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Comparison of infusions of phenylephrine, norepinephrine, and mephentermine on maternal hemodynamics and neonatal outcomes in caesarean section under spinal anaesthesia

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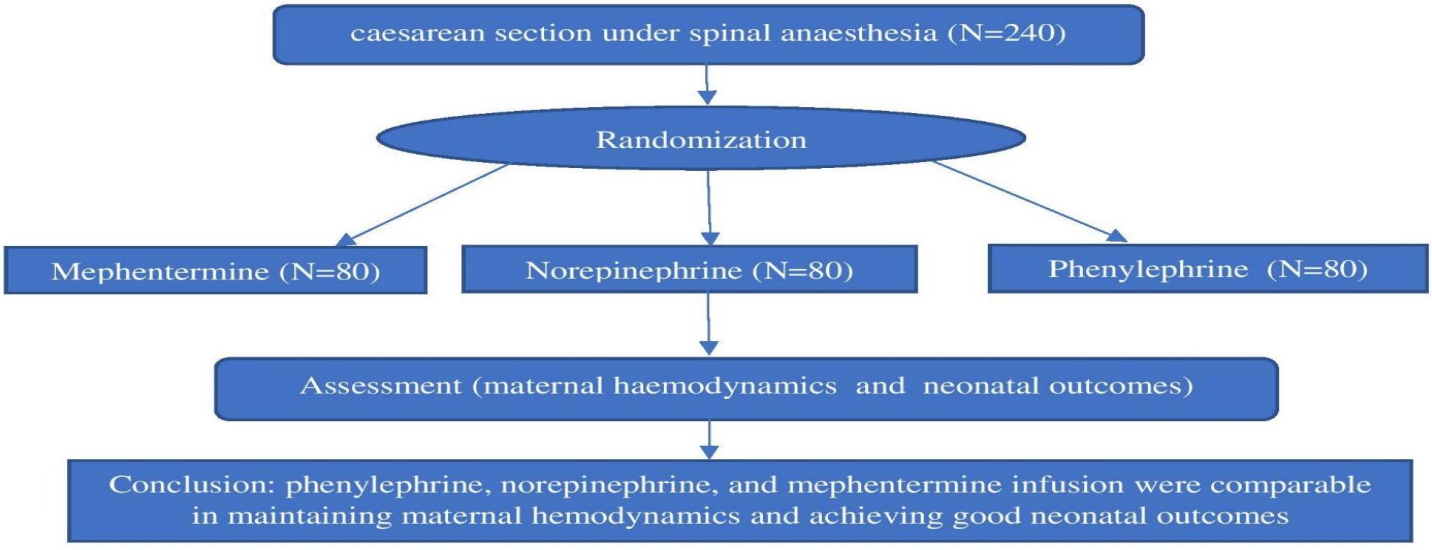
ABSTRACT

Although the subarachnoid block is the preferred anesthetic technique for the caesarean section, on the downside it is often associated with complications like maternal hypotension. We compared phenylephrine, norepinephrine, and mephentermine infusions to maintain blood pressure during the caesarian section under subarachnoid block. Our study included 240 parturients with singleton-term pregnancies undergoing a caesarian section under spinal anesthesia. Following spinal anesthesia till the delivery of the baby, parturients randomly assigned to three groups received phenylephrine, norepinephrine, and mephentermine infusions.



Heart rate, blood pressure, intra-operative nausea and vomiting, neonatal Apgar score, and total rescue vasopressors required were analyzed. Except at 4 min (p=0.006), ANOVA revealed no statistically significant difference in systolic blood pressure between the groups across all time points. Systolic blood pressure showed a significant difference between the mephentermine group versus the phenylephrine group (p=0.013) and the norepinephrine group versus the phenylephrine group (p=0.022) at four minutes post hoc Bonferroni. Except at 15 and 60 minutes (p=0.02 and p=0.001,

respectively), the mean heart rate was comparable among the three groups. The Chi-square test revealed no statistically significant difference in the requirement of rescue drugs among the groups ($\chi 2=1.57$, p=0.45) except at the time point of 4 minutes (p=0.01) when the highest requirement was observed in the phenylephrine group. The Apgar scores amongst the groups were comparable at 1 min (p=0.99) and 5 min (p=0.98). In the lower segment caesarian section under the subarachnoid block, infusions of phenylephrine, norepinephrine, and mephentermine were equally effective in managing maternal hypotension and achieving favorable neonatal outcomes.

Keywords: Phenylephrine, Norepinephrine, Mephentermine, LSCS, Hypotension APGAR Score.

INTRODUCTION

In elective caesarean sections, subarachnoid block (SAB) is the preferred anesthetic technique. However, it does result in hypotension in the vast majority of parturients. The prevalence of hypotension in pregnant mothers can reach up to 70%–80% when pharmacologic prophylaxis is not employed [1]. Untreated maternal hypotension can lead to placental insufficiency with fetal hypoxia and acidosis, thereby resulting in adverse neonatal outcomes [2].

Crystalloid co-loading or preloading and various pharmacological measures have been adopted and investigated to prevent maternal hypotension, but none of them have been proven to be adequate [3-4]. Currently, the vasopressor suggested for preventing and treating spinal anesthesia-induced hypotension (SAIH) in parturients undergoing caesarean delivery under SAB is phenylephrine (PE), a strong alpha-adrenergic receptor agonist. However, PE, by decelerating maternal heart rate (HR) can reduce cardiac output (CO), which may result in negative feto-maternal effects [5]. That calls for exploring other vasopressors with less apparent negative chronotropic effects. Contrary to phenylephrine, norepinephrine exhibits robust alpha-adrenergic receptor action and mild beta-agonist activity, thereby causing a lesser degree of bradycardia with a minimal decrease in CO [1, 6, and 7]. Mephentermine acts by indirectly stimulating beta-adrenergic receptors, causing the release of norepinephrine from its stores and it has a positive inotropic action too. For SAIH, Mephentermine has proved to be just as secure and effective as ephedrine [8].

Various studies have used bolus or infusion of phenylephrine, norepinephrine, ephedrine, and mephentermine either alone or in various combinations. As of now, there are lack of studies comparing phenylephrine, norepinephrine, and mephentermine to determine the most appropriate vasopressor for preventing SAIH with minimal deleterious effects on the mother as well as the neonate. So, this study aimed to compare and evaluate the safety and effectiveness of infusions of phenylephrine, norepinephrine, and mephentermine to prevent SAIH during elective caesarian sections.

MATERIALS AND METHODS

Ethical Statement

This prospective randomized trial was carried out at Kalinga Institute of Medical Sciences, Bhubaneswar, India, a tertiary care institution from September 2021 to August 2022 with approval from the institutional ethical committee (KIIT/KIMS/IEC/410/2020). It was registered with the Clinical Trials Registry of India (CTRI/2020/12/030039).

Study Design and Eligibility Criteria

After obtaining written informed consent, 240 parturients of the American Society of Anesthesiologists (ASA) physical status II, aged between 21 and 40 years, with singleton term pregnancy, undergoing elective caesarean section under spinal anesthesia were enrolled. Exclusion criteria were preexisting pregnancy-induced hypertension, cardiovascular disease, hepato-renal disease, gestational diabetes mellitus requiring insulin therapy, diagnosed abnormal placentation, intraoperative use of uterotonic other than oxytocin, known fetal abnormality, any contraindication to subarachnoid block and known allergy to test drugs.

Randomization, Blinding, and Drugs

The parturients were assigned at random into either of three groups of 80 each using computer-generated randomization codes obtained from sealed, sequentially numbered envelopes. [Figure 1]. Group P received phenylephrine (50 µg/mL) at 0.1 µg/kg/min, Group N received norepinephrine (1mg/ml) at 0.05 µg/kg/min and Group M received mephentermine (30mg/ml) at 3 mg/min in intravenous infusion. All the medication solutions were made in 50 mL syringes by a resident anaesthesiologist not participating in the study, labeled with a trial number, and infused via an exclusive intravenous cannula targeting non-invasive blood pressure (NIBP) at 100% of baseline systolic blood pressure (SBP). The study drugs used were concealed from the anesthesiologist managing the case.

Anesthetic Management and Outcome Measures

Nil per oral status and antacid premedication was ensured as per standardized protocol in compliance with institutional norms. Before shifting to the operating room, an IV line was established, and Ringer's lactate infusion was started. Pulse oximetry, non-invasive blood pressure monitoring, and electrocardiography (ECG) were recorded as part of routine monitoring, and the baseline values of the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate (HR) were noted before administration of SAB.

Dural puncture was done at the L3-L4 interspace using a conventional midline approach with a 25-G Quincke spinal needle under strict aseptic conditions. To achieve a block up to T6 level, 2 ml of 0.5% bupivacaine heavy with 25 µg of fentanyl was injected intrathecally.

Infusion of the study drug solution was started soon after the administration of SAB using a syringe pump. Patients were made supine, and a wedge was placed under the right buttock. SBP, DBP, MAP, and HR were measured every 2 minutes to 10 minutes and then every 5 minutes till the completion of surgery.

In the event of a fall in SBP more than 20% from baseline, it was managed with a rescue bolus of intravenous ephedrine 6 mg or phenylephrine 10 mcg and repeated after 2 minutes in case of lack of response. SBP of 80% or lower than the baseline, or an absolute value of less than 100 mm Hg, was considered hypotension [9]. Bradycardia (defined as HR less than 50/min) was treated with intravenous atropine 0.01 mg/kg [10]. Intravenous ondansetron 4 mg was used to treat episodes of intraoperative nausea and vomiting (IONV). The infusion of the study drug was stopped, and oxytocin (10 IU) was slowly infused after baby delivery. At one- and five-minutes following baby delivery, the attending pediatrician, who was unaware of the study drug, recorded the neonatal Apgar score [11].

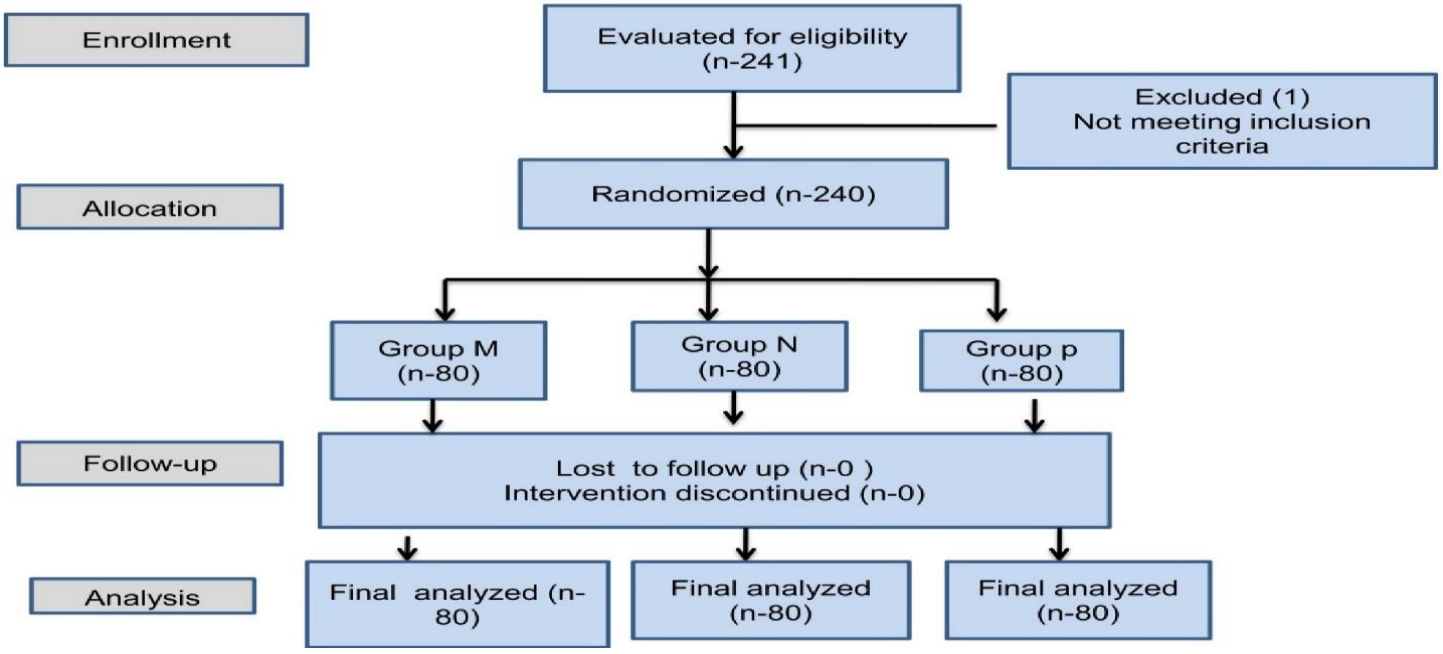
Statistical Analysis

The statistical analysis was carried out using IBM SPSS Statistics software version 26.0 (IBM Corp., Armonk, NY). The mean and standard deviation for quantitative data, and frequency and proportions for qualitative variables, were used to produce descriptive statistics for the explanatory and outcome variables. The ANOVA test was employed to compare the quantitative data (age, spinal injection to delivery time, SBP, DBP, MAP, HR, and APGAR score) between all three groups with the post hoc Bonferroni test for inter-group comparison. Inferential statistics such as the Chi-square test were performed for qualitative variables. P-values less than 0.05 were considered significant.

Sample Size Calculation

Based on the trial by Mohta et al. [12], considering the effect size as 0.45 between phenylephrine and norepinephrine groups, with a 5% level of significance, 90% power and 95% confidence interval the minimum required sample size was 78 in each group. Hence each group comprised 80 patients, yielding a total sample size of 240 (Figure 2).

Figure 1: CONSORT flow diagram



Group M: Mephentermine, Group N: Norepinephrine, Group P: Phenylephrine.

RESULTS

Baseline Characteristics: Concerning demographics and surgical time considerations, all the groups were matched (Table 1).

Table 1: Patient and anesthesia characteristics

Parameters	Phenylephrine (n=80)	Norepinephrine (n=80)	Mephentermine (n=80)	P value
Age (years)	29.35 (4.37)	29.35 (4.37)	29.35 (4.37)	0.188
Body mass index (BMI)	24.25 (3.37)	24.39 (2.66)	24.75 (3.74)	0.806
Spinal injection to delivery time (min)	10.85 (2.42)	11.03 (2.39)	10.36 (1.37)	0.125

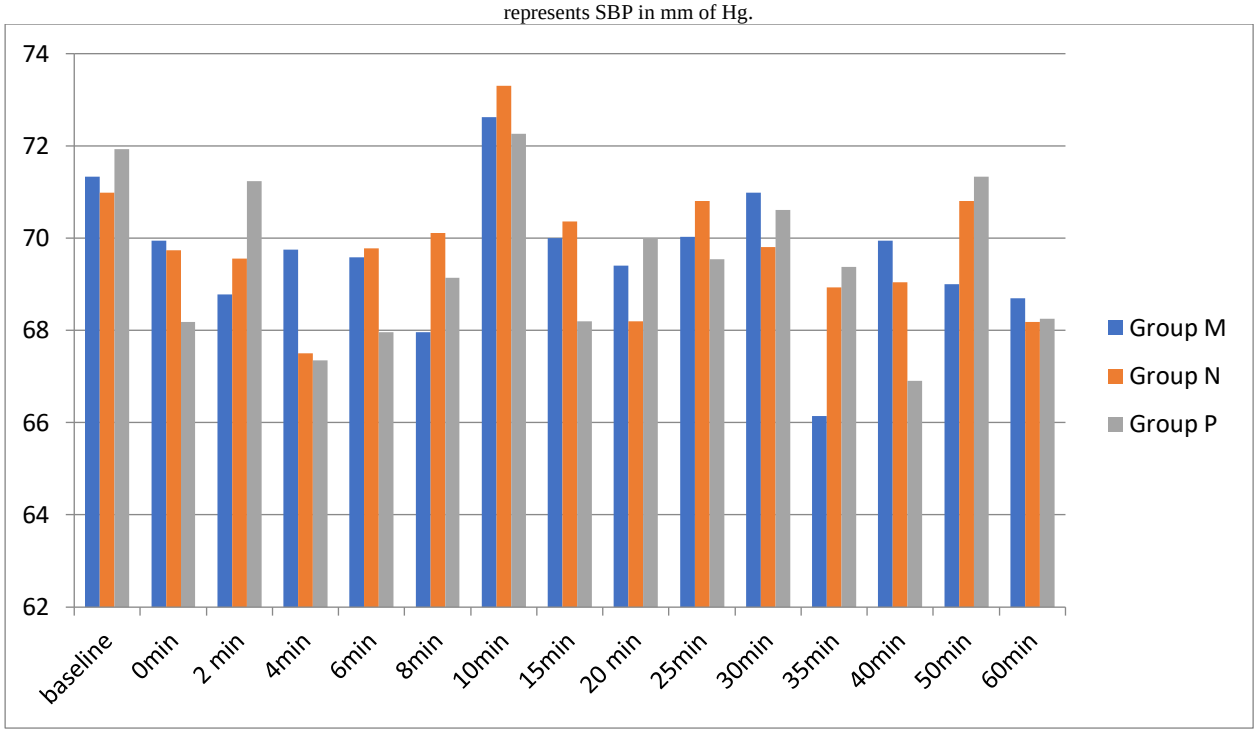
Data represented as mean (standard deviation) and patient numbers. BMI, Body Mass Index.

Systolic Blood Pressure

All the groups showed fluctuations in SBP at different time intervals without any constant rise or decline except at 4 min. With a single instance of 4 minutes (p=0.006), the ANOVA test revealed no statistically significant difference between the groups across all the time intervals (Figure 3). A statistically significant difference was seen between group M v/s group P (p=0.013) and group N v/s P (0.022) at

4 mins.

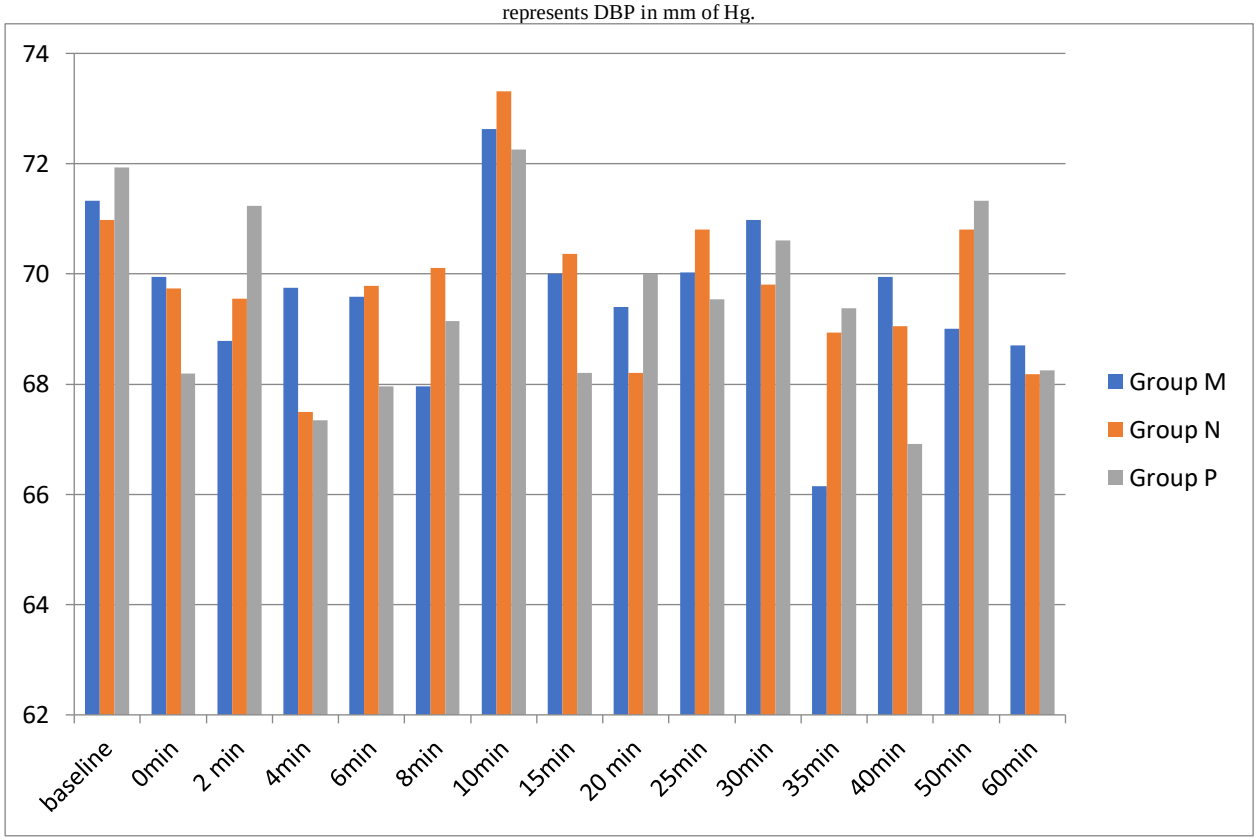
Figure 2: Comparison of mean systolic blood pressure (SBP) among the groups. The X-axis represents the time interval following spinal anaesthesia and the Y-axis represents SBP in mm of Hg.



Diastolic Blood Pressure

At 10 minutes, all groups had an abrupt increase in DBP. The ANOVA test results showed no statistically significant difference among the groups concerning DBP at all the time intervals (Figure 4). The post hoc Bonferroni test used to compare DBP between groups revealed no statistically significant variance.

Figure 3: Comparison of mean diastolic blood pressure (DBP) among the groups. The X-axis represents the time interval following spinal anaesthesia and the Y-axis represents DBP in mm of Hg.

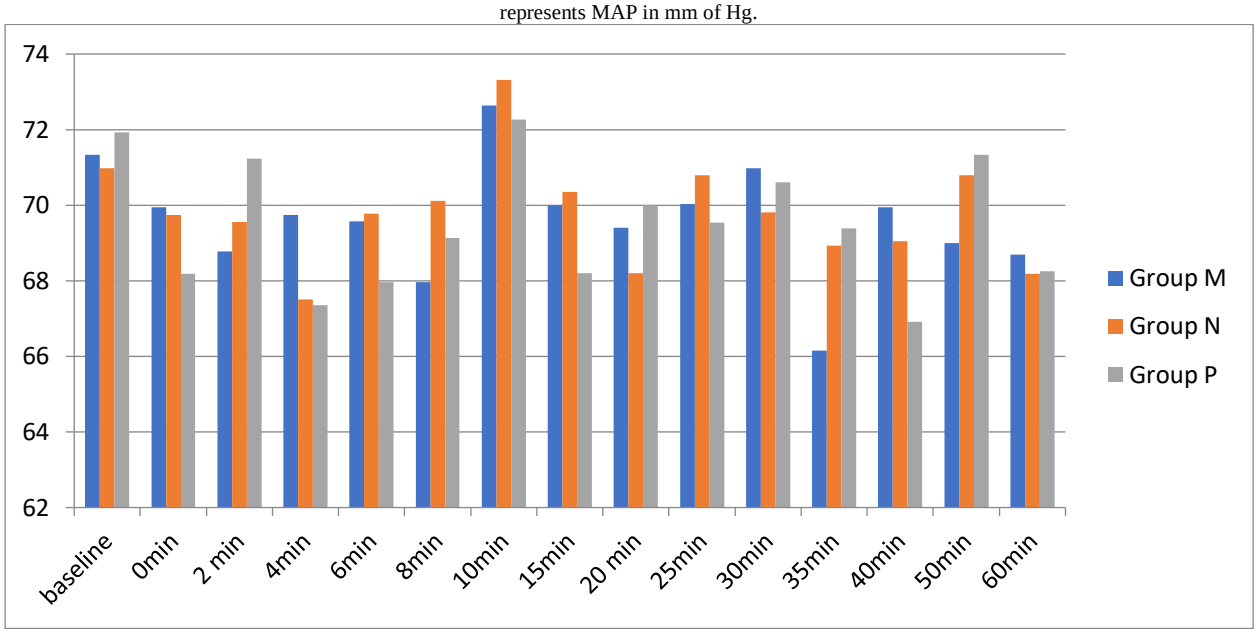


Mean Arterial Pressure

A sudden rise in MAP was seen at 10 min in all the groups without any statistical significance amongst them either on ANOVA

or post hoc Bonferroni test (Figure 5).

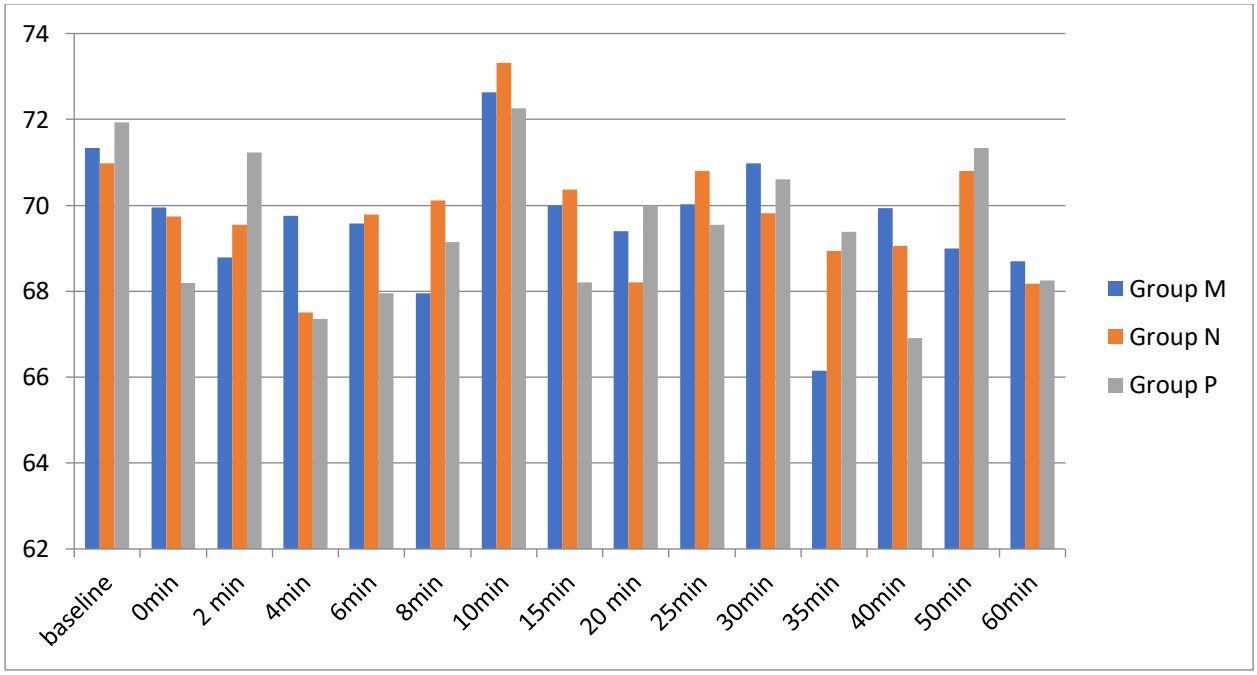
Figure 4: Comparison of mean arterial pressure (MAP) among the groups. The X-axis represents the time interval following spinal anaesthesia and the Y-axis represents MAP in mm of Hg.



Heart Rate

All the groups showed fluctuations in HR at different time intervals without any constant rise or decline. At 60 min, Group M showed the highest rise in heart rate whereas Group N and P revealed a decline in heart rate at 60 min. Except for 15 and 60 minutes (p=0.02 and p=0.001, respectively), the ANOVA test did not reveal any statistically significant differences between the groups (Figure 6). Statistically, there was a difference in the mean heart rate between Group M and Group P at 15 min (p= 0.017) and between Group M and N (p=0.001) as well as Group M and P (p=0.005) at 60 min.

Figure 5: Comparison of mean heart rate (HR) among the groups. The X-axis represents the time interval following spinal anaesthesia and the Y-axis represents heart rate.



Requirement of Rescue Drugs

Out of 240 parturients 12 (5%) patients required rescue drugs, out of which 6 (7.5%) patients were in group P, and 3 (3.8%) patients each were in groups M and N. The Chi-square test revealed no statistically significant association of rescue drugs with the groups ($\chi 2$=1.57, p=0.45) (Table 2). At 0 and 2 min, rescue drug was given to 2 patients, which increased to 4 patients at 4 min. At 6 and 8 mins, the rescue drug was given to 4 patients in group P. Similarly, at 15 and 30 min, the rescue drug was given to 1 patient in group N. The Chi-square test showed a statistically significant association of rescue drugs with

the groups at 4-minute time intervals (p=0.01) with the highest need in group P.

Table 2: Distribution of the subjects based on the rescue drug requirement.

Rescue analgesia required		Group			Total
		M	N	P	
No	Count	77	77	74	228
	%	96.2%	96.2%	92.5%	95.0%
Yes	Count	3	3	6	12
	%	3.8%	3.8%	7.5%	5.0%
Total	Count	80	80	80	240
	%	100.0%	100.0%	100.0%	100.0%
Chi-square value- 1.57					
p-value- 0.45					

Data are presented as number or percentage, Group M: Mephentermine, Group N: Norepinephrine, Group P: Phenylephrine.

Incidence of Hypotension

Hypotension was seen in 4 patients at 4 min, out of which 3(1.2%) belonged to Group P and 1 patient (1.2%) to Group M [Table 3]. At 8 min, 3 patients showed hypotension. Nausea/Vomiting was seen in 1 patient at 4 min (Group M), 10 min (Group N), 20 min (Group M), and 25 min (Group N) (Table 3). Hypertension was seen in 1 patient at 8, 10, and 15 min in Group N. The Chi-square test showed no statistically significant association of hypotension, hypertension, and nausea/vomiting with the groups at all the time intervals (p>0.05).

Table 3: Comparison between studied groups as regards maternal complications

complications	Group M (n=80)		Group N (n=79)		Group P (n=80)		P-Value
	N	%	N	%	N	%	
Hypotension	1	0.444	0	0	3	1.3	0.36
Nausea/Vomiting	1	0.4	0	0	0	0	0.366
Hypertension	0	0	1	0.4	0	0	0.366

Data are presented as number or percentage, Group M: Mephentermine, Group N: Norepinephrine, Group P: Phenylephrine.

APGAR score

The mean APGAR score at 1 min was slightly higher in Group P- 7.70 ± 0.644, followed by Group M and N. Similarly, the mean APGAR score at 5 min was slightly higher in Group P-8.70 ± 0.644. According to the ANOVA test, no statistically significant difference between the groups was found at 1 min (p=0.99) or 5 min (p=0.98). (Table 4). The post hoc Bonferroni test found no statistical significance when evaluating intergroup APGAR scores at 1 and 5 minutes.

Table 4: Comparison of the mean Apgar score among the groups using ANOVA.

Time intervals	Groups	Minimum	Maximum	Mean	S.D.	p-value
APGAR Score at 1 min	Group M	7	9	7.69	.608	0.99
	Group N	7	10	7.69	.667	
	Group P	7	9	7.70	.644	
APGAR Score at 5 min	Group M	8	10	8.69	.608	0.98
	Group N	8	10	8.69	.628	
	Group P	8	10	8.70	.644	

Data represented as mean (standard deviation) and patient numbers. Group M: Mephentermine, Group N: Norepinephrine, Group P: Phenylephrine.

DISCUSSION

For maintenance of blood pressure during caesarean section under spinal anesthesia, we assessed the effects of phenylephrine, norepinephrine, and mephentermine to find the optimum one that can be administered in fixed-rate infusions without having any adverse feto-maternal effects. Although the subarachnoid block is extremely effective, it has several drawbacks, including hypotension, and less control over the extent of the block [8, 13]. The anesthetist remains concerned about such a drawback despite several attempts to curtail it [6, 14]. Preloading or co-loading with intravenous fluids, application of lower limb compression stockings, left uterine tilt, using the right local anesthetic to achieve the right height, and using vasopressor are some of the common strategies that have been adopted in clinical settings to prevent SAIH [15]. SAIH can be prevented and treated with vasopressors, although their selection has been debated [16].

Systolic blood pressure, Diastolic blood pressure, and mean Arterial pressure

Our study revealed no significant difference in SBP and DBP among all three groups at all-time points except at 4min (p=0.006), with group P having the lowest mean SBP. These findings are similar to the findings from the study by Singh et al., who evaluated the effects of intravenous norepinephrine (N group) and mephentermine (M group) on blood pressure under spinal anesthesia for cesarean delivery where both the groups had identical SBP and DBP [17]. Norepinephrine and phenylephrine were evaluated for maintaining SBP in LSCS with a computer-controlled closed-loop feedback system, and Ngan Kee

found a higher response percentage in both groups [18]. This finding is consistent with our observations. According to Goel et al., the values of SBP were comparable after 6 minutes from the start of the study solution until the delivery of the baby. Still, they were significantly lower in the phenylephrine group than the norepinephrine group in the first 2 minutes from the start of the study solution to 6 min ($P < 0.05$) [19]. The study by Singh et al. showed a higher response rate and need for multiple boluses of norepinephrine which may be attributable to the drug's quicker onset of the action and shorter half-life when compared to mephentermine [17]. Similar results have been observed in studies by Chandak et al., Singh et al., and Sinha et al. [13, 21, and 22]. However, in the study by Ali CV et al., a decreasing trend of SBP and DBP was perceived in both phenylephrine and norepinephrine groups except for a substantial rise in SBP at 14 minutes ($p=0.026$) and DBP at 8 minutes ($p=0.019$) in norepinephrine group [23]. In our study, the MAP was comparable among the groups P, N, and M at all-time points.

Heart Rate

The mean HR was comparable at different time intervals among all the 3 groups, whereas when the Post Hoc Bonferroni test was applied, there was a significant difference in HR between Group M and Group P at 15 mins. Singh et al., however, observed that the HR was analogous for the first 10 minutes before considerably increasing in Group M thereafter [17]. As observed by Chaturvedi et al., subjects receiving mephentermine had a higher mean heart rate while for those who received phenylephrine, the mean heart rate dropped dramatically [20]. The outcome was consistent with research by Kaur et al. [24]. Similar results comparing norepinephrine with phenylephrine have been reported by other researchers [5].

Incidence of Hypotension

There was no significant association between hypotension and Hypertension in the groups at all the time intervals. All groups were comparable in terms of rescue drug requirements. Kaur et al. in their study observed that subjects who received ephedrine (100.0%) and mephentermine (97.67%) had a higher incidence of hypotension than subjects who received phenylephrine (66.67%), which was statistically significant ($P = 0.001$) [24]. However, in the study by Goel et al more parturients in group N had at least one episode of hypotension compared to group P, where the variations were statistically insignificant. This shows that both vasopressors are equally effective in maintaining blood pressure, which is consistent with our findings. [19].

Adverse Events and APGAR Score

There were no appreciable differences in the incidences of nausea and vomiting between any of the three groups which is in accordance with studies by Singh et al. and Goel et al., [17, 19]. Based on the analyses in our study, there was no discernible difference in the mean APGAR scores among the three groups at time points 1 and 5 minutes. Similar results were observed in several randomized trials [6, 17, 25-28].

Drug Potency

In our study, the equipotent dosage of three study drugs was determined based on an earlier study showing phenylephrine and norepinephrine in a ratio of 20:1 (100 g: 5 g) as equipotent. [1]. The potency ratio of norepinephrine and mephentermine was not established because they had never been compared for the treatment of SAIH. Phenylephrine and mephentermine have a potency ratio of 11.9:1, according to the study by Mohta et al., [29]. Mohta et al. also conducted another study to determine the potency of mephentermine (5mg infused over 30 minutes) for the prevention of post-spinal hypotension and discovered a potency ratio of ephedrine to mephentermine of 1:6.8. [30]. Based on all these findings we devised our infusion regimens.

Limitations

Due to logistical issues in our institutional healthcare setting, it was not possible to carry out maternal and cardiac output measurement and umbilical cord blood gas analyses. Our study participants were limited to parturients scheduled for elective LSCS only.

CONCLUSION

In parturients undergoing elective LSCS under SAB, the efficacy of intravenous phenylephrine, norepinephrine, and mephentermine infusion was comparable in terms of maintaining maternal hemodynamics. All three vasopressors were effective likewise in mitigating nausea and vomiting in mothers and producing good neonatal outcomes. To arrive at a consensus on a safe and efficacious choice of vasopressor, more exhaustive studies are needed on various vasopressors used in category 1 and 2 caesarian deliveries.

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