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Original Research Article

Comparison of efficacy of low-dose norepinephrine infusion with low-dose boluses of norepinephrine in managing hypotension among parturients undergoing caesarean section under the subarachnoid block

S Shrieaswari[1],*, M P Sujatha[1]

[1] *Dept. of Anaesthesiology, Sri Devaraj Urs Medical College, Kolar, Karnataka, India*

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ABSTRACT

Background: Spinal anesthesia is increasingly popular over general anesthesia due to several advantages. Hypotension can complicate spinal anesthesia during a cesarean section, which could have negative repercussions on the mother and fetus. This study is aimed to compare the efficacy of low-dose norepinephrine infusion with low-dose boluses of norepinephrine in managing hypotension among parturients undergoing cesarean section under subarachnoid block.

Materials and Methods: Ninety-nine parturients without comorbidities who underwent caesarean section with spinal anesthesia received norepinephrine were considered. They were divided into three groups. Group A- Parturient received a norepinephrine infusion of 1 mcg/min and a rescue bolus of 3 mcg to treat hypotension. Group B- Parturient received a Norepinephrine bolus of 3mcg to treat hypotension. Group C- Parturient received a Norepinephrine bolus of 5 mcg to treat hypotension. All the vitals at different intervals, number of norepinephrine boluses, the total amount of norepinephrine consumed, maximum sensory level achieved, time for baby extraction following subarachnoid block, and any adverse events were documented.

Results: No statistical difference was noted in the study group's demographics. However, there was a significant difference in mean systolic blood pressure between the groups from skin incision to baby extraction at T6 and T8. In addition, the mean arterial blood pressure of the two groups differed significantly throughout the period from baby extraction to skin suturing. Between the groups, there was a substantial difference in the total number of boluses needed. The total number of boluses required was maximum in group B, followed by group C. Group A required the minimum number of total norepinephrine boluses.

Conclusion: A prophylactic norepinephrine infusion is an effective and straightforward method of reducing the incidence and magnitude of hypotension following spinal anesthesia for cesarean section with no adverse effect.

1. Introduction

Spinal anesthesia is increasingly becoming popular over general anesthesia due to several advantages. Spinal anesthesia provides a profound analgesic effect, less blood loss during surgery, hemodynamic stability, and beneficial surgical conditions.[1]

In addition, spinal anesthesia for new mothers offers better pain control, mobility, and a quick return to daily activities improving their quality of life. The complications of this anesthetic procedure include arterial hypotension, circulatory and respiratory depression, and neurological alterations.[2] Hypotension is considered the most frequent complication of spinal anesthesia,developing in almost 16-33% of patients who had this method of anesthesia.[3,4] Several different processes may cause hypotension caused

* *Corresponding author*.
E-mail address: jabarali2009@gmail.com (S. Shrieaswari).

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by spinal anesthesia. Significant hypotension may be caused by lower cardiac output, reduced systemic vascular resistance, or a combination of both.[5] Both the mother and the growing fetus may be affected by hypotension. The mother may experience dizziness, nausea, and vomiting. Further, there may be apnea, unconsciousness, pulmonary aspiration, and cardiac arrest in severe hypotensive cases. Reduced uteroplacental blood flow may be caused by hypotension. It may lead to hypoxia, fetal acidosis, and injury or cerebral depression in neonates.[6]

Anesthetics have used different approaches to avoid hypotension following cesarean following spinal anesthesia. Delivering intravenous vasopressors is the most usual method for the prevention of hypotension.[7–9] Prophylactic administration of phenylephrine may result in managing the hypotension during cesarean section.[10] However, since phenylephrine has the potential to lower cardiac output and induce bradycardia, it is only helpful in people with cardiovascular illness.[11] Norepinephrine is a potential substitute for other vasopressors, including phenylephrine. Conclusive evidence indicates that norepinephrine reduces cardiovascular inhibitory effects and lowers bradycardia risk.[12]

A study demonstrated that term parturient undergoing cesarean delivery under the subarachnoid block had received a set of intermittent norepinephrine bolus of 3, 4, 5, 6, 7, or 8 mcg whenever systolic pressure falls below 20% of baseline. The result derived estimated dose of norepinephrine to prevent spinal-induced hypotension in the cesarean section was 5.49 μg.[13] Nevertheless, none of the trials examined the effectiveness of low-dose norepinephrine infusion with low-dose boluses in treating hypotension in cesarean-section parturients.

This study is a prospective randomized clinical trial comparing the efficacy of low-dose norepinephrine infusion with low-dose boluses in managing hypotension among parturients. The study will determine the incidence of spinal hypotension of norepinephrine and total boluses administered.

2. Materials and Methods

A randomised double-blind clinical study was conducted on 99 patients undergoing elective cesarean section under Spinal Anesthesia at a Tertiary Care Hospital and Research Centre, in Tamaka, Kolar, from January 2020 to May 2021. A total of 99 patients were divided into three groups with 33 patients in each group.

Patients (parturient) with a willingness to participate in the study were included, with an age range between 18-30 years, followed by ASA grade 2, normal singleton pregnancy with 37 weeks of gestation, and undergoing cesarean section under sub-arachnoid block. Patients with antepartum hemorrhage, pre-eclampsia, cardiovascular disease, arrhythmias, fetal abnormalities, recent use of vasoactive medications, and diabetes were excluded from the study. All participants in the study underwent pre-anesthetic evaluation and written informed consent. Result values were recorded using a proforma.

Patient randomization was conducted by using the simple random sampling method. Patients were nil per oral for six hours and were given routine antacid prophylaxis with IV Ranitidine 150 mg before surgery.

Parturients were randomly allocated into one of the three groups:

Group A- Parturients received a Norepinephrine infusion of 1mcg/min and a rescue bolus of 3mcg to treat hypotension.

Group B- Parturients received a Norepinephrine bolus of 3 mcg to treat hypotension.

Group C- Parturients received a Norepinephrine bolus of 5 mcg to treat hypotension.

On arrival in the operating room, routine monitoring devices like five lead electrocardiogram, non-invasive blood pressure, and pulse oximeter were connected, and baseline vitals was noted. 18G IV access was secured, and normal saline was started. They were positioned on the operating table in the supine position with a left lateral tilt.

Parturients were positioned in the left lateral position. First, the area where the needle would go through the skin was sterilized, and then lidocaine 2% was injected. Then the subarachnoid block was given using a 25-gauge Quincke Babcock spinal needle at L3-L4 vertebral interspace with 10mg of 0.5% heavy bupivacaine. Immediately after the subarachnoid block, the parturient was made supine and vital parameters were recorded every 2 minutes till the extraction of the baby. From the timing of extraction of the baby, the vital parameters were measured every 5 minutes till subcutaneous skin suturing. Following extraction of the baby, 15U of oxytocin was added to 500ml of normal saline and given at 10ml/kg/hr.

Parturients in Group A was started on Norepinephrine infusion immediately after Subarachnoid Block. Group B and Group C participants received norepinephrine boluses on developing hypotension.

A fall in heart rate to less than 60 beats/min was considered bradycardia, for which IV Glycopyrrolate 0.2mg was given. A fall in mean arterial pressure of 20% of baseline was considered hypotension. An increase in mean arterial pressure of >20% of baseline was considered hypertension, for which the study drug was stopped temporarily.

Parturients not responding to 3 boluses of norepinephrine were given IV Ephedrine 6mg to treat hypotension. Before and after baby extraction if the boluses exceed more than 3 ephedrine will be given of average 5.7 mg for both. All the vitals at different intervals, number of norepinephrine boluses, the total amount of norepinephrine consumed, maximum sensory level achieved, time for baby extraction

following subarachnoid block, and any adverse events were documented in the proforma.

The numbers of patients, percentages, and the mean and standard deviation of the data are all shown. One-way ANOVA was used to examine the disparity between continuous variables. Pearson chi-square tests were used to compare the categories of information. With a two-tailed test, P values below 0.05 were considered significant. IBM-SPSS 21.0 was used for the statistical analysis.

2.1. *Sample size calculation*

The sample size was calculated using the mean total boluses reported in the research effectiveness and safety of various norepinephrine regimens for spinal hypotension prevention in cesarean section: To detect a 12.3 mcg of total boluses between the groups with SD of 15 mcg with 80% power and 1% level of significance, a sample of 66 (33 in each group) would suffice. Based on the values taken from the reference article[14] mean total boluses consumption for the group 1 was 19.7, group 2, 6.9. The sample size calculation was done by using the formula:

n = 2sp2[z1-$\acute{\alpha}$/2+z1-]2 μd2

sp2 = s12 + s22

Where, s12= Standard deviation in the first group

s22= Standard deviation in the second group

μd2= Mean difference between the samples

$\acute{\alpha}$ = Significance level

1- = Power

3. Results

No statistical difference in age, height, weight, BMI, HB, or platelet was noted in the study groups' demographics. Still, the study groups have a significant difference in WBC and blood sugar (Table 1).

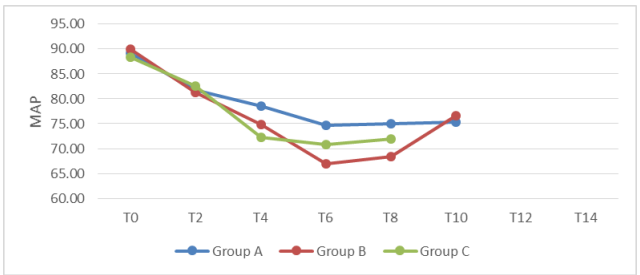

Fig. 1: Mean arterial pressure from skin incision to extraction of baby

The mean arterial pressure among the groups is shown in Figure 1. Except at T6, the groups do not show any significant difference between the mean arterial pressures from skin incision to extraction of the baby (Figure 1).

There was a significant difference in mean arterial blood pressure among the groups throughout the period from baby extraction to skin suturing, as presented in Figure 1.

Table 2 shows the time taken for extraction of the baby following the subarachnoid block. Again, there was no significant difference between the time taken among the groups.

Table 3 shows the number of boluses of norepinephrine before baby extraction and after baby extraction. A significant difference was found between the groups' total number of boluses required. The total number of necessary boluses was maximum in group B, followed by group C. Group A needed the minimum number of total norepinephrine boluses. Each group significantly differed in the number of boluses required before baby extraction. In addition, a significant difference was found among the groups in the number of necessary boluses after baby extraction.

Table 4 denotes each group's mean total drug consumption (μg). Again, there was a significant difference between the groups. Group A requires the highest drug quantity, while group B requires a minimum amount of the drug.

Table 5 indicates the specific inter-group differences between the mean drug consumption. Comparing group, A to group B or group C, revealed a statistically significant difference. Group B differed significantly from Group A and Group C, whereas Group C and Group D did not.

4. Discussion

Spinal anesthesia increases the risk of hypotension. It is characterized by reduced uterine blood flow and low placental perfusion resulting in acidosis and hypoxemia in the fetus. In addition, if the mother's blood pressure is reduced by 30% of the baseline and remains persistently, there is an abnormal alteration in the APGAR and neurobehavioral scores. Spinal anesthesia may also result in the alteration of fetal heart rate and reduces intervillous blood flow. To avoid fetal problems, doctors must either prevent or treat hypotension as soon as possible. The management of hypotension in the mother is equally critical. It is because hypotension promotes nausea and vomiting in the mother. Also, it may cause the mother to be reluctant to endure spinal anesthesia.

Vasopressor medications have been the subject of intensive study in recent years to treat hypotension produced by spinal anesthesia during obstetric surgery.[15] There are several important characteristics of vasopressors. The ideal vasopressor should have a quick onset of action, be less expensive, easily available, and not adversely affect the mother and fetus. Additionally, placental perfusion is not negatively impacted.[16] According to the results of a study, norepinephrine is just as efficient as phenylephrine in avoiding spinal hypotension. Further, its use after a cesarean section is associated with a greater cardiac output (CO) and a lower risk of unfavorable HR effects than

Table 1: General characteristics of the patients

Variables	Group A		Group B		Group C		P-value
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Age	24.30	3.87	25.30	3.86	24.52	3.97	0.550
Height	156.06	1.46	155.45	1.82	156.06	1.90	0.267
Weight	68.79	5.68	69.55	5.95	69.52	6.76	0.852
BMI	28.27	2.24	28.81	2.17	28.58	2.81	0.663
HB	11.44	1.44	11.80	1.38	11.26	1.58	0.327
WBC	11.94	2.37	12.12	3.80	10.20	2.48	0.018
Platelet	226090.91	72293.40	235363.64	77227.27	246000.00	68270.60	0.540
Blood Sugar	98.79	7.78	102.79	9.49	103.76	8.47	0.050

Table 2: Time is taken for extraction of the baby following subarachnoid block(sab)

Group	Time Taken for extraction of the baby following SAB		Total	P-value
	8.00 mins	10.00 mins		
Group A	32	1	33	0.600
Group B	32	1	33	
Group C	33	0	33	
Total	97	2	99	

Table 3: Total boluses before and after baby extraction

Variables	Mean Standard Deviation			P-value
	Group A	Group B	Group C	
Total no. boluses of norepinephrine	2.06 ± 0.86	5.73 ± 1.23	3.85 ± 0.36	<0.0001
Before Baby Extraction	1.39 ± 0.97	2.18 ± 0.88	2.27 ± 1.07	0.001
After Baby Extraction	0.67 ± 0.78	3.55 ± 1.18	1.58 ± 1.12	<0.0001

Table 4: The mean of total drug consumption

Group	Mean Standard Deviation	P-value
Group A	41.94 ± 6.87	<0.0001
Group B	17.18 ± 3.70	
Group C	19.24 ± 1.82	
Total	26.12 ± 12.17	

Table 5: Intergroup analysis of mean drug consumption

(I) Group		Mean Difference (I-J)	P-value
Group A	Group B	24.76	<0.0001
	Group C	22.70	<0.0001
Group B	Group A	-24.76	<0.0001
	Group C	-2.06	0.221
Group C	Group A	-22.70	<0.0001
	Group B	2.06	0.221

phenylephrine.[14] Pregnant women with preeclampsia and normotensive pregnant women's maternal norepinephrine levels were compared, and it was discovered that parturients with preeclampsia had significantly higher levels of the hormone. This finding raised questions about whether these women would still be sensitive to exogenous norepinephrine.[17]

According to a study by Minzter et al in 2010, Norepinephrine had no impact on the fetal arterial perfusion pressure, and the fetoplacental microcirculation was unaffected.[18] In a study, Left Uterine Displacement (LUD) was not given post-administration of spinal anesthesia. LUD's reliability in preventing aortocaval compression is compromised by the fact that it is rarely achieved properly in daily practice, which could complicate the

procedure for the surgeon.[19] The use of a drug such as norepinephrine with mild -adrenergic receptor activity, counter-balancing the reflex slowing of heart rate due to the potent -adrenergic receptor activity, would demonstrate similar vasopressor efficacy as phenylephrine, conveying hemodynamic stability to the parturient, but without the excessive adverse negative chronotropic effects of phenylephrine.[20]

In a study patients were divided three groups and administered different doses for managing spinal anesthesia-induced hypotension. Ninety-nine patients were included in the study. In addition, there may be fewer instances of tachycardia, maternal intraoperative nausea and vomiting (IONV), and higher pH, base excess (BE), and decreased HCO3-, lactate in umbilical artery blood as compared to phenylephrine with norepinephrine.[21]

In the first group, group A, the study population received norepinephrine infusion at 1mcg/min immediately after the subarachnoid block. The infusion was prepared in a 50ml syringe with a concentration of 10mcg/ml, starting at 6ml/hr. Hypotension was defined as a decrease in mean arterial pressure below 20% of baseline, and a norepinephrine bolus dose of 3mcg was given to treat hypotension. Group B study population received a norepinephrine bolus of 3 mcg given over 30 seconds to treat hypotension. Group C study population received a norepinephrine bolus of 5 mcg given over 30 seconds to treat hypotension.

Our study has only been conducted on healthy women scheduled to have a caesarean section. Thus, the results of this study may not be valid for women with underlying medical conditions, such as preeclampsia, reduced uteroplacental blood flow, and patients with non-reassuring fetal HR patterns. Low-dose norepinephrine infusions or boluses are equally effective in avoiding hypotension in parturients following subarachnoid block. We measured the parameters in two different phases. One phase constitutes the period from skin incision to the extraction of the baby, and the second phase comprises the time from the extraction of the baby to skin suturing. Prophylactic administration of norepinephrine has been shown in trials to be beneficial in controlling spinal anesthesia-induced maternal hypotension. Unfortunately, even after receiving prophylaxis, some women had hypotension and required further administration of vasopressor medications in the form of boluses. There has been little research on the usage of norepinephrine for bolus delivery.

Basic factors such as age, weight, and height do not vary significantly among the participants in our research. This result aligns with the results obtained from Chen et al., which also do not find any significant difference between the basic characteristics of the participants among groups.[14] Parameters with no significant difference among groups were also reported in Hasanin et al.[22]

We took heart rate every 2 minutes from the time of incision until the time of the baby's extraction. Again, we have found no significant difference among the groups regarding the above characteristics. We have also measured the cardiovascular parameters such as systolic blood pressure, heart rate, diastolic blood pressure, and the mean arterial pressure from the extraction of the baby to skin suturing at each 5 minutes interval. Although there was no significant difference in heart rate among groups, a significant difference was reported in systolic blood pressure from T10 to T35 and diastolic blood pressure among groups during the period between T10 to T30. In addition, the average arterial blood pressure also varied significantly between the T10 and T35 groups.

Analyzing systolic, diastolic, and mean arterial blood pressure revealed a few important things. First, there was no difference between the efficacy of norepinephrine in Group A and Group C from the extraction of the baby to skin suturing a few times, and normal pressure is found in group A while the other times, patients in group C have normal pressure. However, when we took the values of diastolic pressure and the mean arterial pressure, we found that patients in Group A were closer to normal most of the time compared to group C.

Thus, although a higher dose of norepinephrine is given to the patients in group A (due to infusion), this group shows good control over the blood pressure during spinal anesthesia. Our findings are consistent with Kee et al., that concluded that although a higher dose of norepinephrine was given to patients in the infusion group, hypotension was less common in this group. Adverse effects on neonatal health are not seen.[23]

When compared to the dosages used by Kee et al., in which Group A was given an norepinephrine infusion 0-60 mL/h (0-5 μg/min) diluted with saline, and Groups B were given a bolus syringe containing 1 mL norepinephrine 5 μg/mL (5 μg) of saline, the latter two groups' dosages are significantly different.[23]

We also measured the time taken for extraction of the baby after spinal anesthesia, and there was no significant difference between the groups. Our results were in line with the results of Choudhary et al., in which there is no significant difference in the duration of surgery.[24]

The total number of boluses and total drug consumption were also calculated. There was a substantial variation in the overall number of boluses. Patients with group B required maximum boluses, i.e., 5.73 ± 1.23. However, the drug in each bolus in the group was less than those administered in Group C, the overall drug consumption in group B was the least, and there was a considerable difference between the two groups. These results were in contrast to those found in Choudhary et al., in which no discernible change existed between the total doses among groups.[24] There was also an intergroup study of the mean total drug intake.

When comparing mean drug consumption between group A to group B and group C, a significant difference was found between group A and other groups. While comparing the mean drug consumption between group B to group A and group C, there was no discernible change between group B and group C. A significant difference was found in mean drug consumption between group B and group A. On comparing group C to group, A and group B, there was no significant difference in mean drug consumption between group C and group B. A significant difference was found in the mean drug consumption between group C and group A.

There was no measurement of maternal cardiac output in our study. But some studies have found that a mother's heart rate can stand in for cardiac output.[12]

The recent expression of the agreement for managing post-spinal hypotension recommends that ephedrine be the second-line drug for managing spinal anesthesia-induced hypotension in patients with an administration of α-agonists as primary treatment. However, in this study, we did not use phenylephrine because of the availability of limited data about the occurrence of cardiac depression when two potent α-agonists are used simultaneously. There were reports of norepinephrine bolus protocols in obstetric anesthesia.[25]

In nearly every caesarean procedure, clinicians administer vasopressor as prophylactic therapy. However, there are no set guidelines and protocols for the use of vasopressors. The top two vasopressors used in obstetrics operations to treat hypotension are phenylephrine and ephedrine. Phenylephrine is considered a first-line due to its low risk of causing fetal acidosis. However, phenylephrine has adverse effects, such as diminished cardiac output and reflex bradycardia.[26]

The drug used in our study has powerful α-adrenergic and some β-adrenergic agonistic activity. It is a possible alternative to phenylephrine due to its low risk of interfering with cardiac functioning.[27] Thus, norepinephrine can be used in women with poor cardiac function and low baseline heart rate where phenylephrine is contraindicated.

The adverse effects of the study drug, like reflex bradycardia and hypertension, weren't found to exist in our study. In addition, there are no adverse effects on the newborn according to the APGAR score.

5. Conclusion

In conclusion, our study suggests that prophylactic Norepinephrine infusion is an effective and straightforward method of reducing the incidence and magnitude of spinal anesthesia-induced hypotension for cesarean section. When compared, 5mcg boluses provided better control of spinal hypotension than 3mcg boluses of norepinephrine among parturients undergoing cesarean section followed by 1mcg boluses of norepinephrine. Group A demanded the most drug, followed by group C, and group B demanded the least amount of overall drug use.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

S Shrieaswari, Senior Resident

M P Sujatha, Professor

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