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A Comparison of Bolus Doses of Norepinephrine and Phenylephrine in the Treatment of Hypotension During Spinal Anaesthesia for Caesarean Section.

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Abstract

Phenylephrine is the first line choice for prevention and treatment of hypotension during a caesarean section under spinal anesthesia. However significant bradycardia caused by phenylephrine, is a concern. As a result, norepinephrine boluses have recently been proposed as an alternative to phenylephrine boluses.This study aim to compare the bolus doses of norepinephrine and phenylephrine to treat spinal hypotension during caesarean section and to compare the effects of phenylephrine and nor epinephrine on maternal heart rate, neonatal APGAR score and neonatal blood gas values. A randomized prospective double blinded study was conducted in 52 parturients of ASA 2 category, within age 20-40years undergoing elective caesarean section under subarachnoid block. Parturients in group N received 4mcg of norepinephrine and group P receive 50mcg of phenylephrine. Blood pressure and heart rate was monitored every 2 min till 10 min, and thereafter every 5 min till the end of surgery. APGAR score at 1 and 5 min were assessed and foetal umbilical blood was sent for ABG analysis within 5 minutes of cord clamping. The results were analysed statistically using SPSS software. The number of bolus doses of vasopressors required to treat hypotension was significantly lower in N group (P< 0.01). The frequency of change in maternal heart rate from the baseline was more with phenylephrine compared to nor epinephrine. However, no significant bradycardia (HR<50) was noted in either group. The changes in maternal blood pressure and foetal parameters were comparable between the groups. There were no episodes of tachycardia or hypertension in both the groups. Norepinephrine boluses can be considered as an alternative to phenylephrine boluses for treating hypotension during caesarean section as it maintains the maternal hemodynamics and has a comparable effect on foetal parameters.

Keywords: Caesarean section, hypotension, norepinephrine, phenylephrine.

Introduction

Caesarean sections are nowadays performed under the subarachnoid block to prevent the risk of airway complications and fetal complications of general anaesthesia and physiological changes in pregnancy (1). During a caesarean delivery under the subarachnoid block, maternal hypotension is a physiological reaction that leads to unfavourable maternal consequences, including nausea, vomiting, dizziness, and even cardiovascular collapse. Reduced systolic pressure in mothers impairs

uterine blood flow and fetal circulation, resulting in postnatal brain damage, hypoxia, and fetal acidosis, which can be harmful (2). Hypotension induced by spinal anaesthetics is a prevalent and clinically significant issue in up to 70% of cases. Problems with hypotension affect both the mother and the fetus. So adequate treatment with intravenous fluids and vasopressors can tackle these harmful consequences on the mother and the newborn (3).

Hypotension can develop in pregnant patients for a variety of reasons, including extensive sympathetic blockade that lowers systemic vascular resistance, Exaggerated neural blockade brought on by contraction of subarachnoid space as a result of pregnancy's physiological changes and aortocaval compression brought on by the fetoplacental unit(4). A drop in uteroplacental flow, poor fetal oxygenation with asphyxial stress, and fetal acidosis are all harmful outcomes of hypotension, especially if it is prolonged and severe (5). Subarachnoid block-induced hypotension, uteroplacental ischemia, and intervillous hypoxemia, which are hallmarks of severe preeclampsia, may trigger persistent hypoxic fetal placental vasoconstriction, which can result in fetal placental hypertension and "Cor placentale." Catecholamine production brought on by stress can lower uterine blood flow and cause fetal hypoxia. As a result, anxiety and increased catecholamine levels can influence the heart rate patterns of mothers (6,7).

A physiological reaction like hypoxic pulmonary vasoconstriction is hypoxic fetoplacental vasoconstriction. It corrects the placental maternal/fetal (Qm/Qf) circulatory matching for ventilation/perfusion (V/Q) mismatch (8). Hypoxemic fetoplacental vasoconstriction may be interfered with by vasopressor medications used to treat hypotension. Hypotension-related maternal and neonatal morbidity has inspired the exploration of a wide range of techniques, both alone and in combination, for its prevention and treatment (9). The most often non-pharmacologic methods are intravenous infusions of crystalloids as co-load and left uterine displacement. In terms of physiology, co-loading is superior to preloading (10-12).

The ineffectiveness of non-pharmacological methods to treat elective hypotension has resulted in the need for a vasopressor during subarachnoid block for caesarean delivery. When selecting a suitable vasopressor for obstetrics, various criteria need to be considered, including effectiveness for maintaining blood pressure, non-cardiovascular maternal effects, the convenience of administration, direct and indirect fetal effects, cost, and availability (13).

Vasopressors raise mean arterial pressure and enhance systemic vascular resistance to prevent hypotension following spinal anaesthesia(14). Phenylephrine is considered the first-line agent for treating hypotension in caesarean section due to its quicker onset, lower frequency of fetal acidosis, reduced placental transit, and reduced nausea and vomiting in the mother (3). However, as a pure α1- agonist the disadvantage of this medication is dose-dependent reflex bradycardia and decreased cardiac output, which may have a negative impact on the outcomes for both the mother and the fetus (15).

Norepinephrine is a powerful α -adrenergic receptor agonist with a minimal effect on the β -adrenergic receptor. It could be more favorable than phenylephrine due to its reduced propensity to decrease heart rate and cardiac output reflex (16).The use of norepinephrine for spinal hypotension treatment is a recent advance, so there are limited clinical trials. This study aimed to compare the number of bolus doses of norepinephrine and phenylephrine used to treat maternal hypotension… used to treat maternal hypotension in parturient undergoing subarachnoid block for cesarean section. The secondary objective is to compare the effects of phenylephrine and norepinephrine on maternal heart rate, neonatal APGAR score, and neonatal blood gas values.

Materials and Methods

A randomized double-blinded study was performed at a tertiary care hospital in patients undergoing elective cesarean section under subarachnoid block. The study was conducted for 18 months after obtaining ethical clearance and written informed consent from patients. The research followed consort guidelines and adhered to the ethical principles of the Declaration of Helsinki. Parturients between 20 and 40 years of age with a singleton pregnancy scheduled for elective cesarean delivery under spinal anaesthesia and met the American Society of Anesthesiologists (ASA) physical class II requirements were included in the study. Parturients with phenylephrine or norepinephrine allergies or hypersensitivity, heights of <145 or >170 cm, any hypertensive disease or preeclampsia, cardiovascular or cerebrovascular illness, or anomalies in the fetus were excluded from the research. The study also excluded participants who refused to give consent, those with preterm gestation or multiple gestations, had any contraindications to spinal anaesthesia and had a level of subarachnoid block >T4.

Patients who met the inclusion and exclusion criteria were randomized into group N (norepinephrine) and Group P (phenylephrine). Metoclopramide 10 mg and ranitidine 40 mg were administered orally to all parturients on the night before and the morning of the procedure as premedication. As per guidelines, the NPO condition was attained-8 hours for solid food and 2 hours for pure liquids. An 18-gauge intravenous cannula was placed in the operating room, and standard monitoring with non-invasive electrocardiography, pulse oximetry, and arterial pressure was set up. The baseline vitals were recorded. Then, 15 mL/kg of lactated Ringer's solution was loaded. Parturients were then positioned in the left lateral position. After infiltrating the skin with 2 ml of 2% lignocaine, the lumbar subarachnoid space was blocked at the L2-L3 or L3-L4 level with 2 mL of 0.5% hyperbaric bupivacaine using a 25G Quincke needle.

The parturient was then made supine with a wedge placed under the right buttock. Supplemental oxygen at a flow rate of 5 L/min was administered using a facemask. After being diluted and loaded into similarly coded 10ml syringes by an anaesthetist in the recovery, group N was assigned to receive norepinephrine in the dose of 4 mcg/ml bolus, while group P was set to receive phenylephrine in the dose of 50 mcg/ml bolus, anytime the systolic arterial pressure fell below 20% of the baseline. An anesthesiologist in the operating room treated hypotension with a vasopressor-labelled syringe and gathered data for analysis. The vasopressor used was concealed from both the patient and the anesthesiologist. The sensory blockage was found to be at its highest level. During the intraoperative period, the following parameters were measured: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and Spo2. Blood pressure and heart rate were checked every 2 minutes until 10 minutes, and then every 5 minutes until the procedure was completed. A value of 20% below the normal value was measured and recorded. When the MAP fell below 20% of baseline, group P patients got a 50mcg intravenous bolus of phenylephrine, while group N patients received a 4mcg intravenous bolus of norepinephrine. Immediately following the baby's delivery, oxytocin was administered as a 10U slow IV infusion and a 5U IV bolus. The entire dose of vasopressor and intravenous fluid administered throughout the surgery was documented, along with any instances of hypotension, bradycardia, tachycardia, or hypertension. Bradycardia was defined as a heart rate (HR) of below 50 beats per minute (bpm) and was treated with 0.6 mg of intravenous atropine.HR over 120 bpm was deemed tachycardia. Hypertension was defined as a 20% rise in systolic blood pressure from baseline. The incidence of hypertension following norepinephrine or phenylephrine boluses was reported. APGAR scores in the first and fifth minutes were recorded. Within five minutes of the cord clamped, a sample of the umbilical vein was obtained and

submitted for an ABG study. The pH, pCO2, bicarbonate, and base excess were observed. A pH <7 is referred to as fetal acidosis. The Time taken for skin incision to infant birth was noted. Instances of nausea, vomiting, or Light headedness brought on by maternal hypotension were also noted.

The primary objective of our study was to determine how many intravenous bolus doses of norepinephrine or phenylephrine were needed to treat spinal hypotension in individuals receiving a subarachnoid block for cesarean delivery. The secondary goals included comparing maternal and fetal outcomes, such as the Apgar score and umbilical vein blood gases, for incidences of bradycardia, hypertension, nausea, and vomiting.

A minimum sample size based on the mean and standard deviation from the previous study with 99% confidence and 90% power was calculated as 26 in each group. All the statistical analysis was done in IBM SPSS 20.0 (SPSS Inc, Chicago, USA). For all continuous variables, the results are presented as mean ± standard deviation, and for categorical variables, as frequency. The association between two categorical variables was determined using Pearson's Chi-square test with continuity correction. For comparing the mean of continuous parameters among two categories, an independent sample t-test was used. The average Apgar score within the groups was compared using a paired sample t-test at 1 and 5 minutes. A difference with a P value of 0.05 was regarded as statistically significant.

Results and Discussion

The study comprised 52 patients who were allocated arbitrarily into two groups (Fig.1).

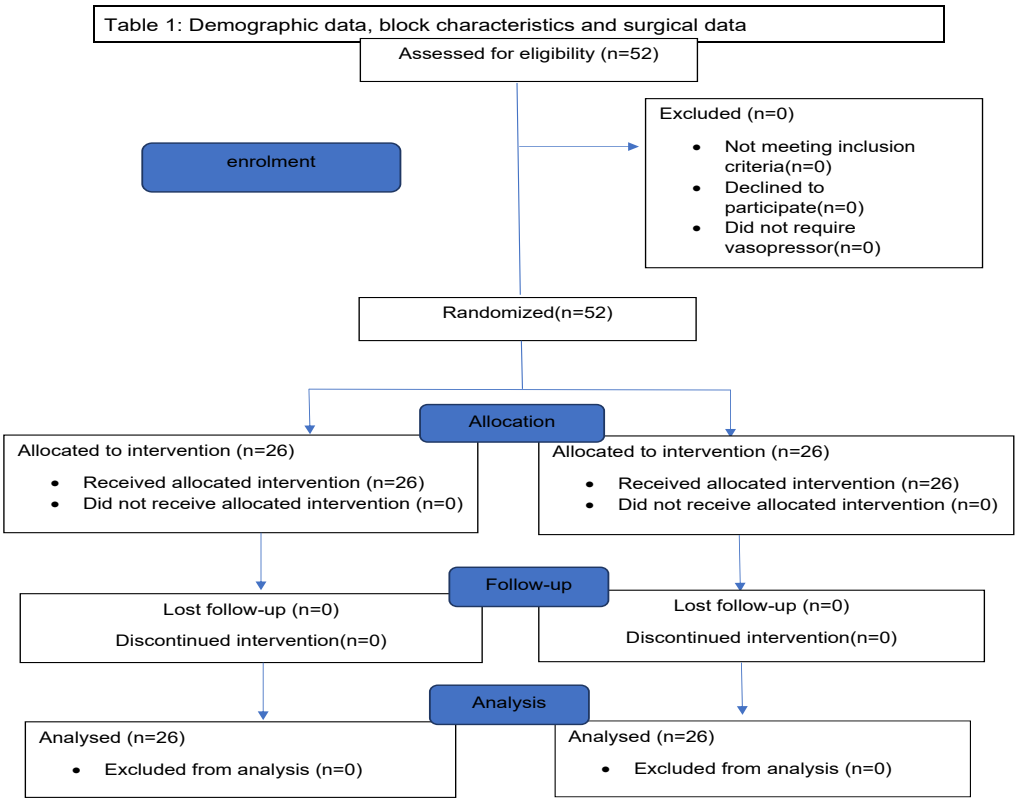


Figure 1.Consort flow diagram

Comparison of bolus doses of norepinephrine and phenylephrine in caesarean section

Table 1: Demographic data, block characteristics and surgical data			
Demographic data	**Group N(n = 26)**	**Group P(n = 26)**	**P value**
Age	29.6 ± 4.3	28.4 ± 2.4	0.225
Weight	71.8 ± 9.2	75 ± 9.4	0.217
Height	157.2 ± 4	157.8 ± 4.3	0.620
Dermatomal block			
T4	18 (69.2)	14 (53.8)	0.254
T5	8 (30.8)	12 (46.2)	
Skin incision to delivery	9.6 ± 1.9	9.5 ± 1.7	0.819

The mean age in group P was 28.4 ± 2.4 years and in group N was 29.6 ± 4.3 years. The mean weight in group P was 75 ± 9.4 kg and in group N was 71.8 ± 9.2 kg. The mean height of patient in group P was 157.8 ± 4.3 cm and in group N was 157.2 ± 4 cm.The patient demographics of both groups were comparable in age, height, weight, and ASA physical status. All patients attained sufficient spinal block height above T5, and the level of block height achieved was comparable across the groups with a p value > 0.05. In group N 69.2% parturients had height of block up to T4 and 30.8% parturients had block height up to T5. In group P, 53.8% had height of block up to T4 and 46.2% of parturients had a height of block up to T5. Additionally, the time taken for skin incision to delivery was comparable. Mean time between skin incision to delivery of the baby in group P was 9.5 ± 1.7 min and in group N was 9.6 ± 1.9 min (P = 0.842). (Table 1).

The number of boluses of vasopressors used to treat spinal hypotension was significantly lower in group N patients and was statistically significant (p<0.01) (Table 2) The incidences of nausea in the Group N and Group P showed no statistically significant differences. None of the patients in both the groups had any episodes of vomiting. (Table 3)Umbilical blood gas analysis and other neonatal outcomes are shown in Table 4.

Table 2 : Number of bolus doses of vasopressors			
Number of bolus doses	Group N (n = 26)	Group P (n = 26)	p
1	16 (61.5)	4 (15.4)	p<0.01
2	7 (26.9)	11 (42.3)	
3	3 (11.5)	8 (30.8)	
4	0 (0)	3 (11.5)	

Table 3: Distribution of nausea and vomiting based on group				
Nausea	N Group		P Group	
	Count	Percent	Count	Percent
No	26	100.0	26	100.0
Yes	0	0.0	0	0.0

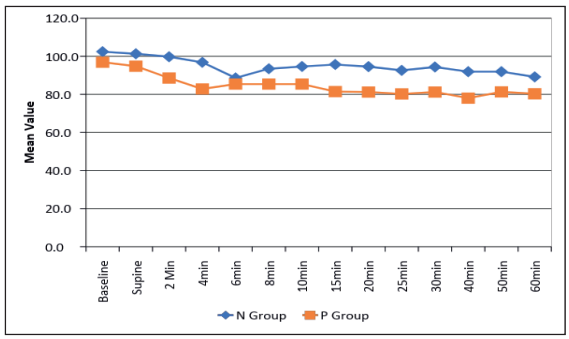
Table 4 : The mean umbilical artery pH in group P was 7.3 ± 0.1and in group N was 7.3 ± 0.1.				
		Group N (n = 26)	Group P (n = 26)	p
Umbilical pH		7.3 ± 0.1	7.3 ± 0.1	0.960
PCO2		50.5 ± 9.7	51.5 ± 11.6	0.734
PO2		19.7 ± 7.8	21.7 ± 8.6	0.371
HCO3		21.8 ± 2.5	23 ± 2.6	0.107
Base excess		-3.2 ± 1.8	-2.8 ± 1.8	0.446
APGAR 1	8	0 (0)	1 (3.8)	
	9	26 (100)	25 (96.2)	
APGAR 5	8	0 (0)	0 (0)	
	9	26 (100)	26 (100)	

The mean umbilical artery pH in group P was 7.3 ± 0.1and in group N was 7.3 ± 0.1. The The neonatal umbilical artery pH were similar. in the phenylephrine group. PCO2,PO2,HCO3 and base excess were comparable and there was no statistical difference. The mean Apgar score at 1 min and 5 min were also similar. The mean Apgar sore in group P at 1 min was 8 for 3.8% and 9 for 96.2% and at 5 min was was 9 for all patients (100%) [Table 4].

The mean Apgar score in group N at 1 min and 5 min was 9 for all the patients (100%). No neonate had fetal acidosis, defined as pH <7.18.

Maternal hemodynamic parameters such as HR, SBP, DBP, and MAP were comparable between the two groups. The baseline heart rate was 96.9 ± 11.9 beats/min and 102.4 ± 13.8 beats/min in P group and N group respectively (*P* = 0.131). On comparison of maternal heart rate between group N and group P, group P patients had more frequency of change of heart rate from the baseline in 2minutes to 10 minutes till the delivery of the baby and thereafter continued till the end of surgery which was statistically significant (p<0.05) (fig 2).

Figure 1. Comparison of Maternal heart rate at different periods between two groups



However, no patients developed significant bradycardia (HR<50) .On comparison of systolic and diastolic blood pressure between group N and group P, there is no episodes of hypotension(<20% from the baseline) or hypertension(>20% from the baseline) in both the groups and the results are comparable (Fig 3 and Fig 4).

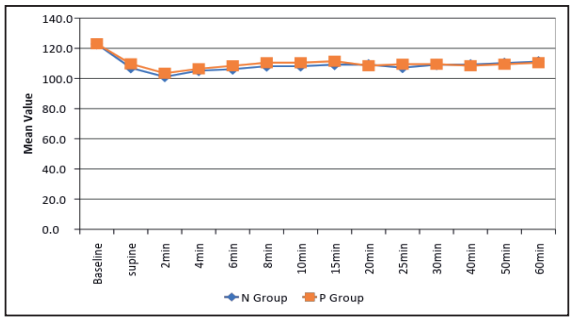


Figure 3. Comparison of systolic blood pressure at different periods

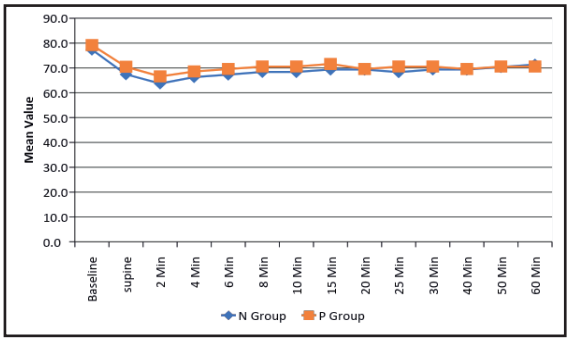


Figure 4. Comparison of mean arterial pressure at different periods

Mean Arterial Pressure (MAP) (Figure 5) amongst the two groups were comparable between group N and group P, and there was no episodes of hypotension(<20% from the baseline) or hypertension(>20% from the baseline) in both the groups.

The subarachnoid block is the preferred method for an uncomplicated caesarean section to prevent general anaesthesia risks. It is technically simple and reliable and provides a rapid onset of dense lumbosacral and thoracic anaesthesia with low doses of local anaesthetic and opioids. However, its main drawbacks are the short duration of anaesthesia and difficulty in controlling the degree of sensory blocking. In addition, significant sympathetic blockade brought on by subarachnoid block results in hypotension, which can happen in up to 85%

of cases(17).Several measures for the prevention and treatment of spinal block-induced hypotension are used in clinical practice, such as co-loading with crystalloid and colloid infusion, wrapping of lower limbs with compression stockings or bandages, administering an optimal dose of local anaesthetic and achieving an optimal spinal block level, left tilt positioning, and administering inotropes and vasopressors. Neonates of women with subarachnoid block-induced hypotension were found to have significant acidosis (18).

This study was conducted among 52 parturients scheduled for elective cesarean delivery under spinal anaesthesia and met the American Society of Anesthesiologists (ASA) physical class I and II requirements. It compared the effects of intermittent bolus doses of norepinephrine and phenylephrine in treating spinal-induced hypotension during caesarean section.

The study's findings demonstrated that intermittent boluses of intravenous norepinephrine could effectively treat spinal hypotension while having no adverse effects on neonatal or maternal outcomes. Also, norepinephrine required significantly fewer bolus doses than phenylephrine to treat spinal hypotension. The vasopressor can be infused or administered in intermittent boluses to treat spinal-induced hypotension in pregnant women. International consensus statement on vasopressor use for the management of post-spinal hypotension recommends prophylactic vasopressor infusion (19). Infusions provide tighter blood pressure management with less anesthesiologist involvement (20). In environments with limited resources, when infusion pumps are either unavailable or seldom available, the use of intermittent boluses of the medication may be practical. As a result, several hospitals employ bolus doses of phenylephrine to treat hypotension brought on by subarachnoid blockade, even when phenylephrine infusions are superior to boluses.

According to the study's findings, patients in group P had significantly lower heart rates than those in group N between 2 and 4 minutes and again between 10min and until the end of surgery. This difference was statistically significant. Interestingly, none of the patients experienced marked bradycardia (HR< 50 bpm).. Sharkey et al. (21) research from 1993 similarly revealed that the N group experienced less bradycardia than the P group. The more pronounced fall of HR in group P was a result of its α-adrenergic agonist characteristics, which have a dose-related tendency to lower heart rate (HR) and cardiac output (CO), occurring even when blood pressure is maintained at baseline (22).

On the other hand, norepinephrine's direct positive chronotropic and reflexive negative chronotropic activities resulted in a lesser decline in HR. Norepinephrine is a weak-adrenergic agonist, inhibiting the reflex lowering of heart rate. Many studies comparing norepinephrine and phenylephrine came to similar conclusions (23).

Other maternal measures, such as SBP, DBP, and MAP, were comparable between the two groups. Mean arterial pressure (MAP) is more important than systolic blood pressure as a determinant of organ perfusion. Because of the unique nature of low-resistance uteroplacental vessels that handle the massive increase in uterine perfusion throughout gestation, maternal-placental blood flow is driven by maternal arterial pressure (24). The percentage drop in placental perfusion is related to the percentage fall in maternal arterial pressure rather than the absolute pressure reduction.

The fetal acid-base status of umbilical cord blood and newborn Apgar scores were similar but not statistically significant between the two groups. In recent research of over 600 singleton pregnant women, it was discovered that umbilical arterial pH was identical between norepinephrine and phenylephrine. In contrast, phenylephrine was linked with a greater risk of bradycardia (25). However, researchers have found that norepinephrine has a better umbil-

ical arterial base excess than phenylephrine (26). Vallejo et al. (27) discovered comparable results in their investigation. They found no variations in the proportion of Apgar scores at 1 and 5 minutes or in umbilical venous cord blood gases across groups. Similarly, maternal and fetal outcomes, and similar umbilical blood gas readings in healthy parturients, have been reported in studies using norepinephrine and phenylephrine (25,28).

The dosing protocol for this study was developed from findings of earlier research by Puthenveettil N et al (16) and Ngan Kee et al (25) we used 4 µg of norepinephrine to treat hypotension as 4 µg of norepinephrine was found to be equipotent to 50 µg of phenylephrine. In a study by Mohta et al (15), norepinephrine was 11 times more potent than phenylephrine, and 100µg phenylephrine was equivalent to 9 µg of norepinephrine.

There are controversies regarding the use of norepinephrine through peripheral veins, but none of the patients in our study developed any irritation or side effects from the drug. Also, norepinephrine is considered cheaper than phenylephrine.

The limitation is that we did not measure maternal cardiac output directly while using a vasopressor drug. Furthermore, a large sample size could have provided better knowledge about the effects on both mother and the fetus.

The primary drawback of the current study was that we did not track the cardiac output while using a vasopressor to maintain the systolic pressure but measured heart rate, which is regarded as the “best surrogate indicator of cardiac output during cesarean delivery.” Additionally, a bigger sample size may have offered a more comprehensive view of the impacts on the mother and the fetus.

Conclusion

Norepinephrine intermittent boluses are beneficial in treating spinal anaesthesia-induced hypotension following caesarean delivery. With norepinephrine, fewer bolus dosages were necessary. Phenylephrine is equivalent to newborn arterial blood gases and Apgar scores. Boluses of norepinephrine can be substituted for phenylephrine.

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