Original Article

Norepinephrine Versus Phenylephrine for the Prevention of Post Spinal Hypotension in Cesarean Section

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ABSTRACT

Background: Hypotension following spinal anesthesia in the cesarean section is common despite adequate fluid loading. The recommended medication to treat spinal hypotension during cesarean section is phenylephrine. Norepinephrine bolus has recently been proposed as an alternative to phenylephrine bolus. Our study's objective was to evaluate the efficacy of bolus doses of phenylephrine and norepinephrine in treating spinal-induced hypotension after cesarean delivery.

Methods: One hundred and eighty parturient, ASA II, aged above 18 years, planning an elective cesarean section under anesthesia were randomly assigned by the lottery method into the two groups. Group P received Phenylephrine 50 µg intravenous bolus, and Group N received 5 µg of Norepinephrine intravenous bolus to prevent spinal-induced hypotension.

Results: The incidence of hypotension after the prophylactic bolus dose of study drugs was 25.6% in group N and 32.2% in group P. The number of rescue bolus doses of the studied drug that were required to treat hypotension was lower in Group N than in group P (25.6% vs 32.2 %). The Mephentermine that was required to treat hypotension was also lower in Group N than in Group P (11.1% vs 12.2 %). The changes in heart rate and mean arterial pressure after the injection of the study drug were comparable.

Conclusion: Prophylactic Norepinephrine and Phenylephrine bolus dose were equally effective in the prevention of spinal-induced hypotension during cesarean section.

Keywords: Cesarean section, Hypotension, Norepinephrine, Phenylephrine, spinal, vasopressors.

ARTICLE INFORMATION	**Source of Support**: Nil	**Conflict of Interest**: None
Received: 13 July 2022	**Accepted**: 20 August 2022	**Published Online**: 30 August 2022

INTRODUCTION

Cesarean section is defined as birth through the incision in the lower abdomen and uterus.[1] In the United State, it has occupied 30% of all modes of delivery and most the of common surgical procedure[2]. In Paropakar Maternity and Women´s Hospital, Kathmandu, frequency of cesarean section (CS) was 27.4% in the fiscal year 2016/2017.[3] For CS, spinal anaesthesia is the most popular regional anesthetic due to its ability to provide a rapid and reliable onset of anesthesia, relax muscles adequately[4], avoid airway manipulation and prevent risk to mother and fetus from the toxicity of the drug used in general anesthesia.[5]

Spinal anesthesia has some adverse effects such as hypotension, post-dural puncture headache, and urinary retention. The most common among them is post-spinal anesthesia hypotension. The incidence of hypotension after the cesarean section was 24.8% in our setup.[6] Many pharmacological and non-pharmacological measures were applied to lower the post-spinal hypotension.[7-8] The standard practices for

the management of post-spinal hypotension are fluid loading, pharmacological agents, and positioning protocols. The use of vasopressors is often recognized as an effective method for reducing post-spinal hypotension.[9] The different types of vasopressors have been used in the reduction of the incidence of hypotension in obstetric practice.[10] Numerous factors need to be taken into account when selecting an appropriate vasopressor in obstetrics. These include effectiveness, maternal side effects other than raising blood pressure, usability, direct and indirect fetal effects, and availability.

Mephentermine, Ephedrine, Phenylephrine, and Norepinephrine are among the vasopressors frequently used to treat post-spinal hypotension. The rationale of our study is Phenylephrine increases blood pressure but it is associated with decreases in heart rate and cardiac output. But Norepinephrine acts on β_1 adrenergic receptors, causing an increase in heart rate and cardiac contractility. It has less metabolic effects on fetus, such as acidosis. So Norepinephrine can be effective alternative vasopressor for the prevention of post-spinal hypotension in cesarean section. Our study's objective was to investigate the use of norepinephrine as an alternate treatment for post-spinal hypotension during cesarean delivery because it has fewer adverse effects on heart rate and maternal blood pressure than other vasopressors.

MATERIALS AND METHODS

This comparative double-blinded interventional study was completed in Paropakar Maternity and Women's Hospital, Thapathali, Kathmandu from October 2019 to December 2019. The NAMS institutional review board and the Paropakar Maternity and Women's Hospital institutional research committee gave their approval. According to the study by Dong L et al.[11], the incidence of bradycardia in the groups receiving Norepinephrine was 2% and Phenylephrine was 13%, thus the sample size was determined to be 90 in each group. By using formula $N= 2(Z\alpha + Z(1-\beta)^{2} pq/d^2$, type I error (Z) = 1.96, the confidence interval is 95% and $Z(1-\beta) = 0.842$, the power is 80%. This study covered all elective cesarean deliveries performed under spinal anesthesia during the period. The exclusion criteria were parturient allergic to the study drugs, pregnancy-induced hypertension, and relative contraindication to spinal anesthesia. All of the parturients in the study underwent pre-anesthetic exams, and their informed consent was obtained before surgery, the parturients were instructed about what would happen and kept off of food for eight hours. By using a lottery, the subjects who signed up for the study were split into two groups, Group N and Group P, each with 90 participants. The subjects and the investigator who were involved in the study were kept blinded. An anesthesiologist who was not involved in this investigation prepared the medication. The entire process was carried out by the researcher who was participating in the study, and he documented the results. ECG, blood pressure (NIBP), and pulse-oximeter were attached when the patient arrived in the operating room, and the baseline vitals were recorded. All parturients were pre-medicated for aspiration prophylaxis with an injection of Ranitidine 50 mg intravenous and Metoclopramide 10 mg intravenous 30 minutes before surgery as per hospital protocol. Before administering the spinal anesthetic, all patients were pre-loaded with Ringer Lactate 10 ml/kg over 15 minutes. Subjects were placed in the sitting position. Using 10% Povidone Iodine, the skin was cleaned under aseptic conditions. The site of spinal needle insertion was located; skin infiltration was done with 2ml of 2% lidocaine local anesthesia. The L3-L4 or L4-L5 intervertebral spaces were punctured with a 27 gauge Whitacre needle. Once the free flow of cerebrospinal fluid was obtained, 2.2 ml of 0.5% hyperbaric bupivacaine was administered at the rate of 0.2 ml per second. Subjects were kept in the supine position with a 15º left bed tilt after the medication was administered.

Vitals were recorded immediately following SAB. The subjects were kept in this position while receiving a bolus dose of the study medicines. Group N received 1ml (5µg/ml) of Norepinephrine and Group P received 1 ml (50µg/ml) of Phenylephrine. Until the baby was delivered, oxygen was given as per hospital procedure at a rate of 2 liters per minute through a nasal prong. Haemodynamic variable like mean arterial pressure (MAP) and heart rate (HR) was monitored every 2 minutes up to 20 minutes. Hypotension after SAB was defined as 20% fall in blood pressure from the baseline value or MAP less than 60 mmHg. When hypotension occurred, Group P and Group N each received a rescue bolus dosage of

50 mg of phenylephrine and 5 mg of norepinephrine, respectively.

Both groups received 6 mg of mephentermine for the hypotension that was not improved by the study drug's rescue dose. Bradycardia was defined as a maternal heart rate below 50 beats per minute (bpm), and it was treated with 0.6 mg of atropine intravenously (IV). The observer who was conducting the study documented all the essential information, including HR, SBP, DBP, and adverse effects including hypotension and bradycardia.

Data collection was done using a pre-made data collection sheet. They were filled in an excel sheet. The Numeric outcome score was generated from the dummy tables. Statistical Package for the Social Sciences version 16 was used to analyze it. Analyzed data were presented in the form of tables, graphs, and charts. The student's t-test was applied to variable data such as MAP, HR, age, and BMI. Significant data was defined as a p-value of less than 0.05.

RESULTS

Hundred and eighty parturients were involved in our study, 90 in each group. The demographic characters showed the age of the subjects ranged from 18-35 years. The mean age in Group N was 26.37 ±4.48 years and in Group P was 25.19 ±4.47 years, (p=0.08). The mean BMI in Group N was 26.45± 2.55kg/m^2 and in Group P was 26.41±2.47kg/m^2 (p=0.91) which was shown in Table 1. Mean baseline MAP of Group N was 84.90±6.21 mmHg and Group P was 84.10±6.43mm Hg which were comparable. The MAP of both study groups which was recorded after SAB at the interval of 2 to 20 minutes was comparable (Table 2 and Figure 1)**.**

In this study we compared heart rate changes between two groups, the mean baseline HR was 91.97±16.59 bpm in Group N and 93.30±12.89 bpm in Group P which were comparable. The HR in both groups after SAB was measured at the interval of every 2 minutes for 20 minutes. The measured HR were comparable. There was no incidence of bradycardia in either of the study groups. HR was well maintained in both groups. There was a slightly decreased in HR in the first 2 to 4 minutes after SAB in both groups and was not statistically significant, this was depicted in Table 3 and Figure 2.

Table 1: Demographic data of parturient

Variable	**Group N (Mean ± SD)**	**Group P (Mean ± SD)**	**P-value** (independent t-test)
Age (Years)	26.37 ± 4.48	25.19 ± 4.47	0.08
BMI (kg/m^2	26.45 ± 2.55	26.41 ± 2.47	0.91

Table 2: Comparison Mean Arterial Pressure (MAP) Changes between Two Groups.

Variable **MAP**	**Norepinephrine (N)** **Mean ± SD**	**Phenylephrine (P)** **Mean ± SD**	**p-value** (Student t-test)
Baseline	84.90 ± 6.21	84.10 ± 6.43	0.397
Immediate after SAB	84.14 ± 13.39	85.34 ±11.13	0.514
2 min	80.84 ± 16.30	82.53 ± 13.24	0.447
4 min	77.65 ± 11.57	74.72 ± 13.36	0.117
6 min	76.14 ± 12.71	73.40 ± 11.06	0.124
8 min	74.54± 16.08	74.28 ± 10.76	0.900
10 min	77.53 ± 11.80	74.41 ± 11.26	0.071
12 min	78.94 ± 11.11	76.74 ± 10.96	0.183
14 min	78.58 ± 12.11	76.86± 9.52	0.290
16 min	77.11 ± 12.07	74.34 ± 11.71	0.120
18 min	75.67 ±15.76	73.51 ±10.14	0.277
20 min	76.47 ± 13.06	73.07 ± 11.43	0.065

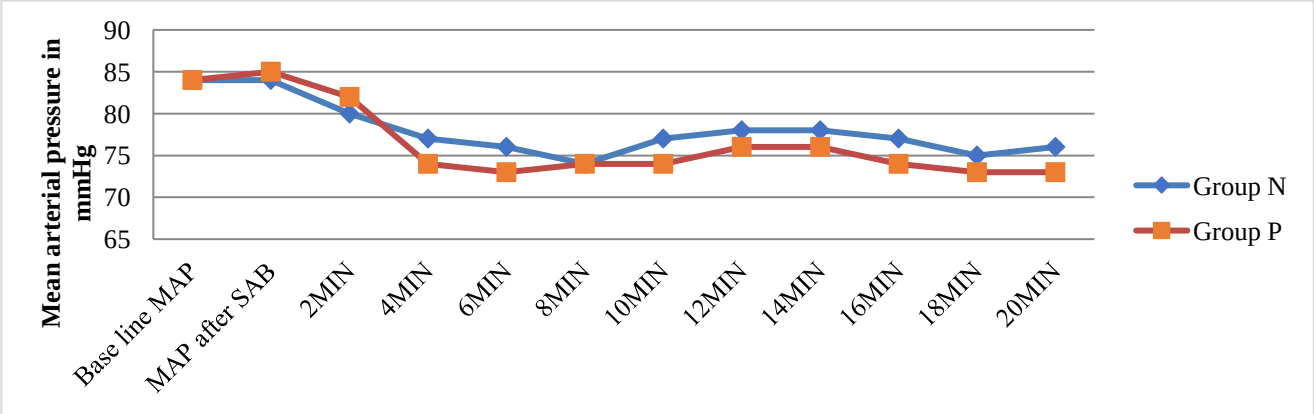

Figure1: Comparison of MAP Changes Between two Groups

Table 3: Comparison of Mean of Heart Rate Changes Between two Groups N= 180

Variable **Heart Rate(HR)**	**Norepinephrine (N)** **Mean ±SD**	**Phenylephrine (P)** **Mean ±SD**	**p-Value** Student t-test
Baseline HR	91.97±16.59	93.30±12.89	0.551
Immediate HR after SAB	90.47±17.07	90.88±15.72	0.858
2 min	87.57±15.44	85.34±15.78	0.339
4 min	90.90±17.41	89.62±17.63	0.625
6 min	94.05±18.75	90.84±16.24	0.221
8 min	91.77±17.65	90.03±17.23	0.503
10 min	89.83±17.17	89.57±16.49	0.919
12 min	92.80±16.04	89.57±16.49	0.919
14 min	92.30±16.34	90.73±16.81	0.527
16 min	94.82±16.43	93.68±17.09	0.651
18 min	95.95±18.88	95.76±16.23	0.943
20 min	96.87±15.21	97.03±16.32	0.947

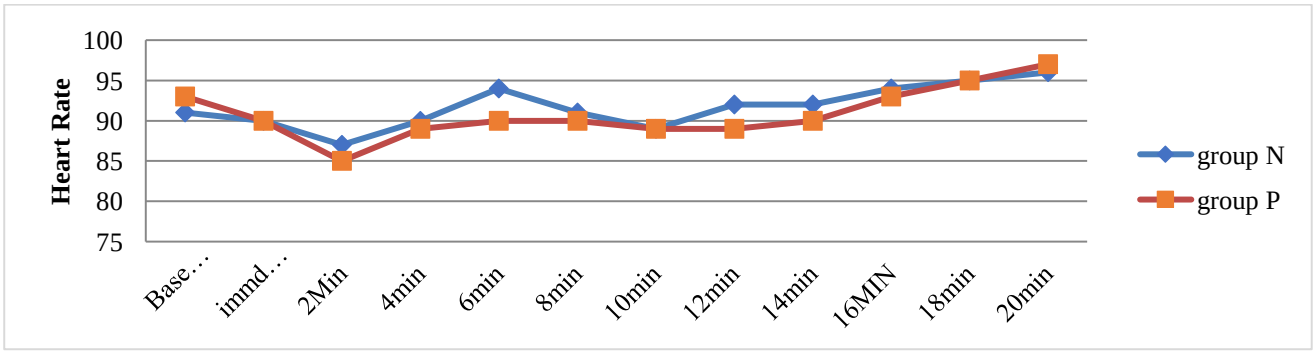

Figure 2: Comparison of Mean Heart Rate Between two Groups

DISCUSSION

The mean baseline MAP of Group N was 84.90±6.21 mmHg and Group P was 84.10±6.43 mmHg which was comparable. After spinal anesthesia the mean atrial pressure of both study groups which was recorded at the interval of 2 minutes to 20 minutes was comparable. MAP decreased in both groups but it was not statistically significant (p-value >0.05). The incidence of hypotension in Group N who needed the rescue dose of 5 µg of Norepinephrine was 25.6%. Among 25.6% of the parturient, 11.1 % of parturients needed Mephentermine 6 mg to maintain the MAP of 60 mmHg. In Group P, the incidence of hypotension was 32.2%, and those who were treated with Phenylephrine 50 µg. The 12.2% of parturients were treated with Mephentermine to control hypotension despite receiving the rescue dose of the same study drug. In the study done by Puthenveettil N et .al,[12] they

discovered that the MAP of the study medications did not differ significantly from one another. They defined hypotension when MAP decreased 20% from the baseline value. Significantly fewer vasopressor boluses were required to treat hypotension in Group N (1.40±0.577 vs. 2.28±1.061, p=0.0001). The rescue vasopressor used in both groups was less than in our study. It may be that they used a low dose of intrathecal local anesthetic agent 1.8ml of 0.5% of heavy bupivacaine. However, 2.2 ml of 0.5% heavy bupivacaine was used as the intrathecal local anesthetic drug in our investigation.

Sharkey Aidan M. et .al[13] in their study found that the incidence of hypotension in Group N was 37.5% and in Group P was 39.4%. They had a high incidence of hypotension than in our study because they had used a higher concentration of injection heavy bupivacaine (0.75%). In their study co-lading was done by 10ml/kg, which was not enough to prevent spinal-induced hypotension. They had defined hypotension as when systolic blood pressure decrease <80% of baseline. They administered the study drug when SBP was below the baseline. In their study, they used Phenylephrine 100 µg and Norepinephrine 6 µg. But in our study, we used 0.5% heavy bupivacaine. The preloading was done with a 15ml/kg ringer lactate solution. In their study, the proportion of parturients that required the rescue boluses of Ephedrine was lower in Group N as compared to Group P (7.2% of N versus 21.4% of N, p-value <0.03).

In the study done by Vallejo MC et al,[14] percentage of patients who needed rescue vasopressor boluses did not differ between the two groups (Group P: 65.8% vs. Group N 48.8% (p=0.12). The percentage of patients who received one bolus of phenylephrine was comparable in both groups (Group P: 52.6% vs. Group N: 46.5%; p=0.58). However, more individuals received one bolus of Ephedrine in the Phenylephrine (Group P 23.7% vs. 2.3% Group N) (*P*<0.01). They used fixed-rate infusions of Group P (phenylephrine 0.1 g/kg/min) or Group N (norepinephrine 0.05 g/kg/min) for the parturient in their trial. To maintain systolic blood pressure, rescue bolus interventions of phenylephrine 100 mg for hypotension or ephedrine 5 mg for bradycardia with hypotension were given as needed.

In our study, the incidence of hypotension in Group N was 25.6 % and the need for a rescue dose of the same study drug was 25.6%. Mephentermine was necessary for the 11.1% of parturients. Similarly, Group P experienced an episode of hypotension at a rate of 32.3% and required rescue doses of the same study medicine. Mephentermine was necessary for the 12.2 % subjects. The percentage of need for rescue vasopressor was high in Group P in both studies. Compared to the previous study, there was a low incidence of hypotension in both groups in our study. The reason behind that difference was due to the use of the higher volume of intrathecal local anesthetic drugs. Their 500 ml of ringer lactate solution preloading volume was insufficient. Their definition of hypotension was when their SBP decreased below 120mmHg but in our study, we used 2.2ml of an intrathecal local anesthetic drug, and the rate of preloading of fluids was 15ml/kg which was higher than their study.

In the study done by Mohta M et.al[15,] they found that 42% in the Phenylephrine and 38% in the Norepinephrine group developed further episodes of hypotension. They used Phenylephrine 100µg as a rescue bolus dose when the second episode of hypotension occurred. But they did not define how many parturients had received Phenylephrine for the treatment of hypotension. When compared to our study, their study had a higher rate of hypotension. It is that they have defined hypotension when SBP drops 20 % from baseline or SBP <100 mmHg.

In our study, the baseline HR was 91.97±16.59 bpm in Group N and 93.30±12.89 bpm in Group P which were comparable but it was not statistically significant p-value 0.55). Following SAB, both groups' HRs were monitored for 20 minutes at intervals of every 2 minutes. Between the two groups, there was no statistically significant difference in the HR measure at any given time. Bradycardia did not occur in either of the research groups.

In the study done by Puthenveettil N et al,[12] the baseline HR in Group N was 94.68 bpm and in Group P was 96.68 bpm and which was similar to our study. After SAB, the HR was decreased in both the study groups, bradycardia occurred frequently in Group P though (4% vs 20%, p = 0.192) It had no statistically significant value. In their study, Group N received 4 µg of Norepinephrine and Group P received 50 µg of Phenylephrine to treat as an intravenous bolus for spinal-induced hypotension. They had been taking

vital signs every two minutes up to the tenth minute of the procedure, and every minute after that. Their study period was long, so more incidences of bradycardia were recorded. Despite the same dose of the study drug used in our study we didn´t find any incidence of bradycardia. The rapid infusion of the bupivacaine injection on the subarachnoid space during spinal anesthesia can cause rapid spread of the drug causing adverse effects like bradycardia. The Studied have shown that bupivacaine given in the fractionated dose SAB has minimal impact on hemodynamics. In our study, we have given bupivacaine@0.2ml/sec. The speed of the drug infusion has not been mentioned in their study.

In the study done by Sharkey Aidan M. et. al[13] the incidence of bradycardia in Group N was 10.7% and in Group P was 37.35%. The p-value was 0.007 which was statistically significant. It could be because they utilized 0.75% strong bupivacaine in a larger volume for SAB. They also used the greater study dose to prevent hypotension during cesarean section. In their study, bradycardia was defined when HR <60bpm. But in our study, there was no incidence of bradycardia, because we had used a low dose of heavy bupivacaine for spinal anesthesia. In the study done by Vallejo MC et. al[14], they found that heart rate was statistically similar between the two groups ($p<0.05$) but they didn't mention the incidence of bradycardia. In their study Group P received (0.1µg/kg/min) and Group N (0.05 µg/kg/min) infusion of study drugs. . In the study done by Mohta M et. al[15] 10 % parturient of Group N and 8% parturient in Group P had bradycardia. The causes behind that may be due to that, their definition of bradycardia was when HR <60 bpm But in our study we had defined bradycardia as when heart rate fall below 50 bpm, the dose of study drug was Norepinephrine 5 µg and Phenylephrine 50µg. In our trial, the study medication was administered as a preventative measure right after the SAB, but in other investigations, the vasopressor was only administered once bradycardia had already developed. This may be the reason for more incidences of bradycardia in their studies. In our study, we were not able to measure beat-to-beat changes in mean arterial pressure.

CONCLUSION

Phenylephrine and Norepinephrine were equally effective in the prevention of post-spinal hypotension in cesarean section. Norepinephrine can be used as an alternative drug for the treatment of spinal anesthesia-induced hypotension in cesarean section.

Acknowledgements: We want to express our gratitude to all the subjects who took part in the study. We acknowledge the assistance of the entire faculty of the anesthesiology department, the department of obstetrics and gynecology, and the operation theater staff.

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