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ORIGINAL RESEARCH

Prophylactic Use of Continuous Norepinephrine at a Dose of 0.05 mcg/kg BW/min in Spinal Anaesthesia for Cesarean Section Patients in Ketapang

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ABSTRACT

Background: Norepinephrine infusion decreases hypotension after spinal anesthesia during a cesarean section. There is an increasing attitude toward using norepinephrine to prevent spinal hypotension. There hasn't been much investigation on the use of norepinephrine in spinal anesthesia in Indonesia, particularly for cesarean sections in rural areas.

Methods: In this single-blinded norepinephrine group. Randomized clinical trial: The norepinephrine group was given continuous norepinephrine before spinal anesthesia. Parturients for elective and emergency cesarean section were allocated to receive norepinephrine infusion (0.05 mcg/kg BW/mnt. Our primary outcome was the incidence of hypotension within 36 min of spinal anesthesia administration. Secondary outcomes included side effects such as nausea, vomiting, and chills during surgery.

Result: In total, 92 patients were enrolled. Of these patients included in the final analysis. Patients who suffered hypotension showed hypotension at minute zero and minute twelve (14.13 %), minute twenty-four (13.04 %), and minute thirty-six (18.47 %)—the frequency of chills and nausea/vomiting. Three (3.26 %) and eight (8.89 %) participants in the norepinephrine group reported feeling chills and nausea/vomiting.

Conclusion: prophylactic norepinephrine infusion may reduce HR without increasing the risk of post-spinal hypotension following cesarean delivery.

Keywords: Hypotension; Spinal anesthesia; Norepinephrine; Cesarean section.

INTRODUCTION

For patients undergoing cesarean sections, spinal anesthesia is the best option technically. Post-spinal anesthetic hypotension is one of the most frequent consequences following cesarean delivery, and without pharmaceutical prevention, the prevalence of hypotension can reach up to 70% to 80%. Ephedrine and phenylephrine are two of the more popular vasoactive medications. While phenylephrine is linked to a high incidence of bradycardia, ephedrine has a slow onset of action and a protracted duration, making appropriate blood pressure titration challenging. Fetal tachycardia may manifest as ephedrine passes through the placenta quickly. Complications such as nausea, vomiting, and fetal compromise may result from this. Unexpectedly, fetal acidosis risk is increased by the preventative procedures of fluid preload, lateral tilt, and vasoactive drugs. It has been demonstrated that the fetal acid-base balance is less favorable following ephedrine administration than following phenylephrine administration, even in healthy parturients with no fetal impairment[1].

Currently, ephedrine has become the first-line standard for the management of hypotension in cases of obstetric anesthesia because it is safe to use, easy to obtain, and often used by anesthesiologists.

Recently, norepinephrine has been studied as a vasopressor for sustaining arterial blood pressure during spinal anesthesia for Caesarean delivery. Norepinephrine is a potent alpha-adrenergic receptor agonist with similar vasoconstrictor activity to phenylephrine. But unlike phenylephrine, norepinephrine also has mild beta-adrenergic receptor agonist activity that prevents the bar reflective declines in heart rate and cardiac output that frequently happen with unopposed stimulation of vascular alpha-adrenergic receptors. Therefore, using norepinephrine instead of phenylephrine may lead to higher maternal hemodynamic stability. It has been proposed that norepinephrine is the best vasopressor for obstetric spinal anesthesia[2].

By administering a prophylactic norepinephrine dosage at 0.05 mcg/kg BW/min, post-spinal hypotension was reduced from 62.24 % to 17.53 % in another trial[3].

Since there hasn't been much investigation on the use of norepinephrine in spinal anesthesia in Indonesia, particularly for cesarean sections in rural

areas, this study was carried out to gather information.

METHODS

From July through September 2022, pregnant women who underwent cesarean sections at RSUD Dr. Agoesdjam and RSIA Permata Bunda Ketapang West Kalimantan served as the study's subjects. For the sampling, consecutive samples were taken from research participants who met the inclusion and exclusion criteria. The number of participants in the research sample was calculated to be 92 using simple random sampling. ASA II, gestational age greater than 18 years, ASA II, and spinal anesthetic procedures were required for inclusion. Patients who satisfied the following criteria were excluded: hypertension, morphological anomalies of the heart and blood vessels, DM, thyroid, BMI > 40 kg/m2, neurological problems (stroke, seizures), and usage of cardiac drugs/hypertension. Patients with failed spinal anesthesia and bleeding greater than 750 ml were excluded from the study.

The study included people who had spinal anesthesia operations performed during elective or emergency cesarean births. It was both prospective and observant. The study aimed to assess how continuous norepinephrine prophylaxis affected blood pressure measurements to prevent hypotension by spinal anesthetic during cesarean delivery. Data was collected at minutes 0, 12, 24 and 36. Minute 0 was the time after spinal anesthesia was performed on the patient and he was laid down.

The norepinephrine solution was created by mixing one ampoule of norepinephrine (4 mg/4 ml) with up to 50 ml of distilled water in a 50 ml syringe. The patient was then linked to the solution via an extension tube and entryway. A 0.05 mcg/kg/min norepinephrine dose was administered using a syringe pump. An RL + triway infusion was already set up when the patient entered the surgery room. Ondansetron 4 mg IV and dexamethasone 5 mg IV were used as premedication, and the patient was then put on a non-invasive monitoring device (NIBP, O2 saturation). Norepinephrine is injected for two to three minutes before spinal anesthesia.

Hyperbaric Bupivacaine 12 mg with adjuvant intrathecal morphine 100 mcg for spinal anesthesia. After performing aseptic procedures, the patient was made to sit down, and an intrathecal injection of spinocaine was administered at L4-L5 using a No. 26 spinocaine needle. The

spinal block height was assessed after the patient was placed back supine after the intrathecal injection. Before and every 12 minutes following spinal anesthesia, vital Signs (BP, pulse, and MAP) and side symptoms (nausea, vomiting, and chills) were recorded. A 0.5 ml bolus of norepinephrine solution and 25 mg of pethidine are administered for hypotension. IV is administered for shivering. Using SPSS version 27.0 for Windows, the data will be processed and presented in tables and graphs.

RESULT

The study involved 92 RSUD Dr. Agoesdjam and RSIA Permata Bunda Ketapang patients. They were scheduled to have a cesarean section under spinal and regional anesthesia and met the inclusion and exclusion criteria for the study. In the norepinephrine group, there were 92 participants. The characteristics of the research subjects can be seen in Table 1.

Table 1. Characteristics of Research Subjects

Variable	Norepinephrine group N= 92
Age	
Mean±std	27,90±6,60
Median	27,00
Range(Min-Max)	18 - 45
Height (cm)	
Mean±std	151,02±6,74
Median	150,00
Range(Min-Max)	139 -170
Weight (kg)	
Mean±std	65,11±10,22
Median	65,00
Range(Min-Max)	46 - 90
BMI	
Mean±std	28,55±4,25
Median	27,62
Range(Min-Max)	20,08 - 42,81

Table 2 compares systolic blood pressure (TDS) reduction between the second and the zero, twelve, twenty-four, and thirty-six minutes. The statistical tests at minutes 0 and 24 revealed a statistically significant difference, indicated by a p-value of 0.05. While the P value for the 12th and 36th-minute systolic blood pressure drop

variables was more significant than 0.05 (p-value 0.007), it is not statistically significant. Thus, it may be explained why Systolic Blood Pressure has a statistically similar mean (TDS). Table 2 compares diastolic blood pressure (TDD) reduction between the second and the zero, twelve, twenty-four, and thirty-six minutes. The statistical tests revealed a statistically significant difference at the 0^{th}(p-value 0.001),12th minutes (p-value 0.001), and at the 24th (p-value 0.001)and 36th minutes (p-value 0.001). This explains why most of the mean differences in TDD are statistically significant.

Table 2. Characteristics of Blood Pressure, MAP, Pulse in the Norepinephrine Group N=92

Variable	T-2	T0		T12		T24		T36	
			P value		P value		P value		P value
Systole			0.003		0.081		0.001		0.007
Mean±std	125,53±13,399	120,51±17,075		122,60±15,416		119,07±12,942		120,63±14,797	
Median	124,50	121,50		123,00		118,00		120,00	
Range(Min-Max)	101 - 154	86 - 155		87 -168		90 - 159		79 - 158	
Diastole			0.001		0.001		0.001		0.001
Mean±std	77,57±10,447	70.46±13.549		72.2±12.094		71.14±11.986		69.15±13.450	
Median	77,00	70,00		72,00		71,00		70,00	
Range(Min-Max)	54 - 104	35 - 105		39 - 96		46 - 97		35 - 101	
MAP			0.001		0.002		0.001		0.001
Mean±std	91,34±13,072	85,72±16,269		86,97±12,702		84,70±12,977		84,72±13,846	
Median	92,00	84,50		86,00		83,50		84,50	
Range(Min-Max)	66 - 138	49 - 140		54 - 122		57 - 122		53 - 119	
Pulse			0.274		0.001		0.001		0.001
Mean±std	91,04±16,336	89,42±17,742		82,40±15,154		84,66±13,423		81,72±13,306	
Median	89,00	86,00		80,50		84,00		79,00	
Range(Min-Max)	61 - 137	61 - 137		43 - 131		62 - 124		49 - 128	

Note: for numerical data, the p-value is tested by paired samples test if the data is usually distributed with the Wilcoxon signed ranks; try an alternative if the information is not normally distributed. The value of significance is based on the value of $p<0.05$. The * sign indicates the value of $p<0.05$, which is statistically significant.

Table 2 compares the mean arterial pressure (MAP) drop between the second minute and the 0th, 12th, 24th, and 36th minute. Statistics tests at the 0^{th} (p-value 0.001), 12^{th} (p-value 0.002),24^{th} (p-value 0.001), and 36th minutes (p-value 0.001) revealed a statistically significant difference, denoted by the p-value 0.05. In light of this, it may be understood why most of the mean differences in MAP are statistically significant.

Table 2 compares the drop in pulse between the second minute and the 0th, 12th, 24th, and 36th minute.

Statistics tests conducted at the 12th (p-value 0.001), 24th (p-value 0.001), and 36th minutes (p-value 0.001) revealed statistically significant differences, as shown by the p-value of 0.05. The P value for the variable measuring the decline in systolic blood pressure at the 12th minute was higher than 0.05 (p-value 0.081), indicating that it is not statistically significant. Therefore, it makes sense that pulse accounts for most of the statistically significant mean differences.

Table 3. The incidence of hypotension

Variable	Norepinephrine group N=92							
	T0	P value	T12	P value	T24	P value	T36	P value
Hypotension		< 0.001*		< 0.001*		< 0.001*		< 0.001*
Yes	13 (14,13 %)		13 (14,13%)		12 (13,04%)		17 (18,47%)	
No	79 (85,87%)		79 (85,87%)		80 (86,96%)		75 (81,53%)	

In Table 3, the prevalence of hypotension is displayed. Thirteen (14.13 %) of the 92 participants in the norepinephrine group showed hypotension at minute zero and minute twelve (14.13 %), minute twenty-four (13.04 %), and minute thirty-six (as many as 17 participants) (18.47 %). A statistically significant difference in the incidence of hypotension was seen, as demonstrated by the p<0.05.

Table 4 displays the frequency of chills and nausea/vomiting. Three (3.26 %) and eight (8.89 %) of the 92 norepinephrine participants reported chills and nausea/vomiting. The p-value of 0.05 indicates a statistically significant difference between shivering.

Table 4. Number of Side Effects

Variable	Norepinephrine group N=92	
		P value
Nauseous vomit	3 (3,26%)	<0.005*
Shivering	8 (8,89%)	<0.005*

DISCUSSION

There is still a concern with Preventing and treating maternal hypotension caused by spinal anesthesia after cesarean section. Many studies have been done to avoid the harmful effects of hypotension by providing the best way to prevent these occurrences. Fluids, medications, reduced local anesthetics, and mechanical methods like patient posture can all be used to avoid hypotension. It is intended to enhance intravascular volume by giving fluids via intravenous infusion before spinal anesthesia. Norepinephrine, ephedrine, and phenylephrine are a few examples of vasopressor medications that are frequently administered[4].

Norepinephrine has modest -adrenergic receptor action. -adrenergic receptor agonist action. Hence, it may be a suitable vasopressor alternative to safeguard maternal blood pressure and have fewer adverse effects on heart rate and cardiac output. In the literature, it was discovered that administering preventative norepinephrine is more effective at preventing postspinal hypotension compared to phenylephrine or ephedrine. The phenylephrine pure-agonist action is one of the primary justifications for the start of research on norepinephrine in obstetric anesthesia; it is reported to cause reflex bradycardia and diminished heart performance due to activation of the baroreceptors. One advantage of norepinephrine over Phenylephrine is that it does not cause maternal bradycardia. We didn't see any differences in bradycardia incidence across the groups. However, there is a large discrepancy in HR readings[5].

Norepinephrine is more effective than ephedrine at preventing and treating spinal hypotension, and it also has fewer adverse effects on heart rate in patients having lower limb orthopedic procedures[6].

Ninety-two women with spinal anesthesia for a cesarean section participated in this study. The prophylactic injection of norepinephrine at a dose of 0.0 5 mcg/kg, BW/min was seen in this investigation. The basis for selecting a dose of 0.05 mcg/kg/min is because several previous studies have used this dose. The choice of minute 2 is because, from the time the patient is laid down on the operating table, norepinephrine is administered until the spinal anesthesia is performed, which takes

approximately 2 minutes. Systolic blood pressure characteristic data revealed statistically significant similarities, but diastolic blood pressure, MAP, and pulse revealed statistically significant differences. Comparison of incidence of hypotension differed at 0, 12, 24, and 36 minutes statistically significantly.

Norepinephrine was found to sustain maternal blood pressure during cesarean delivery with few bouts of hypotension, nausea, vomiting, chills, and tachycardia. This relates to various earlier investigations that have been conducted.

Norepinephrine infusion shows potential neonatal benefits compared to ephedrine bolus in individuals undergoing elective cesarean sections under spinal anesthesia, causing less hypotension and tachycardia[7]. The effectiveness of norepinephrine bolus five mcg versus ephedrine bolus 10 mg in preventing maternal hypotension after cesarean section under spinal anesthesia was examined. They showed that the norepinephrine bolus group had lower maternal blood pressure, heart rate fluctuations, and less need for rescue, i.v. Bolus. Despite using a different norepinephrine bolus dose of 5 mcg, their findings are consistent with the current study regarding the stability of Maternal hypertension in the norepinephrine group.

To prevent maternal hypotension during cesarean section under spinal anesthesia, Xu and colleagues compared norepinephrine infusions of 4 mcg/min with ephedrine infusions of 4 mg/min. Compared to ephedrine infusion, they showed that norepinephrine infusion was linked to fewer instances of tachycardia,

reduced heart rate variation, systolic blood pressure, and better fetal outcomes, as evidenced by higher base excess and lower lactate readings. The current investigation's conclusions differ from those of Xu and his colleagues in this region because the fetal outcomes for the norepinephrine and ephedrine groups were comparable[9].

To prevent maternal hypotension after cesarean section, Wang et al. tested the effectiveness of norepinephrine bolus four mcg and ephedrine infusion bolus 4 mg. Even under spinal anesthesia, they showed that norepinephrine bolus was linked to reduced incidences of bradycardia and tachycardia, as well as more significant

base excess and lower lactate levels. Only bolus doses were successful in this study's two groups, albeit this may be due to the study's exclusion of preeclamptic parturients, who may have had different types of pregnancies[10].

Treatment with norepinephrine was found to reduce the incidence of IONV regarding maternal outcomes. There is consensus that the etiology of IONV is the reactive and multifactor treatment of established hypotension, as practiced research today, compared to preventive medicine, has previously been linked to a higher risk of IONV.

Vasopressor infusion before the onset of hypotension. Some circumstances, such as maternal demography, a history of IONV or motion sickness, surgical operations may have caused IONV,
certain drugs and opioids used during surgery or peritoneal traction[11].

CONCLUSION

According to our findings from prospective research, prophylactic norepinephrine infusion may reduce HR without increasing the risk of post-spinal hypotension following cesarean delivery, improving the stability of hemodynamics and raising the risk of bradycardia. Although prophylactic norepinephrine infusion successfully reduces spinal-induced hypotension during cesarean deliveries, more study is required to confirm this. The literature lacks sufficient investigations on the subject.

CONFLICT OF INTEREST

The Authors declare that have no conflict of interest.

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