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Original Article

Effect of granisetron in attenuation of hypotension following spinal anaesthesia in parturients undergoing elective caesarean section - a double blind randomized controlled trial

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Abstract

Background: Spinal anaesthesia have side effects like hypotension and bradycardia, which may be induced by sympathetic blockade and Bezold-Jarisch reflex (mediated by peripheral serotonin receptor, 5-HT₃ type). The objective of the study was to evaluate the effects of type 3 serotonin receptors blockade by intravenous granisetron pre-treatment in spinal induced hypotension in parturient undergoing elective caesarean section.

Methods: Fifty six parturient with American Society of Anaesthesiologists Physical Status I and II undergoing elective caesarean section were assigned randomly to receive either Normal Saline (control) or Granisetron 1mg intravenously five minutes before spinal anaesthesia. Spinal anaesthesia was performed with 2.2 ml 0.5% hyperbaric bupivacaine solution and then heart rates, systolic blood pressure, diastolic blood pressure, mean arterial pressure were recorded every two and half minutes for ten minutes and then every five minutes for till end of surgery after. Hemodynamic parameters were compared with baseline in each group.

Results: Change in mean, systolic and diastolic arterial pressure compared with baseline value were comparable in both the groups, but use of ephedrine as rescue vasopressor drug was significantly reduced in granisetron group. The episodes of hypotension, nausea/vomiting and shivering were comparable in both groups.

Conclusions: Type 3 serotonin blockade by intravenous granisetron pre-treatment does not reduce spinal induced hypotension in parturient undergoing elective caesarean section; however there is reduction in need of rescue vasopressor.

Keywords: Granisetron; Hypotension; Spinal anaesthesia

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Introduction

Maternal hypotension is a recognized complication of spinal anaesthesia with an incidence of as high as 80% that may compromise the welfare of both mother and the baby.¹ The incidence of hypotension has been estimated to be as high as 50–60% in obstetric, non-labouring patients. Blockade of sympathetic efferent is the principal mechanism by which spinal anaesthesia produces cardiovascular derangements.² There are several methods to minimize maternal hypotension after spinal anaesthesia like preloading or co-loading of IV fluid, positioning, use of vasopressors and compression devices.^{3,4,5} The decrease in preload caused by spinal anaesthesia may initiate vagally-mediated cardiodepressor reflexes, the Bezold Jarisch Reflex, which may be mediated by peripheral serotonin receptors (5-HT₃ type).⁶ However, to date, only few studies have shown the role of ondansetron and granisetron in the prevention of the Bezold-Jarisch reflex,^{7,8} concerning the possible reduction in spinal anaesthesia related adverse cardiovascular effects through blockade of these receptors. Hence this study was designed to evaluate effects of intravenous granisetron pre-treatment in blood pressure and heart rate after spinal anaesthesia in elective caesarean section.

Methods

We conducted study to evaluate the effects of intravenous granisetron pre-treatment in spinal induced hypotension in parturient undergoing elective caesarean section as primary outcome and compare incidence of shivering, nausea and vomiting after spinal anaesthesia, with and without pre treatment of iv granisetron as secondary outcome.

After approval of the medical ethics committee and obtaining written consent from each patient, this study was conducted in BP. Koirala Institute of Health Sciences. Fifty six parturient, with American Society of Anesthesiologists Physical Status I and II, aged from 20 to 40 years scheduled for elective cesarean section were included in this study. Women with contraindication for neuraxial block (like disturbed hemodynamic, coagulation defects), hypersensitivity history to local anaesthetics or study drug, hypertensive disorders of pregnancy, patients receiving selective serotonin reuptake inhibitors or migraine medications) or patient refusal were excluded from the study.

We calculated sample size based on pilot study done on total of 20 patients with 10 patients in each group which showed mean blood pressure drop of 32 mm of Hg in the control and drop of 20 mm of Hg in the experimental group with standard deviation of 16. With calculation based on these figures, 28 patients per group are required to have 80% chance of detecting, as significant at the 5% level, a decrease in primary outcome measure from 32 in control group to 20 in the experimental group. For sample size calculation, online calculator was used.⁹

This was a prospective, randomized, double blinded, clinical study. Computer generated random number sequence maintained in a sealed envelope was used. Group allocations were done after arrival of the patient in the patient holding area of the operation theatre. Group A received 10 ml of 0.9% Normal saline intravenously 5 minutes prior to spinal anaesthesia over 30 sec and group B received 1 mg of Granisetron diluted to 10 ml of 0.9% normal saline intravenously 5 minutes prior to spinal anaesthesia over 30 sec. The study drug was given by a nursing staff not involved in observing the outcome variables. The anaesthesiologist, involved in measuring haemodynamic parameters, recording the presence of side effects like nausea, vomiting, rigor and discomfort, and the patient herself remained unaware of the group allocations.

Prehydration was done with Ringer's Solution 20ml/kg/h over 30 min just prior to spinal anaesthesia. Baseline systolic blood pressure (SBP), diastolic pressure (DBP), mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO₂) and respiratory rate (RR) were measured before solution administration, about 5 min before patients were positioned for spinal anaesthesia. Under aseptic precautions lumbar puncture was performed with 25 gauge spinal needle (Quincke's needle) through midline approach with patient in left lateral decubitus position at L3-L4 or L4-L5 position. After free flow of CSF, 2.2 ml of 0.5% injection bupivacaine (heavy) was injected. Patients were placed in the supine position with 15° leftward tilt. Baseline HR, SBP, DBP, MAP, SpO₂ and RR were recorded and then at 2.5-min intervals up to 20 min, followed by 5-min intervals until the end of surgery. Upper sensory levels were assessed twice at 5-min intervals with cold sensation (using alcohol swab) and the level of motor blockade was assessed according to the Bromage scale. Decrease of systolic blood pressure to <100mm of Hg or to more than 20% less than baseline readings, whichever is low, was treated with Ephedrine 5 mg iv; HR <50 beats/min was treated with iv atropine 0.6 mg. Shivering was treated with iv Pethidine 25 mg. Nausea and vomiting was treated with iv Metoclopramide 10mg. When ephedrine or atropine were necessary, only values obtained before these medications were analyzed. Pain that occur after spinal anaesthesia was treated with iv Fentanyl 50 mcg, but if persisted was considered a failed spinal anaesthesia, converted to general anaesthesia, and the patient excluded from the study. If blood loss exceeds allowable loss, blood transfusion was started and case was excluded from the study. Untoward effects like nausea, vomiting, shivering were noted in remarks.

Statistical Analysis

The lab measurement values were entered into the proforma. At the completion of the project, the collected data were entered into and analyzed using Microsoft Excel or SPSS software 21 for Windows. Data were expressed as mean value and 95% confidence interval. If more

than 25% of cell frequency had expected value less than five, Fischer's exact tests were used. Bar diagram for the categorical presentation and line graph for trend analysis were used to explore the corrected data. Wisker box plot graph was used to present median, 1st quartile, 3rd quartile, minimum and maximum range of continuous data. Students t test for continuous independent variables was used for comparing results (after verification of homoscedasticity with the Levene test). Chi square test was used for categorical variable with Yates' correction if necessary. The 'p-value' thus calculated using these tools were considered statistically significant if less than 0.05.

Results

Fifty six patients were included in the study. The demographic data (Table 1), baseline haemodynamic parameters (Table 2), sensory and motor block obtained were not significantly different among the groups.

Table 1: Demographic parameters

Variable	Group A (n=28)	Group B (n=28)	p-Value
Age in years (mean± SD)	27.07±3.934	27.14±4.395	0.949
Weight in kilograms (mean ± SD)	62.46±7.105	60.11±6.568	0.203
Height in centimeters (mean ± SD)	157.79±2.500	157.79±2.780	1.00
BMI(kg/m ²)	25.069±2.6414	24.116±2.3036	0.156

Table 2: Baseline hemodynamic parameters and duration of surgery

Variable	Group A (n=28)	Group B (n=28)	p-Value
Duration of surgery (min) mean ± SD	44.82±14.999	47.32±12.132	0.496
HR baseline (beats per min) mean±SD	95.79±16.495	90.29±10.917	0.148
SBP baseline (mm of Hg) mean ±SD	118.32±7.597	114.71±9.100	0.113
DBP baseline(mm ofHg) mean±SD	74.25±7.648	72.14±10.725	0.401
MAP baseline mean ± SD	90.24±8.555	86.64±9.740	0.148
Spo2 baseline mean ± SD	98.43±1.289	98.68±1.249	0.464
RR baseline Mean ± SD	16.75±1.456	16.07±1.412	0.082

There were no significant differences in SBP, DBP, MAP, HR, SPO₂, RR values between the groups at the same time point. 19 patients (67.8%) had hypotension in saline group while 13 patients (46.4%) had hypotension in granisetron group which was treated with IV ephedrine. When comparing between groups, saline group had multiple episodes (more than three) of hypotension in seven patients while none of the patients in granisetron group had hypotensive episodes more than two. (Figure 1)

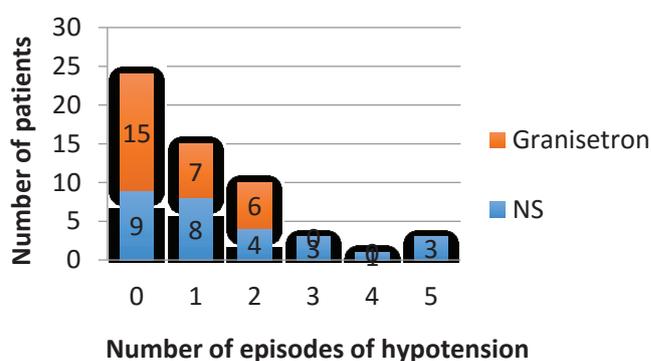


Figure 1: Comparison of hypotensive episodes and number of patients suffering from hypotension

Use of granisetron before giving spinal anesthesia significantly reduced dose of ephedrine as rescue vasopressor in case of hypotension (Table 3). There were no statistically significant differences in occurrence of nausea/vomiting, shivering, pain/discomfort.(Table 4)

Table 3: Comparison of dose of ephedrine:

Variables	Group A (n=28)	GroupB (n=28)	Mann – whitney U test	P value
Mean±SD	7.86±8.21	3.39±4.09	272.5	0.039

Table 4: Incidence of other side effects of the spinal anaesthesia in two groups

Variables	A (Normal saline)	B (Granisetron)	P value
Shivering n(%)	5(17.9%)	2(7.1%)	0.419
Pain/Discomfort n(%)	3(10.7%)	1(3.6%)	0.611
Nausea/ Vomiting n(%)	6(21.4%)	1(3.6%)	0.106

Discussion

Hypotension and bradycardia during spinal anesthesia are common side effects of this procedure. Hypotension is due to a decrease in systemic vascular resistance and central venous pressure, due to sympathetic block, and blood redistribution. The mechanism responsible for bradycardia is not clear. Blockade of the sympathetic cardioaccelerator fibers originating from T1-4 spinal

segments is often suggested as the cause. The fact that bradycardia is more common with high blocks supports this mechanism. However, significant bradycardia sometimes occurs with blocks that are seemingly too low to block cardioaccelerator fibers. Diminished venous return has also been proposed as a cause of bradycardia during spinal anesthesia. Intracardiac stretch receptors have been shown to reflexively decrease heart rate when filling pressures fall.¹⁰ Another mechanism for bradycardia and hypotension is, in response to hypovolaemia, stimulation of cardiac sensory receptors in the left ventricle induces the Bezold-Jarisch reflex (BJR). The Bezold-Jarisch Reflex is an inhibitory response usually described as a cardioinhibitory reflex triggered by stimulation of intracardiac receptors and its consequences include bradycardia, vasodilatation, and hypotension. Spinal anaesthesia-related triggering of Bezold-Jarisch reflex is known to result from stimulation of 5-HT₃ receptors in vagal nerve endings.^{6,11} But, there had been few studies which showing limitation of spinal anaesthesia-related adverse cardiovascular effects through blockade of 5-HT₃ receptors. The most important finding in our study was the observation of significant decrease in use of vasopressors in patient who were given IV granisetron prior to the initiation of spinal anesthesia. Ephedrine causes maternal tachycardia and depresses fetal Ph and base excess. This reduction in use of vasopressor would be crucially useful for risk population such as elderly patient who don't tolerate excess fluid infusion or pregnant women in whom the administration of vasoconstrictors can have adverse effects on uterine blood flow.

There are different studies which have revealed the effectiveness of different strategies for the prevention of spinal anaesthesia induced hypotension such as pre or co-loading of IV fluid, use of vasopressors, left lateral tilt.^{3,4,5} But none of these techniques alone was sufficient in eliminating hypotension.¹¹ This study was done to test the effectiveness of intravenous granisetron prophylaxis for the prevention of spinal anaesthesia induced hypotension and bradycardia. Animal studies have shown the use of granisetron in the prevention of the Bezold Jarisch Reflex which occurs following spinal anaesthesia due to severe decrease in preload. Tsikouris et al found the use of granisetron in the prevention of neurally mediated hypotension upon head upright tilt testing associated with systemic vasodilatation.¹² Radoslaw et al found that 8 mg intravenous ondansetron (5-HT₃ antagonist), attenuates the SBP and MAP drop in spinal anesthesia.¹³ Sahoo et al found use of 4mg of intravenous ondansetron in parturients undergoing caesarean section under spinal anaesthesia cause decrease in fall of SBP and MAP in treatment group.¹⁴ Shrestha et al concluded that 40mcg/kg of intravenous granisetron when given 5 minutes before spinal anaesthesia does not decrease the incidence of hypotension and bradycardia but attenuates the decrease in diastolic blood pressure.¹⁵

The incidence of hypotension in our study was 57.1% which was comparable to previous data.^{7,10} Radoslaw et al and Sahoo et al used ondansetron but we used granisetron. Though both granisetron and ondansetron are from same group of drug, these differences between the effects may be due to the action of ondansetron on mixed receptors and the high selectivity of granisetron on 5-HT₃ receptors but minimal affinity of it for other 5-HT receptors, adrenergic, histaminic, dopaminergic, or opioid receptors.¹⁶ This effect of granisetron may be due to its 5-HT₃ receptor antagonism, serotonin being the mediator for spinal anaesthesia triggered Bezold Jarisch reflex resulting in hypotension, bradycardia and vasodilatation.

Regarding the limitations of the study, oscillatory method was used for noninvasive blood pressure measurements but invasive blood pressure monitoring would give more precise assessment of haemodynamic changes. Different dose of granisetron was not compared. Doses as low as 5 mcg/kg have been used to effectively decrease post operative nausea and vomiting; however we selected the standard dose of granisetron 1 mg approved by FDA and used in our institution. In addition we couldn't compare each time interval haemodynamic parameter with baseline value due to occurrence of hypotension in early period and had to exclude data then after, so larger number of patient are needed to evaluate the potential effect of granisetron on haemodynamic alteration in each time point. Also, we couldn't comment on incidence of bradycardia due to its absence in our study sample and may need more sample size to comment on this. As only few literatures are available, further studies are warranted to determine the exact role of granisetron in decreasing post spinal hypotension.

From this double blind, randomized, prospective study, it was concluded that granisetron when given at 1 mg intravenously 5 minutes before spinal anaesthesia does not cause decrease in incidence of hypotension and bradycardia but cause reduction in dose of ephedrine as rescue vasopressor in case of hypotension.

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