as a vasopressor agent for treatment of hypotension in women undergoing caesarean section under spinal anaesthesia.

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