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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Comparison of intermittent boluses of noradrenaline vs. phenylephrine for spinal anesthesia induced hypotension during cesarean delivery

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ABSTRACT

Background and Objective: Maternal hypotension is a common consequence of spinal anesthesia for cesarean delivery (CD). A vasopressor is recommended in addition to adequate fluid loading to raise mean arterial pressure in pregnant women. Phenylephrine, a pure α–adrenergic receptor agonist, is the first-line agent to manage it. However, phenylephrine is associated with dose-dependent reflex bradycardia and decreased cardiac output. Noradrenaline is suggested as an alternative due to its mild beta-adrenergic effect, which results in a greater heart rate and cardiac output than phenylephrine. We compared the effectiveness and adverse effects of intermittent boluses of noradrenaline with phenylephrine to treat spinal-induced hypotension during CD.

Methodology: A randomized controlled trial was conducted at Bach Mai Hospital, Vietnam, from May 2020 to August 2020. There were 120 pregnant women undergoing elective CD under spinal anesthesia enrolled in the study and divided randomly into two groups: the Group N and the Group P. Group N patients were given noradrenaline 6 µg as an intravenous bolus, and Group P patients were given phenylephrine 100 µg to treat spinal-induced hypotension. The primary outcome was the number of bolus doses of vasopressors needed to treat maternal hypotension. Secondary outcomes were bradycardia, hypertension, nausea, vomiting, umbilical arterial blood gases, and APGAR scores.

Results: The number of boluses of vasopressors needed to treat hypotension and maternal hemodynamic changes was equivalent in both groups. The incidence of bradycardia, nausea, and vomiting in the two groups was not significantly different. No pregnant woman suffered from unintended hypertension. APGAR scores were 7 and above at one min and 10 and above at five min for all cases. There were no differences in umbilical arterial pH values between the two groups (7.33 vs. 7.34; $P > 0.05$).

Conclusion: Noradrenaline 6 µg and phenylephrine 100 µg boluses were equally effective in treating spinal-induced hypotension in parturients undergoing cesarean delivery with similar neonatal and maternal outcomes.

Abbreviations: CD - Cesarean Delivery; HR - Heart Rate; CO - Cardiac Output; SVR - Systemic Vascular Resistance; SBP - Systolic Blood Pressure; ED 90 - 90 Percent Effective Dose

Key words: Anesthesia, Spinal; Hypotension; Cesarean Delivery

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1. INTRODUCTION

Maternal hypotension is a common complication after spinal anesthesia for cesarean delivery despite of fluid loading, which can affect 90 percent of women.[1] It is a physiological response that contributes to adverse maternal and fetal outcomes. Thus, effective prevention and management of spinal – induced hypotension are important issues that should be continuously investigated in order to minimize adverse effects on mothers and fetuses.[2] In addition to intravenous fluid loading, prompt and appropriate treatment of hypotension with vasopressors is essential to prevent detrimental maternal and fetal effects. Phenylephrine is considered the first-line vasopressor in obstetric anesthesia to manage maternal spinal – induced hypotension because it causes lower incidence of acidosis in fetus compared with ephedrine.[3] Recently, noradrenaline has been suggested as a potential alternative to phenylephrine because it is a potent vasopressor with mild β-adrenergic properties. Therefore, it does not have potential to cause bradycardia and reduce cardiac output as much as phenylephrine.[4,5] The purpose of our study is to compare the effectiveness of intermittent intravenous boluses of noradrenaline with phenylephrine to manage hypotension during spinal anesthesia for cesarean delivery.

2. METHODOLOGY

A randomized controlled trial was conducted at Bach Mai Hospital, Hanoi, Vietnam from May 2020 to August 2020. The Research Ethics Committee of Bach Mai Hospital (No 3365/QD-BM) approved the study. Written informed consent was obtained from all patients after adequate information regarding the study requirements, purposes, and risks. The inclusion criteria were: aged 20-40 y, ASA physical status I and II, height 150 to 160 cm, scheduled for elective cesarean sections, healthy singleton pregnancy beyond 36 weeks' gestation. Exclusion criteria were: parturient with a contraindication to spinal anesthesia; allergy to noradrenaline or phenylephrine; severe cardiovascular disease; fetal abnormalities; and patient refusal.

One hundred twenty patients who met the inclusion criteria were subjected to a complete history taking, physical examination. Patients were randomly divided into Groups N (who received noradrenaline) and P (who received phenylephrine) to treat hypotension. In the operating room, an 18-gauge intravenous cannula was placed, and standard monitoring with non-invasive arterial pressure, electrocardiography and continuous pulse oximetry was established. The baseline vital signs were recorded. The parturients were transfused with 6 ml/kg of normal saline before the intrathecal injection. Spinal anesthesia was performed at L2-L3 level with 0.03 mg fentanyl and 8 mg of 0.5% hyperbaric bupivacaine for patients with height of 150-155 cm, or 8.5 mg for those of 156-160 cm, using 25G Whitacre needle in the left lateral position. The patients were then positioned supine, administered oxygen 3L/min via nasal prongs. The highest level of sensory blockade achieved was evaluated with alcoholic skin prep 5 min after spinal injection. Blood pressure and heart rate were recorded every minute within first 10 min, and every 2 min until the end of the surgery. Noradrenaline diluted in a 20-ml syringe to give noradrenaline 2 µg/ml when needed. Phenylephrine 50 µg/ml was used in a 10-ml pre-filled syringe. When systolic arterial pressure dropped below 20% of the baseline (defined as hypotension), Group N received 6 µg (3 ml) noradrenaline and Group P received 100 µg (2 ml) phenylephrine as intravenous boluses and repeated further doses until the blood pressure was stable. Patients who developed bradycardia (HR < 60 bpm) were given 0.5 mg atropine intravenously. Hypertension is defined as a 20% increase in systolic blood pressure. After delivery, the mothers were given 10 IU of oxytocin by slow infusion. APGAR scores were noted by pediatrician at 1 and 5 min. An umbilical arterial sample was taken at the time of birth for blood analysis. Fetal acidosis was defined as pH < 7. The adverse effects on parturient such as nausea and vomiting, were also noted.

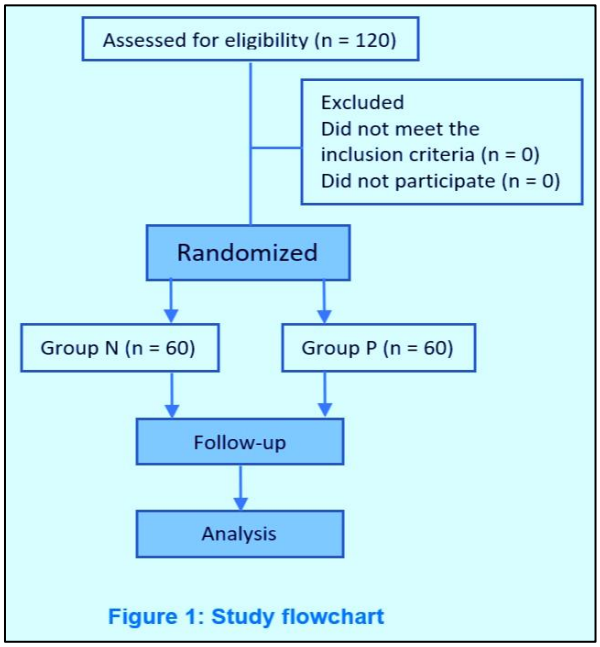

Figure 1: Study flowchart

Table 1: Patient characteristics and surgical data

Characteristics		Group N (n = 60)	Group P (n = 60)	P - value
Maternal age (y)		28.7 ± 3.12	29.23 ± 3.63	P > 0.05
Weight (kg)		64.3 ± 8.02	66.42 ± 8.39	
Height (cm)		156.95 ± 4.84	157.67 ± 4.97	
Fluid transfusion (ml)		898.1 ± 95.55	920.8 ± 83.7	
Spinal block level	T4	10	13	
	T6	60	60	
	T8	60	60	
	T10	60	60	
Onset time (min)		2.61 ± 0.46	2.58 ± 0.52	
Induction to delivery time (min)		8.24 ± 1.67	8.13 ± 1.55	
Duration of surgery (min)		41.24 ± 1.09	42.6 ± 1.35	

Data presented as Mean ± SD

Table 2: Hemodynamic changes and maternal complications

Variables	Group N (n = 60)	Group P (n = 60)	p-value
Number of boluses of vasopressor	1.67 ± 0.77	1.87 ± 0.9	P > 0.05
Bradycardia	0 (0%)	2 (3.33%)	
Unintended hypertension	0	0	
Nausea/vomiting	5 (8.33%)	8 (13.33%)	
Skin color change at injection site	0	0	

Data presented as mean ± SD or n (%)

Table 3: Fetal outcomes (mean ± SD)

Parameter	Group N (n = 60)	Group P (n = 60)	p-value
Fetal weight (kg)	3.36 ± 0,27	3.41 ± 0,26	P > 0.05
Apgar score at 1 min ≥ 7	100%	100%	
Apgar score at 5 min ≥ 10	100%	100%	
Umbilical arterial blood analysis			
pH	7.33 ± 0.27	7.34 ± 0.03	
pCO2	49.92 ± 5.93	53.42 ± 7.95	
pO2	17.33 ± 6.39	19.25 ± 7.05	
HCO3-	27.52 ± 2.35	26.93 ± 1.96	
Lactate	1.25 ± 0.24	1.43 ± 0.26	

Data presented as mean ± SD or %

The data of the patients were collected through questionnaires, physical examinations, and medical records, including patient characteristics before surgery (age, weight, height, ASA physical status classification system) and during surgery (arterial blood pressure, heart rate, number of doses of noradrenaline and phenylephrine, spinal block level, fluid transfusion, nausea, vomiting, APGAR scores, umbilical arterial blood analysis)

Statistical Analysis

Statistical analysis was performed using SPSS 20.0. Continuous variables are presented as mean ± standard deviation (SD) or median (lower quartile-upper quartile), while categorical variables are presented as percentages. The Student's t-test or the Mann-Whitney U-test were used for comparison between continuous variables. The chi-square test was used for the categorical variables. The odds ratio and 95% confidence intervals were calculated with the two-sided P values less than 0.05 indicating statistical significance.

3. RESULTS

One hundred twenty patients undergoing elective CD were assessed for eligibility during the study period. They were randomly allocated into 2 treatment groups: Group N (n = 60) and Group P (n = 60). Maternal characteristics, with respect to age, weight,

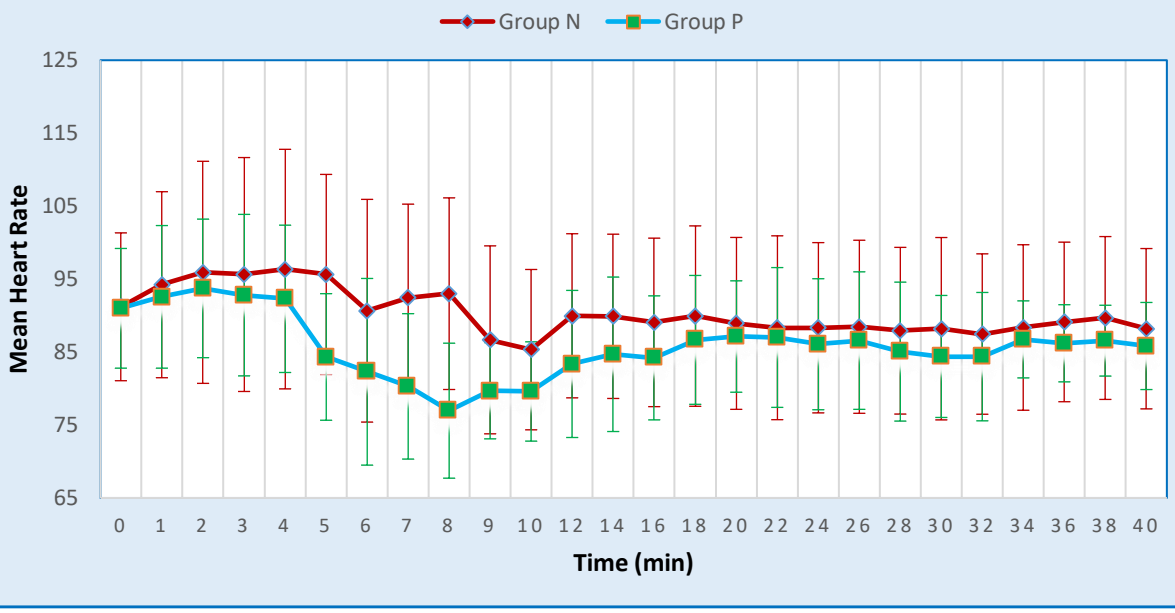

Figure 2: Comparative mean heart rate (beats/min) in two groups

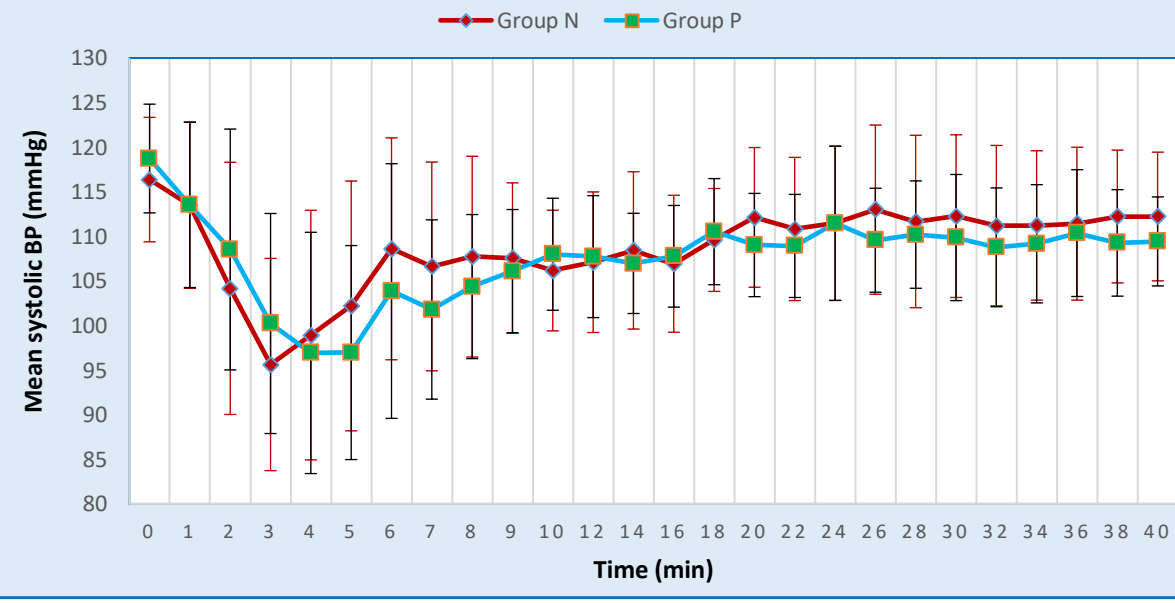

Figure 3: Comparative mean systolic blood pressure (mmHg) in two groups

height, were comparable and showed no statistically significant differences between two groups. All patients achieved a spinal block height of T6. The surgical times and total intravenous fluid transfused were comparable between groups (Table 1). The number of boluses of vasopressors required to manage hypotension was similar in two groups of patients (1.67 ± 0.77 vs 1.87 ± 0.9, 0.05). There were no significant differences in systolic blood pressure and the time at which hypotension occurred between two groups during both the predelivery and postdelivery periods (Figure 1). Maternal heart rate from 5 min to 12 min after intrathecal injection was lower in Group P than that in Group N ($P < 0.05$); at other times, the heart rate was similar in both groups (Figure 2). The incidence of bradycardia in two groups was also not significantly different (0% vs 3.33%, $P > 0.05$). Maternal complications such as nausea, vomiting and unintended hypertension are shown in Table 2. In terms of fetal outcomes, no statistical differences were noted (Table 3)

4. DISCUSSION

The results of our study showed that intermittent bolus doses of noradrenaline and phenylephrine were equally effective in treating spinal anesthesia-induced hypotension during cesarean delivery. The number of boluses was less in patients in which noradrenaline was used as compared to phenylephrine. The incidence of bradycardia was lower in noradrenaline group; the differences, however, were not statistically significant. In the first-published study to look at an intermittent bolus regime of noradrenaline to treat low blood pressure caused by the spinal anesthesia during a cesarean delivery, patients who were given noradrenaline had much less bradycardia than those who were given phenylephrine.[5] Research conducted on fifty pregnant women by Puthenveettil et al. showed similar results.[4]

Maternal hypotension is a common consequence of spinal anesthesia for cesarean sections because of a decrease in SVR and an increase in HR as a compensation to maintain blood pressure and cardiac output. Thus, the use of phenylephrine, a pure α-1 adrenergic agonist, was suggested as a first-line agent to treat hypotension in parturient.[6,7] Previous studies showed evidence that phenylephrine titrated to maintain maternal blood pressure at or near the baseline value can reduce the incidence of nausea and vomiting.[8] The use of phenylephrine, however, often causes a reflex reduction in HR and thus in CO, and this may cause undesirable effects on both the mother and the fetus.[9] Recently, intravenous intermittent boluses of noradrenaline were suggested as an alternative to phenylephrine for management of spinal-induced hypotension in cesarean sections, because noradrenaline was effective for hypotension treatment while preserving CO.[3] The mechanism is that noradrenaline acts on β-adrenergic receptors in addition to α adrenergic receptors. As a result, noradrenaline can cause an increase in both contractility and HR, increase in SVR, and thus mean blood pressure. Thus, the advantage of noradrenaline is that it preserves CO, and the incidence of reflex bradycardia is less than phenylephrine.[10]

Various studies have been conducted to find equipotent dose of intermittent boluses of noradrenaline and phenylephrine. The 90 percent effective dose (ED 90) of intermittent bolus of noradrenaline is 6 μg and that of phenylephrine is 100 μg.[10,11] Mohta et al. showed that noradrenaline was 11 times more potent than phenylephrine, so 100 μg phenylephrine was equivalent to 9 μg noradrenaline.[12] In the study conducted by Ngan Kee, 8 μg noradrenaline was approximately equivalent to 100 μg phenylephrine.[13] Based on ED 90 of intermittent boluses of noradrenaline and phenylephrine, we used the dose of 6 μg noradrenaline and 100 μg phenylephrine to manage spinal-induced hypotension in parturients in our study. Intermittent boluses of noradrenaline were as effective as phenylephrine in managing hypotension, and the incidence of bradycardia was lower than that of phenylephrine. The same dose of noradrenaline and phenylephrine used in the study by Sharkey AM et al. showed maternal hemodynamics and heart rate were less fluctuating with noradrenaline compared to phenylephrine.[5]

Maternal adverse effects such as nausea, vomiting, and unintended hypertension were reported less frequently with noradrenaline than with phenylephrine.[10,14] Our study, conducted on one hundred twenty parturient, observed no cases of unintended hypertension. The incidence of nausea and vomiting was similar in both groups. The mechanism of nausea and vomiting during cesarean sections was due to the use of intrathecal opioids and hypotension. Patients using noradrenaline experienced less nausea and vomiting, reflecting better cerebral and gut perfusion, less serotonin release, and less stimulation of brainstem vomiting center.[3]

There are concerns about the administration of vasopressors via peripheral veins because of vasoconstriction and skin necrosis. All vasopressors theoretically have a potential risk of tissue ischemia with extravasation when used peripherally. Recent studies, however, showed no evidence to support the concern that the use of noradrenaline increases the risk of tissue ischemia and necrosis.[3,10,13,15] Our results showed similar results with no skin ischemia in either group. The explanation can be that noradrenaline was diluted before being used and administered in a running fluid; spinal anesthesia causes an increase in peripheral perfusion, and noradrenaline does not counteract this effect.[16]

Regarding the safety of vasopressors in the fetus, the APGAR scores and umbilical arterial blood analyses were comparable between the two groups in our study. There were no statistical differences, and all values were in the normal range. The results were similar to those of the study conducted by Xu et al.[3] In the study by Ngan Kee, parturients receiving noradrenaline showed a lower level of noradrenaline in umbilical blood, a higher pH value, and a higher oxygen content than parturients receiving phenylephrine. This was because noradrenaline was thought not to cross the placenta, and the use of noradrenaline caused less fetal stress than phenylephrine.[17] The difference, however, was not statistically significant.

5. LIMITATONS

We did not evaluate invasive blood pressure or measure cardiac output directly. The benefits of noradrenaline and phenylephrine in the treatment of hypotension after spinal anesthesia for cesarean delivery and their adverse effects need further research.

6. CONCLUSION

In women undergoing elective cesarean delivery under spinal aesthesia, intermittent boluses of noradrenaline (6 µg) and phenylephrine (100 µg) used to treat spinal-induced hypotension were equally effective with similar maternal and neonatal outcomes.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of Interest

No potential conflict was declared by the authors.

9. FUNDING

No external or industry funding was involved in this study.

10. Authors' contribution

NTT: Concept and conduct of the study

HNC: Data collection and analysis

ANTH: Literature search and manuscript editing

THD: Statistical analysis and editing

QNS: Manuscript editing and review

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