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Original Research Paper

Anaesthesiology

A COMPARATIVE STUDY OF PHENYLEPHRINE, MEPHENTERMINE AND NOREPINEPHRINE IN THE TREATMENT OF HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION

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ABSTRACT

Background: Post-spinal hypotension is a common complication during caesarean sections under spinal anaesthesia, necessitating effective management protocols. Previous studies have explored various vasopressors, such as norepinephrine, phenylephrine, and mephentermine, to control this condition, but comparative effectiveness and safety remain under investigation. **Objective:** This study aims to compare the efficacy and safety of mephentermine, phenylephrine, and norepinephrine in managing hypotension during spinal anesthesia for caesarean sections. **Method:** A total of 114 patients undergoing elective caesarean sections were randomly assigned to three groups, Group P (phenylephrine 100 mcg IV), Group M (mephentermine 6 mg IV), and Group N (norepinephrine 6 mcg IV). Blood pressure, heart rate, and neonatal outcomes (APGAR scores) were monitored and recorded at various intervals. Each group consisted of 38 patients. The primary outcome was the maintenance of mean arterial blood pressure, while secondary outcomes included heart rate, number of bolus doses required, and APGAR scores of the newborns. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0. Observations were described in terms of proportions, and statistical analysis was performed using chi-square tests and Student's t-tests where applicable. A p-value of less than 0.05 was considered statistically significant. Age group distribution, mean age, and mean weight among the groups were compared using chi-square and ANOVA tests, respectively, with detailed results indicating no significant differences across groups in these parameters. **Results:** The norepinephrine group exhibited quicker blood pressure control compared to the other groups. The mean blood pressure was higher in the norepinephrine group, with significant differences observed in diastolic and systolic blood pressure across the study period. The phenylephrine group reported higher rates of bradycardia, while the mephentermine group showed higher incidences of tachycardia. APGAR scores were statistically similar across all groups, indicating no significant difference in neonatal outcomes. **Conclusion:** Norepinephrine demonstrated superior efficacy in blood pressure management with fewer incidences of bradycardia and comparable neonatal outcomes, making it a preferable choice over phenylephrine and mephentermine for treating post-spinal hypotension during caesarean sections.

KEYWORDS : Hypotension, spinal anesthesia, cesarean section, phenylephrine, mephentermine, norepinephrine, vasopressors, maternal outcomes, neonatal outcomes.

INTRODUCTION

In modern medicine, caesarean sections have become increasingly common worldwide. Although both regional and general anaesthesia are viable choices for this procedure, the use of general anaesthesia has notably decreased in recent years due to its higher risk of maternal mortality related to anaesthesia. As a result, spinal anaesthesia has become the preferred option for performing caesarean sections. [1] Regional anaesthesia, including spinal or epidural anaesthesia, reduces the risks associated with general anaesthesia. These risks involve the aspiration of gastric contents into the lungs, intubation challenges, maternal awareness during surgery, postoperative maternal gastric ileus, and fetal exposure to medications. [2] However, a common complication following a subarachnoid block is hypotension, defined as a drop in blood pressure exceeding 20% from the baseline mean arterial pressure. [3] Severe maternal hypotension can reduce blood flow to the uteroplacental unit, causing fetal bradycardia and acid-base imbalances. Prolonged hypotension may also result in neurological changes in the newborn. Although some believe that the duration of hypotension is as critical as its severity, with short episodes potentially having minimal effects, the associated risks highlight the need to prevent or quickly manage hypotension. In mothers, hypotension can decrease cerebral blood flow, leading to symptoms like dizziness, nausea, and vomiting. [4]

Phenylephrine is a potent alpha-1 agonist with minimal beta activity, leading to a rapid increase in blood pressure and systemic vascular resistance. It has strong synthetic α-adrenergic activity with low affinity for β-adrenergic receptors. Mephentermine, a sympathomimetic amine, acts both directly and indirectly on α- and β-adrenergic receptors. It has mixed α and β receptor agonist activity, stimulating the release of norepinephrine and adrenaline. This results in increased blood pressure through peripheral venoconstriction and enhanced cardiac output.

Norepinephrine, like phenylephrine, is a potent α-adrenergic agonist, but it also has mild β-adrenergic agonist activity.

METHODOLOGY

The present prospective randomised controlled study was conducted in the Dept. of Anaesthesia, Santosh medical college and hospital, Ghaziabad, U.P over the period of one year from January 2023 to December 2023.

Clearance was taken from the ethical committee of the institute. Among women undergoing LSCS who attended obstetrics 114 women were selected based on inclusion and exclusion criteria.

INCLUSION CRITERIA

Consenting women between the ages of 18 and 40 years undergoing emergency or elective cesarean section and belonging to American Society of Anesthesiologists Class I & II.

EXCLUSION CRITERIA

- Patients suffering from pregnancy induced hypertension.
- Patients belonging to ASA class 3 and 4.
- Patients with contraindications to either phenylephrine, norepinephrine or mephentermine.

A thorough pre anaesthetic checkup was done for all the patients. The patient's detailed clinical history including past and present history, assessment of vitals, general, systemic,

and local examination including vertebral and cervical spine was done On arrival of the patients in operation theatre, IV line was initiated with 18-G cannula; all patients received 20 ml/kg of Ringer's lactate solution intravascular loading before spinal anaesthesia. After preloading, heart rate (HR), non-invasive blood pressure, respiratory rate, and peripheral oxygen saturation (SpO_2) were monitored for the duration of study. Baseline systolic and diastolic blood pressure along with heart rate was obtained.

The three drugs under study for treatment of anticipated hypotension during caesarean delivery were prepared by adding 0.9% NaCl solution to make each dose of equal volume and the concentration of mephentermine 6 mg/ml, phenylephrine 100 mcg/ml, norepinephrine 6mcg/ml.

- Group 1- Patients receiving phenylephrine 100 mcg IV bolus
- Group 2- Patient receiving mephentermine 6 mg IV bolus
- Group 3- Patients receiving norepinephrine 6mcg IV bolus

Spinal anaesthesia was administered using the midline approach and maintaining standard aseptic precautions using a 25 Gauge spinal needle. Bupivacaine 12.5 mg (2.5 mL of 0.5% bupivacaine with dextrose 8% solution) was used at a rate of approximately 0.2 mL/sec for spinal anaesthesia.

The following parameters were monitored during the study period:

- Mean blood pressure every 2 minutes after administration of spinal anaesthesia for next 20 minutes; thereafter every 5 minutes till the completion of caesarean section or at least 45 minutes and subsequently every 30 minutes for rest of the study period.
- heart rate

Hypotension during the study period was treated with repeated one unit (one ml) solution of the drug which was unknown to the interventionist.

Statistical Analysis

It was done by using Statistical Package for Social Sciences (SPSS) version 21.0. The observations were described in terms of proportions. Data was compiled and statistically analyzed using chi square test, students T test where applicable and $p<0.05$ was considered statistically significant.

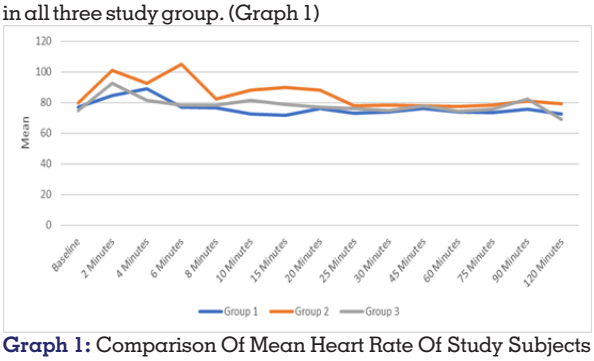
OBSERVATIONS AND RESULTS

Table 1: Comparison Of Mean Heart Rate Of Study Subjects At Different Time Interval Among The Groups

Time Interval	Group 1		Group 2		Group 3		F value	p value
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation		
Baseline	77.11	8.88	79.66	8.37	74.71	8.95	3.046	.052
2 Minutes	84.50	23.78	100.82	31.87	92.74	25.69	3.386	.037*
4 Minutes	89.16	27.81	92.53	25.64	81.47	23.88	1.828	.165
6 Minutes	76.95	19.94	104.97	20.12	78.45	11.20	30.543	.000*
8 Minutes	76.74	11.03	82.42	19.71	78.53	16.47	1.232	.296
10 Minutes	72.71	11.83	87.89	17.27	81.63	16.14	9.497	.000*
15 Minutes	71.82	12.74	89.97	17.41	78.66	14.95	13.915	.000*
20 Minutes	76.29	10.12	88.03	20.19	77.00	14.99	6.720	.002*
25 Minutes	73.11	10.75	77.68	14.39	76.26	9.83	1.493	.229
30 Minutes	73.66	9.67	78.29	12.78	74.89	12.13	1.622	.202
45 Minutes	75.97	10.26	77.66	12.16	77.89	16.30	.241	.786
60 Minutes	73.95	10.45	77.61	12.75	74.34	12.42	1.078	.344
75 Minutes	73.54	10.64	78.19	12.64	75.48	11.03	1.266	.287
90 Minutes	75.67	8.22	80.89	15.87	82.50	11.02	1.516	.233
120 Minutes	72.60	5.04	79.40	17.29	69.20	5.93	1.492	.253

(*Significant if $P<0.05$)

Table 1 shows comparison of mean heart rate of study subjects at different time interval among the groups results revealed that mean heart rate was statistically non significant (P=0.52) at baseline in all three study group.Mean heart rate was statistically significant (P=.037) after 2 minutes in all three study group, mean heart rate was statistically non significant (P=0.165) after 4 minutes in all three study group, mean heart rate was statistically significant (P=0.000) after 6 minutes in all three study group, mean heart rate was statistically non significant (P=0.296) after 8 minutes in all three study group, mean heart rate was statistically significant (P=0.000) after 10 minutes in all three study group, mean heart rate was statistically significant (P=0.000) after 15 minutes in all three study group, mean heart rate was statistically significant (P=0.002) after 20 minutes in all three study group, mean heart rate was statistically not significant (P=0.229) after 25 minutes in all three study group, mean heart rate was statistically not significant (P=0.202) after 30 minutes in all three study group, mean heart rate was statistically not significant (P=0.786) after 45 minutes in all three study group, mean heart rate was statistically not significant (P=0.344) after 60 minutes in all three study group, mean heart rate was statistically not significant (P=0.287) after 75 minutes in all three study group, mean heart rate was statistically not significant (P=0.233) after 90 minutes in all three study group and mean heart rate was statistically not significant (P=0.253) after 1204 minutes in all three study group. (Graph 1)



Graph 1: Comparison Of Mean Heart Rate Of Study Subjects At Different Time Interval Among The Groups

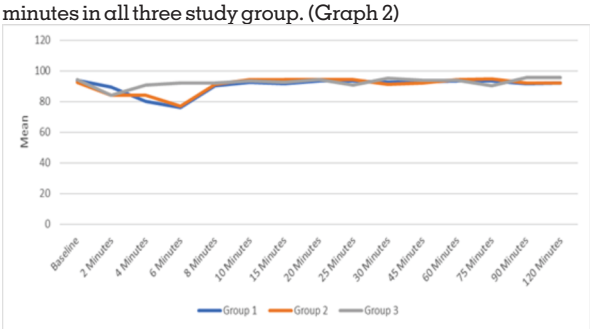
Table 2: Comparison Of Mean Average Blood Pressure Of Study Subjects At Different Time Interval Among The Groups

Time Interval	Group 1		Group 2		Group 3		F value	p value
	Mean	SD	Mean	SD	Mean	SD		
Baseline	93.92	6.05	92.46	6.46	94.39	5.29	1.076	.345
2 Minutes	89.52	11.25	84.16	14.47	83.96	13.49	2.191	.117
4 Minutes	80.31	15.37	83.98	14.68	90.61	11.00	5.432	.006*
6 Minutes	76.21	14.66	76.81	14.64	91.90	6.64	19.052	.000*
8 Minutes	90.09	12.47	91.12	12.59	92.22	6.96	.358	.700
10 Minutes	92.72	9.05	94.17	5.29	93.41	7.73	.352	.704
15 Minutes	91.75	7.45	94.21	5.47	92.39	7.65	1.286	.281
20 Minutes	93.30	4.34	94.27	6.26	94.40	6.38	.421	.657
25 Minutes	93.25	7.60	94.18	5.14	90.90	5.39	2.863	.061

30 Minutes	92.37	5.73	91.09	6.57	95.33	5.99	4.837	.010*
45 Minutes	92.99	5.57	92.27	4.80	93.71	6.63	.601	.550
60 Minutes	93.38	6.04	94.46	6.50	93.75	5.89	.301	.740
75 Minutes	93.20	6.38	94.95	5.24	90.31	6.47	4.021	.021*
90 Minutes	91.50	5.33	92.00	8.41	95.81	4.11	2.098	.137
120 Minutes	92.00	4.00	92.20	6.12	95.53	2.50	1.205	.324

(*Significant if P<0.05)

Table 2 shows comparison of mean average blood pressure of study subjects at different time interval among the groups results revealed that mean average blood pressure was statistically non significant (P=0.345) at baseline in all three study group, mean average blood pressure was statistically non significant (P=.117) after 2 minutes in all three study group, mean average blood pressure was statistically significant (P=0.006) after 4 minutes in all three study group, mean average blood pressure was statistically significant (P=0.000) after 6 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.700) after 8 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.704) after 10 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.281) after 15 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.657) after 20 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.061) after 25 minutes in all three study group, mean average blood pressure was statistically significant (P=0.010) after 30 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.550) after 45 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.740) after 60 minutes in all three study group, mean average blood pressure was statistically significant (P=0.021) after 75 minutes in all three study group, mean average blood pressure was statistically non significant (P=0.137) after 90 minutes in all three study group and mean average blood pressure was statistically non significant (P=0.324) after 120 minutes in all three study group. (Graph 2)



Graph 2: Comparison Of Mean Average Blood Pressure Of Study Subjects At Different Time Interval Among The Groups

DISCUSSION

Within the surgical community, regional blocks such as spinal, epidural, and combined spinal/epidural blocks have become increasingly popular. Despite their effectiveness at lower medication dosages, subarachnoid blocks have drawbacks, including hypotension, less control over the level of blockade, and a shorter duration of anaesthesia. [5] Due to anaesthetic blocking up to the T4 level, 80% of parturients undergoing caesarean sections (CS) experience spinal anaesthesia-induced hypotension (SAIH). Both mother and child can suffer from severe and prolonged SAIH. One of the most significant challenges in obstetric anaesthesia is selecting the optimal management plan for SAIH during CS. Various methods and vasopressors have been tested, but no single approach has proven consistently effective or superior. [6]

The present study demonstrated that all three groups i.e., phenylephrine, mephentermine, and norepinephrine were able to successfully maintain blood pressure in patients after caesarean section patients experienced hypotension brought on by spinal anesthetic. Throughout the study period, a statistically significant increase in both the diastolic and systolic blood pressure was observed following the administration of vasopressors. The nor-epinephrine group had a higher mean blood pressure, even though fluctuations in SBP and DBP were similar between the groups at different points of time. Moreover, single bolus dosage of norepinephrine was found to be more successful at regulating blood pressure in maximal study participants followed by single bolus dosage of mephentermine, however there was not any significant difference in phenylephirine and mephentermine group.

In the current investigation, six to eight minutes following an IV bolus, the mean blood pressure in the nor-epinephrine group was greater than in the other two groups. The difference was statistically significant at both 4 and 6 minutes, with p=0.006 at 4 minutes and 0.00 at 6 minutes. Similar research comparing mephentermine and phenylephrine for maintaining arterial blood pressure under spinal anaesthesia during caesarean delivery was conducted by Ganeshanavar A et al. Mephentermine group showed a substantially lower rise in diastolic blood pressure (p<0.05) than Phenylephrine group at 2, 4, and 6 minutes post-study medications, according to an intergroup comparison. For the first six minutes, the phenylephrine group's increase of systolic arterial pressure was also noticeably higher than that of the other two groups. After then, the distinctions became less. However, in our study, phenylephrine reported higher elevation of mean blood pressure (MBP) from baseline to 2 minutes, later at 4 minutes, better control with mephentermine and further at 6 to 8 minutes almost same values for mephentermine and phenylephrine group. Later analysis, from 10 to 25 minutes, reported MBP elevation with mephentermine as comparative to phenylephrine as well as to norepinephrine. Hence, the present study did not find any significant difference between the groups during the intraoperative period and even towards the end of the surgery, difference was narrowed off for mephentermine and phenylephrine group reporting similar MBP maintenance throughout surgery.

Another study reporting contrary results to our study was study carried by Bhattarai B et al who compared Phenylephrine 25 microgram and Mephentermine 6mg and reported that drugs maintained hemodynamics within 20 percent of the baseline values on intravenous administration. However, significantly the phenylephrine group saw a greater rise in blood pressure within the first six minutes following the bolus, which was contrary to our study as our study as from 4 to 6 minutes, our studied higher elevation with in mean blood pressure with Mephentermine 6mg than Phenylephrine 100 microgram. Moreover, Sahu D et al, Devender D et al reported that Phenylephrine group was significantly high for first 6 min of bolus dose as compared to Mephentermine groups. In our study, the mean blood pressure was higher in group 2 (mephentermine) at 10 to 25 minutes with assessment at every 5 minutes. The mean blood pressure at 20 minutes, 45 minutes and 60 minutes mean blood pressure was comparative in all the three groups with statically insignificant difference (p>0.05). In the present study, blood pressure was controlled with 1 IV bolus dose among 73.7 % subjects in group 1 (phenylephrine), 81.6% subjects in group 2 (mephentermine)

and 89.5% of group 3 (norepinephrine) and remaining of subjects required second dose of IV bolus.

We could find most of the studies comparing phenylephrine, mephentermine, ephedrine, but we could not find any study comparing phenylephrine, mephentermine and norepinephrine. *Hence, as far as we know, this is the first study that compares patients receiving IV bolus of phenylephrine 100 mcg, mephentermine 6 mg and norepinephrine 6mcg.* Amongst the vasopressors ephedrine (and agonist) has a long history of use and has been considered to be the 'gold standard' for prophylaxis and treatment of hypotension due to spinal anaesthesia in patients undergoing caesarean section. [7] There have been recent publications showing the superiority of other treatments and increasing fetal acidity with ephedrine usage. [8] Because phenylephrine can occasionally be linked to maternal cardiac depression, its usage in women with cardiac comorbidities is restricted. [9]

Another vasopressor that was only used in obstetric anaesthesia is norepinephrine. Norepinephrine is a vasopressor with little cardiac depressant effect because of its -adrenergic agonistic activity and weak -adrenergic agonistic activity. These pharmacologic characteristics would make norepinephrine an acceptable replacement for phenylephrine and ephedrine in obstetric anaesthesia. [10] Norepinephrine was recently introduced by Ngan Kee et al (2015) in obstetric anaesthesia through the use of a computer-controlled infusion system. In addition to protocol efficiency, finding a straightforward, workable method for preventing postspinal hypotension during cesarean delivery would be of utmost importance because these days, almost all hospitals undertake cesarean deliveries on a daily basis. Later, norepinephrine infusions that varied between 1.25 g/min and 5 g/min were manually regulated by Ngan Kee et al. (2018). The latter study was constrained, though, because the control group did not receive any vasopressors, hence, more recently, Ngan Kee et al (2020) carried out a second experiment using phenylephrine as the control group and found that norepinephrine was not inferior to phenylephrine for neonatal outcome measured by umbilical arterial pH. This showed excellent evidence in favor of norepinephrine's safety for fetuses during obstetric anaesthesia.

CONCLUSION

The group that received norepinephrine experienced blood pressure control more quickly than the other two groups, whereas the groups that received phenylephirine and mephentermine reported comparable blood pressure control. The nor-epinephrine group had a higher elevation mean blood pressure, even though fluctuations in SBP and DBP were similar between the groups at different points of time.

Neonatal APGAR score were similar among various groups in their study.

Thus, the present study concludes that all three groups i.e., phenylephrine, mephentermine, and norepinephrine were able to successfully maintain blood pressure in patients after caesarean section patients experienced hypotension brought on by spinal anesthetic. Throughout the study period, a statistically significant increase in both the diastolic and systolic blood pressure was observed following the administration of vasopressors. The nor-epinephrine group had a higher mean blood pressure, even though fluctuations in SBP and DBP were similar between the groups at different points of time. Moreover, single bolus dosage of norepinephrine was found to be more successful at regulating blood pressure in maximal study participants followed by single bolus dosage of mephentermine, however there was not any significant difference in phenylephirine and mephentermine group. Hence, the results revealed administration of nor-epinephrine to be superior as comparative to phenylephirine and mephentermine group.

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Ethical Approval: *The study was approved by the Institutional Ethics Committee*

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