Prevention of Hemodynamic Instability: A Comparative Double Blind Study With Phenylephrine On Patients With Un-booked Cesarean Section

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ABSTRACT

Objective — *To compare the use of prophylactic continuous infusion and bolus dose of phenylephrine in preventing hypotension in un-booked patients who underwent emergency cesarean section.*

Study design — *Comparative study.*

Place & Duration of study — *Department of Anaesthesiology, Surgical Intensive Care Unit and Pain Management, Dr. Ruth K M Pfau Civil Hospital Karachi, from February 2019 to August 2019.*

Methodology — *A total of 212 un-booked patients undergoing cesarean section requiring spinal anesthesia were included. Patients were randomly allocated into two groups. Group 1 received continuous intravenous phenylephrine infusion at at the rate of 15ug/kg/min while group 2 received single prophylactic bolus intravenous dose of 50ug phenylephrine. Blood pressure and heart rate were recorded at baseline (before spinal anesthesia), then at 1min, 3min,7min, 10min, 20min, 30min, and 40minutes after subarachnoid injection of hyperbaric bupivacaine. Effectiveness was labelled when there was no hypotensive episode; a decrease in of systolic blood pressure (SBP) of more than 20% from the baseline.*

Results — *A total of 204 patients completed the study and were analyzed for effectiveness which was significantly high in group 1 when compared to group 2 (p =0.018).*

Conclusion — *Among un-booked gravid patients requiring cesarean section, a prophylactic infusion of phenylephrine was more effective in preventing maternal hypotension than a prophylactic bolus dose of phenylephrine.*

Key words — *Phenylephrine, Hemodynamic instability, Spinal anesthesia, Cesarean section.*

INTRODUCTION:

Spinal anesthesia (SA) is the technique of choice for lower segment cesarean section (LSCS).[1] However, it may result in maternal hypotension, the frequency of which is reported as high as 70%–80% when pharmacological prophylaxis is not used.[2] Hypotension after SA for LSCS is defined labeled when the systolic blood pressure (SBP) decreases to <100 mmHg or to >20% fall than baseline readings.[3] The fall in blood pressure causes nausea, vomiting, and lightheadedness, and when severe and sustained, it can impair uterine and intervillous blood flow. This ultimately results in fetal acidosis and neonatal depression. Maternal SBP of 80 mmHg for 5 min almost always results in hypoxic fetal bradycardia.[4]

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Measures which have been described to prevent hypotension after SA include fluid preload, left lateral tilt, and use of vasopressors.[4] However, a Cochrane review of 2006 concluded that no single intervention has been proven to eliminate post-spinal hypotension.[5] Among the vasopressors, ephedrine (a mixed Beta - and Alpha-agonist) was previously recommended as the drug of choice in obstetrics, but there is now increasing evidence that this agent has the propensity to decrease fetal pH and lead to base excess.[6,7] Phenylephrine, a pure Alpha-agonist, is currently considered as the preferred drug to be used in hypotension due to SA in LSCS. However, the American Society of Anesthesiologists (ASA) Practice Guidelines for Obstetric Anesthesia published in 2016 suggest that either intravenous (IV) ephedrine or phenylephrine may be used for treating hypotension during neuraxial anesthesia.[8] They recommend that in the absence of maternal bradycardia, phenylephrine should be considered because of improved fetal acid–base status in uncomplicated pregnancies. The Association of Anesthetists of Great Britain and Ireland (AAGBI) consensus statement published in 2018 by Kinsella et al. recommends a variable rate prophylactic infusion of phenylephrine immediately after the intrathecal injection.[9]

A comparative study is thus required on the use of either infusion or bolus doses of phenylephrine in emergency non-booked LSCS under spinal anesthesia. The aim of this study was to address this question.

METHODOLOGY:

This was a comparative study conducted at the Department of Anaesthesiology, Surgical Intensive Care Unit and Pain Management, Dr. Ruth K M Pfau Civil Hospital Karachi, from February 2019 to August 2019. Approval of research synopsis was taken from College of Physician and Surgeons Pakistan. Patients meeting the criteria were inducted in the study and were randomized through randomization.com into one of the two groups. A total 212 un-booked pregnant women were included, who were American Society of Anesthesiologists (ASA) physical status II, aged between 18-35 years planned for cesarean section. Those who refused to take part, had a contraindication to spinal block, history of hypersensitivity to the drugs used in the study or had a spinal block level of less than T-6 dermatome and those requiring intra-operative blood transfusion, were excluded from the study.

In Group 1 continuous intravenous 0.15 ug/kg/min infusion of phenylephrine (P.E), using a syringe pump after spinal block was given. In Group 2 a single dose of prophylactic P.E 50 ug I/V immediately after the spinal block was used. The drugs were prepared by the departmental pharmacy. For group 1 a 3 ml syringe of containing 1mlN/S and a 50 ml syringe containing 1 ug/ml of P.E was prepared. In group 2 , a 3ml syringe containing 50 ug/ml of P.E in 1ml N/S and a 50 ml syringe containing N/S was prepared. All the syringes were labeled study drug and were allotted a serial number and dispatched to the OR. The theatre consultant was instructed to give study drug in 3ml syringe I/V and then start an infusion of study drug in 50 ml syringe at a calculated rate in ml per hour (rate = patients body weight divided by 6.66) through dedicated I/V line immediately after the spinal anesthesia.

Informed and written consent was taken from patients and potential risk were explained. Patients demographics were recorded (a detailed pre-anesthetic evaluation was done before surgery). In the OR standard monitoring was done with pulse oximeter, NIBP, and ECG. Two large bore 18 G I/V access was obtained. Preload with 500ml of lactated Ringers solution over 15-20 minutes was done. Patient then placed in left lateral decubitus position and blood pressure and heart rate recorded three times with a 3 minutes interval to obtain an average baseline reading. In the sitting position, spinal block was performed at L3-L4 inter space with a 25 G – Quincke needle after local infiltration with 2ml of 2% xylocaine. At a dose of 12 mg of hyperbaric 0.5% bupivacaine at a rate of 1ml / 15 seconds was administered in sub-dural space and the patient was then immediately turned supine with a wedge at right hip for uterine displacement.

Blood pressure and heart rate were recorded as baseline (before spinal anesthesia) then at 1 minute, 3 minutes, 7 minutes, 10 minutes, 20 minutes, 30 minutes and 40 minutes after spinal injection. Intraoperative fluid and blood replacement was done as per standard anesthetic management and syntocinon 10 units IV stat was given after the delivery of baby and an infusion of syntocinon at 0.5 mUnits per min was started. Intraoperative blood loss was replaced by three times the amount of blood with a crystalloid solution in addition to the standard maintenance fluid by weight of the patient which continued throughout the procedure. If a blood loss of more than 1500ml occurred, then it was also noted and if the patients required blood transfusion they were excluded from the study.

In case of intraoperative bradycardia, the anesthesiologists was instructed to give atropine 0.5mg I/V. If the bradycardia persisted even after atropine it was noted and infusion drug was stopped. Spinal level was assessed with the cold stimulation by ice and if a block level of T-6 was not achieved patients were excluded. If intraoperative hypertension developed (SBP or DBP) > 20% fall from the baseline for more than three B.P readings 3 minutes interval apart it was noted and infusion was stopped. Effectiveness was labeled when there was no hypotensive episode (a decrease of more than 20% systolic B.P from baseline or systolic B.P of less than 90 mmHg). If the anesthesiologist felt the need to stop the study drug for patient safety or had to intervene with additional drugs trial was stopped and patient excluded from the study.

Statistical Packages for social science (V.20, SPSS Inc., Chicago, IL, USA) was used to analyze the data. Frequency and percentage were computed for categorical variables like ASA status, parity, effectiveness. Mean and standard deviation was computed for quantitative variables like age, BMI, SBP. The two groups were compared in terms of efficacy, applying Chi square test.

Stratification of age, BMI, ASA status and parity was done to control these effect modifiers on outcome variables. A p value < 0.05 was considered as significant.

RESULTS:

A total of 212 patients were recruited for this study and 204 completed the trial whose data were were analyzed for effectiveness. The mean age of the women was 26.34±4.41years in both the groups. Demographic characteristics of the women with respect to groups is shown in table I. Regarding parity, most of the women were primiparous, 58.82% and 51.96% for the group 1 and 2 respectively. Effectiveness was high in group 1 as compared to group 2 (table II). Heart rate remained within 20% of baseline within both the groups, while the lowest average of systolic B.P was seen at 7 and 10 minutes in both the groups.

Stratification analysis was performed and it was observed that hypotension was significantly high in group 2 than group 1 for below and equal to 25 years of age (p=0.018) while it was not statistically significant for other age groups as shown in table II. It was also not significant between groups according to BMI (table I). Rate of hypotension was not statistically significant between groups in those women who were primiparous while it was significant with multiparous as shown table I.

DISCUSSION:

The hypotension that occurs after spinal anesthesia

Table I: Demographic Characteristics of Study Subjects

Variables	Total Patients	Total Effective	Group 1 Effective/Total Number of Patients	Group 2 Effective/ Total number of patients	P-value
Age (Years)					
<25	99	71	n=44 44/54(81.5%)	n=27 27/45(60%)	0.018
26-30	83	63	32/40(80%)	31/43(72.1%)	0.4
>30	22	16	8/8 (100%)	8/14 (57.1%)	0.052
Parity (n)					
Primiparous	113	87	43/53 (81.1%)	44/60 (73.3%)	0.375
Multiparous	91	63	41/49 (83.7%)	22/42(52.4%)	0.001
BMI (kg/m$^{2)}$					
<25	63	51	31/35(88.6%)	20/28(71.4%)	0.085
25.1-29.9	116	78	43/57(75.4%)	35/59(59.3%)	0.077
30-35	25	21	10/10 (100%)	11/15 (73.3%)	0.125

Table II: Mean Systolic Blood Pressure With Respect To Groups (n= 204)

Systolic Blood Pressure	Baseline		During surgery [Lowest measurement]	
	Group I	Group II	Group I	Group II
Mean (SD)	127.75 (11.9)	125.92 (10.32)	112.24 (10.95)	105.73 (10.53)
Efficacy	**Group 1 n=102**	**Group 2 n=102**	**Total**	**P-Value**
Yes [No Hypotension]	84 (82.4%)	66 (64.7%)	150 (73.5%)	0.004
No [Yes Hypotension]	18 (17.6%)	36 (35.3%)	54 (26.5%)	

in LSCS is a combined effect of sympathetic blockade and aortocaval compression. Aortocaval compression leads to decrease venous return, with less preload and sympathetic block leads to arteriolar vasodilation and decreased systemic vascular resistance. To overcome this preload crystalloid are used but this has been largely replaced by co administration of vasopressors particularly phenylephrine. This response of hypotension is even more pronounced in emergency non booked cesarean section which was the subject of this study because they are more prone to unexpected blood loss owing to lack of follow up. Though the cohort of patients in this study were more prone to hemodynamic instability the results are comparable to a similar study reported in literature.[10]

Different continuous prophylactic dosing regimen of phenylephrine have been studied. A dose of 100 ug/min IV resulted in reactive hypertension in 38% as reported in one study.[11] However, a prophylactic bolus dose of 1.5 ug/kg and 0.25 ug/kg/min were reported as appropriate to prevent the hypotension.[12,13] In this study a weight-based dosing regimen of 0.5 ug/kg/min was used to prevent both hypotensive and reactive hypertensive episodes. In this study utero-placental blood flow or resistance and neonatal outcomes were not studied. Patients who are un-booked and present with fetal distress, must have fetal monitoring. It is evident from literature search that when compared to bolus dose of phenylephrine continuous infusion had better hemodynamic stability while no difference of neonatal outcomes (APGAR score and fetal pH) have been reported.[14] Nausea and vomiting were observed as secondary outcome in our study but these were not significant. In general, it has been reported that women who had their SBP maintained near baseline values with a phenylephrine infusion had a reduced incidence of nausea or vomiting compared to patients who became hypotensive.

The strength of this study was strict inclusion criteria, allocation of the patients to the groups and the assessment. The limitations include only ASA class II though a large group of un-booked patients are ASA III or above. Majority of women in this study were primigravida who have less chances of hemodynamic instability. This study also excluded patients who needed blood transfusion intra-operatively and fetal outcome was no correlated with the prophylactic drug used. Thus future studies may be conducted after considering limitations of this study.

CONCLUSION:

Prophylactic phenylephrine 0.5 ug/kg/min IV infusion was more effective in prevention of intraoperative maternal hypotension than prophylactic IV bolus dose of same drug in un-booked pregnancies.

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Shakil Malik: Acquisition and analysis of data.
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Hanya Javaid: Manuscript drafting and revision.
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