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Original Article

Efficacy of Variable versus Fixed-Rate Infusion of Phenylephrine during Caesarian Section: a study from Rawalpindi, Pakistan

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ABSTRACT

Objective: To compare the efficacy of variable and fixed-rate infusion regimens of phenylephrine in prophylaxis of maternal hypotension during elective Cesarean section.

Study Design: Quasi-experimental study

Place and Duration of Study: Department of Obstetrics and Gynecology at the Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from Feb to Jul 2021.

Methodology: Study included 94 pregnant women all of whom were planned to undergo non-emergent Caesarian section at ≥37 weeks of gestation. Those who were >35 years old or had any history of medical comorbidities were excluded from the study. A fixed infusion regimen was injected to Group-A (n=47) at a continuous rate of 0.75µg/kg/minute, while Group-B (n=47) received a variable phenylephrine dosage, starting at 0.75µg/kg/minute which was increased to 0.9µg/kg/minute in case of hypotension, or reduced to 0.4µg/kg/minute in event of reactive hypertension. Furthermore, 100µg bolus was given if hypotension was noted intraoperatively. Any incidence of hypotension or other adverse events was recorded.

Results: Mean age for variable infusion and fixed infusion groups were 24.6±4.7 and 26.2±4.6 years respectively. Both the groups exhibited a significant role of phenylephrine in hypotension prophylaxis. A slightly lower incidence of hypotension was observed during fixed rate infusion (25.5%) as compared to the variable rate (38.3%). No significant intergroup variability was reported (p=0.954). Headaches and nausea/vomiting were the most prevalent postoperative complaints, with a slightly higher incidence in the variable rate group.

Conclusion: Both variable and fixed rates of phenylephrine infusion yielded a similar outcome during spinal anesthesia in elective C-section.

Keywords: Caesarian Section, Hypotension, Phenylephrine, Spinal Anesthesia.

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INTRODUCTION

From a historical perspective, vasopressor administration during spinal anesthesia has remained a controversial subject for obstetricians. Earlier, it was believed that vasopressors can lead to a drastic reduction in uterine blood supply, which can potentially compromise fetal delivery. This finding was downplayed by later evidence which showed that vasoconstrictors such as ephedrine or phenylephrine had no significant impact on uterine vascular supply.[1] Phenylephrine is a direct-acting alpha-1 receptor agonist and has been broadly utilized to treat arterial hypotension during obstetric surgery.[2] With a normal left ventricular systolic function, phenylephrine can not only efficiently increase peripheral arterial resistance, but also enhance venous return which in turn, increases cardiac output.[3]

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Spinal block is associated with a decline in sympathetic tone which leads to arterial dilatation and eventually precipitates intraoperative hypotension. Loss of sympathetic stimulation also creates venous pooling in the lower limbs due to a poor peripheral venous tone, followed by a drop in systemic blood pressure due to reduced stroke volume.[4] Due to its potent vasoactive mechanism, phenylephrine has been shown to effectively reduce the intraoperative incidence of maternal hypotension during Caesarian section while it also possesses a better efficacy than ephedrine.[5,6] There is however, a lack of worthwhile evidence which indicates the most effective form of phenylephrine infusion that can be used for providing prophylaxis against maternal hypotension in C-section. While a few reports have indicated that variable infusion regimen is a preferable option since it reduces maternal symptoms of hypotension and vomiting, other authors have concluded that fixed infusion is relatively superior since it lessens the

overall frequency of physician interventions during the course of anesthesia.[7,8]

The aim of our study was to compare the relative effectiveness of two opposing infusion strategies (i.e., fixed and variable infusion regimens) of phenylephrine during elective C-section in the presence of spinal anesthesia.

METHODOLOGY

This Quasi-experimental study was conducted at the Department of Obstetrics and Gynecology at the Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from February to July, 2021, after obtaining approval from the Institutional Ethics Review Committee.

Inclusion Criteria: Pregnant women who were planned to undergo a non-emergent Caesarian section at ≥37 weeks of gestation were included.

Exclusion Criteria: Females who were older than 35 years at the time of procedure, those who had any prior history of medical comorbidities including hypertension (chronic or gestational), diabetes mellitus or any documented episode of cardiac arrhythmias and those with a body mass index ≥35 were excluded.

The primary objective of this study was to evaluate the relative effectiveness of fixed and variable rate infusion regimens of phenylephrine in preventing the occurrence of maternal hypotension. Secondarily, the study focused on evaluating the role of the two phenylephrine infusion regimens in preventing the following events: (1) Recurrent intraoperative hypotension; (2) Severe hypotension; (3) Postoperative hypotension, and (4) Nausea and/or vomiting.

An approximated sample size of 88 participants was calculated by using the Cochran formula.

Participants were recruited into the study by using non-probability convenience sampling technique. Our sample population initially comprised of 106. After applying the exclusion criteria, a total of 94 pregnant women were included in the final analysis. An equal number of participants were placed in both the study groups (n = 47) as seen in the patient flow diagram (Figure). A fixed infusion regimen was injected to Group-A (n=47) at a continuous rate of 0.75µg/kg/minute, while Group-B (n=47) received a variable phenylephrine dosage, starting at 0.75µg/kg/minute which was increased to 0.9µg/kg/minute in case of hypotension, or reduced to 0.4µg/kg/minute in event of reactive hypertension.

All the participants were initially assessed for their cardiopulmonary fitness through preoperative measures of surgical fitness i.e., Electrocardiogram (ECG) or echocardiography, chest X-ray, and baseline blood investigations. The participants were also thoroughly briefed about their voluntary participation in the study and an informed consent was obtained. Moreover, an ethical approval was obtained from the institutional review board (ethical review committee #229) while the hospital ethical review committee supervised the entire data collection procedure under standardized guidelines of the Helsinki Protocol.[9]

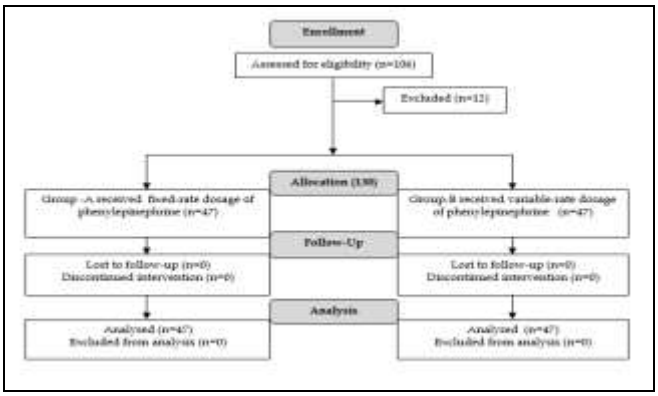

Figure: Patient Flow Diagram (n=94)

Fixed infusion regimen of phenylephrine was started at a dose of 0.75 µg/kg per minute and was continued if the individual's blood pressure did not exceed 20% of the baseline value. However, if the readings dropped substantially (>20%), a supportive phenylephrine bolus (100 µg) was given while phenylephrine infusion was not altered in the latter scenario.

Variable infusion regimen of phenylephrine was commenced at a similar dosing rate of 0.75 µg/kg per minute. If the blood pressure dropped by >20% of baseline value, a phenylephrine bolus (100 µg) was administered while infusion rate was also increased by 20% (~0.90 µg/kg per minute). A rise in blood pressure by >20% was followed by discontinuation of phenylephrine infusion. As the readings returned within the normal range, infusion was resumed but at 0.4 µg/kg per minute.

Intraoperative hypotension was defined as a drop in maternal blood pressure by >20% during C-section.[10,11] Recurrent hypotension was defined as occurrence of a second episode of hypotension after a previous one has been treated. Severe intraoperative hypotension was defined as a drop in maternal blood

pressure by more than 40% during the entire procedure.

Postoperative hypotension was defined as a drop in maternal blood pressure by >20% during the first 3 hours following the delivery of fetus.

Spinal anesthesia was administered preoperatively by using 10 mg (~2 ml) of 0.5% bupivacaine injection (5 mg/ml) through a 25G lumbar puncture needle. Before injecting the local anesthetic, the recipient was placed in a sitting position on the operating table. The subject's neck as well as both hip and knee joints were flexed, and anesthesia administered into the L3/L4 subarachnoid space. The efficacy of spinal anesthesia was confirmed by means of a sensorineural examination. Furthermore, all the participants were asked to maintain a supine head posture during the postoperative recovery period. Phenylephrine was infused intraoperatively through a 20G intravenous branula.[12] Prior to its administration, baseline values for blood pressure and pulse rate were individually recorded in the operating room, following which phenylephrine infusion was commenced either at a fixed or variable rate.

A standardized data collection tool was utilized to document monitoring of the participants' vital signs perioperatively. The two intervention groups (Group-A: fixed-rate versus Group-B: variable infusion) were compared for their particular response to phenylephrine treatment intraoperatively. Patient-related adverse events (i.e., hypertension with >20% rise in blood pressure from baseline, sudden-onset headaches, nausea/vomiting, and bradycardia) were also documented on the data collection proforma.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 23. Mean±SD values were calculated for variables including subject age, pulse rate, and systolic blood pressure. Independent t-test and Pearson's chi-square ($\chi 2$) test were used to assess the statistical correlation of data. A p-value < 0.05 was considered significant.

RESULTS

Mean age values for variable infusion and fixed infusion groups were 24.6±4.7 and 26.2±4.6 years respectively. Anesthesia during Caesarian section lasted for a mean duration of 62±9.9 minutes (Table-I) which was followed by a satisfactory postoperative recovery. No significant difference was observed between the baseline systolic blood pressure and pulse rate values of the two intervention groups.

Table-I: Baseline Parameters of Variable versus Fixed Rate Infusion Groups (n=94)

Baseline Parameters	Group-A (n=47)	Group-B 4(n=47)	*p*-value
Age in years (Mean ± SD)	26.2±4.6	24.6±4.7	-
Duration of Anesthesia in minutes	63.1±10.1	60.8±9.7	-
Preoperative SBP in mmHg (Mean ± SD)	120.6±12.3	119.3±11.6	0.577
Preoperative PR / minute (Mean ± SD)	87.3±19.0	85.8±17.1	0.687

**SBP: Systolic Blood Pressure; PR: Pulse Rate*

Both the variable and fixed rate infusions of phenylephrine significantly prevented any major decline within the subjects' intraoperative blood pressure. However, no statistically significant intergroup variation was reported (p=0.954). Furthermore, episodes of intraoperative hypotension were equally documented within both the groups. Up to 18(38.3%) participants developed hypotension within the variable rate whereas 12(25.5%) experienced hypotension in the fixed rate group. Incidence of postoperative hypotension also showed no definite correlation with the overall rate of PHE infusion. A total of 13 females [Variable rate: 6(12.8%) and Fixed rate: 7(14.9%)] encountered recurrent episodes of hypotension whereas a severe drop in systolic blood pressure was seen among 5 cases only [Variable rate: 3(6.4%) and Fixed rate: 2(4.3%)] (Table-II).

Following complications were observed among the variable rate versus fixed rate infusion participants during phenylephrine administration: hypertension: 6(13%) vs. 6(13%); bradycardia: 3(6.4%) vs. 4(8.5%); headaches: 13(27.7%) vs. 7(15%), and nausea/vomiting: 9(19.2%) vs. 7(15%).

DISCUSSION

This study did not reveal any significant variation between the fixed and variable rates of infusion of phenylephrine in terms of regulating blood pressure alleviation during C-section. Furthermore, evidence did not suggest any significant correlation between the particular rate of infusion of phenylephrine and the incidence of intraoperative or postoperative hypotension. Moreover, occurrence of intraoperative complications was documented to be independent of the mode of phenylephrine infusion. These findings contribute to an efficient strategy in

terms of managing the intraoperative regulation of blood pressure during Caesarian section, and have the potential to improve the systemic outcome of one of the widely conducted operational procedures in Pakistan.

Table-II: Operative Parameters of Variable versus Fixed Rate Infusion Groups (n=94)

Intraoperative Parameters		Group-A (n=47)	Group-B (n=47)	*p*-value
Intraoperative SBP in mmHg(Mean ± SD)		115.6±17.1	115.4±18.3	0.954
Intraoperative rise in SBP(Mean ± SD)		11.4±12.3	12.1±10.7	0.841
Intraoperative drop in SBP(Mean ± SD)		18.7±8.2	16.7±7.9	0.392
Intraoperative Hypotension (%)	Yes	12(25.5%)	18(38.3%)	0.184
	No	35(74.5%)	29(61.7%)	
Recurrent Hypotension (%)	Yes	7(14.9%)	6(12.8%)	0.765
	No	40(85.1%)	41(87.2%)	
Severe Hypotension (%)	Yes	2(4.3%)	3(6.4%)	0.646
	No	45(95.8%)	44(93.6%)	
Postoperative Hypotension (%)	Yes	6(12.8%)	2(4.3%)	0.139
	No	41(87.2%)	45(95.8%)	

Intraoperative use of phenylephrine in concentrations of 33 to 100 µg/min has proven to be substantially beneficial in terms of reducing the incidence of hypotension induced by spinal anesthesia.[13,14] This helps prevent any potential decline in cerebral perfusion and subsequent incidence of nausea or vomiting. In their study, Hasanin *et al*. found that fixed and variable rate regimens of phenylephrine were equally capable of preventing any unprecedented fall in systolic blood pressure, reporting hypotension in 37% and 31% cases, respectively. A continuous infusion strategy therefore, stands superior to the intermittent bolus technique which may lead to perioperative hypotension in up to 67% individuals.[8] No other study besides this has reported a therapeutic comparison between the variable and fixed rate intraoperative infusions of phenylephrine to-date. Another study reported only a minimal (~0.44±4.3) drop in blood pressure among patients receiving continuous phenylephrine infusion during spinal anesthesia.[15] Kumar et al. also reaffirmed this observation by indicating that a continuous prophylactic infusion of phenylephrine is more effective than a therapeutic phenylephrine bolus for preventing intraoperative hypotension.[16] Although a higher number of physician interventions are required to adjust phenylephrine infusion rate according to the individual's systolic blood pressure, variable infusion regimens of phenylephrine have been mostly favored by authors, especially when combined with rapid infusion of crystalloids.[17,18]

In their study, Kumar *et al*. favored the variable dosing pattern of phenylephrine since it led to a lower risk of adverse effects such as hypertension and bradycardia.[16] Nonetheless, a fixed infusion rate of 25-50 µg/min has been correlated with a drastically reduced incidence of reactive hypertension during C-section.[14] Considering the debate of fixed vs variable infusion regimens, a single intramuscular dose of 10 mg/1 ml phenylephrine has been surprisingly found to be superior to its intravenous infusion during administration of spinal anesthesia.[19] A review of contemporary literature however, remains inconclusive regarding the selection of the most suitable phenylephrine infusion regimen for prophylaxis against hypotension.

CONCLUSION

Both variable and fixed rates of phenylephrine infusion yielded a similar outcome during spinal anesthesia in elective C-section.

LIMITATIONS OF STUDY

Our study was quasi-experimental and not a randomized controlled trial, which could have led to statistical errors during data collection and analysis. Furthermore, an ideal population sample should include not only the elective cases of C-section but should also focus on gravid females undergoing emergency C-section, which was not considered in the current study. Moreover, physician interventions were not considered as an outcome measure by the authors which could potentially undermine the significance of our results.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

1,2: Conception, study design, drafting the manuscript, approval of the final version to be published.

3,4: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

5,6: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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