Original Article

Use of Granisetron for prevention of hypotension and bradycardia due to spinal anesthesia: A double blind randomised control trial.

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Abstract
Background: The common adverse effects of spinal anaesthesia include hypotension and bradycardia are due to sympathetic nerve blockade and activation of the Bezold-Jarisch reflex. The Bezold-Jarisch reflex in spinal anaesthesia may be mediated by peripheral 5-HT3 type serotonin receptors. We hypothesized that blockade of type 3 serotonin receptors by using intravenous Granisetron might reduce hypotension and bradycardia induced by spinal anaesthesia.

Methodology: Sixty American Society of Anesthesiologists Physical Status I and II patients undergoing lower abdominal surgeries were randomized to receive either Normal Saline (control) or Granisetron 40 mcg/kg intravenously five minutes before subarachnoid block. Heart rates, systolic blood pressure, diastolic blood pressure, mean arterial pressure was recorded every two minutes for ten minutes and then every five minutes for another twenty minutes. Hemodynamic parameters were compared with baseline in each group.

Results: There was decrease in all measured variables when compared with baseline values in both groups. There was less reduction in diastolic blood pressure in Granisetron group statistically significant at 10, 15, 20, 25 and 30 minutes. However, the less decrease in mean arterial pressure was statistically significant at 30 minutes only. There were no significant differences in systolic blood pressure and heart rate values between the groups.

Conclusions: Granisetron given intravenously does not decrease the incidence of hypotension and bradycardia following subarachnoid block in patients undergoing lower abdominal surgery. However, it attenuates the fall of diastolic and mean arterial pressure spinal anaesthesia.

Key words: Granisetron; Hypotension; Spinal anaesthesia.

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Introduction
The most common hemodynamic adverse effects of spinal anesthesia are hypotension and bradycardia. Incidence of hypotension is 33% (defined as systolic blood pressure <90 mmHg) and that of bradycardia is 13% (defined as heart rate <50 beats/min) in non-obstetric populations. The decrease in preload caused by spinal anaesthesia may initiate vagally- mediated cardiodepressor reflexes, the Bezold Jarisch Reflex. It leads to shift in cardiac autonomic balance toward the parasympathetic nervous system. Different studies have shown that 5-HT3 receptor

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antagonists like Ondansetron and Granisetron are effective in the prevention of spinal anaesthesia induced nausea, vomiting and shivering.\textsuperscript{3,4} Few other studies have shown the role of Ondansetron and Granisetron in the prevention of the Bezold-Jarisch reflex.\textsuperscript{5,6,7} The rationale of conducting this study was to explore whether Granisetron alone can prevent hypotension and bradycardia due to spinal anaesthesia.

Material and methods

The study was approved from Institution Review Board. Patients who fulfilled the inclusion criteria (American Society of Anesthesiologists Physical Status (ASA PS) I and II, age group 18 to 65 years) were enrolled. Written informed consent was taken from all the patients. The patients were randomly assigned into two groups (Group G and Group N), 30 patients in each group, by sealed envelope method. Group G patients received 40 µg/kg of Granisetron (Biogram-3) added to 0.9% of Normal Saline (NS) to make total volume of 5 ml. Group N patients received 5 ml of 0.9% NS. All patients were pre-loaded with 10 ml/kg of Ringers Lactate and were transferred to Operating Room (OR). Baseline systolic blood pressure (SBP), diastolic pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were recorded. The study drug was prepared by Anaesthesia Assistant who was not involved in the study and calculated amount of study drug was given intravenously (IV) 5 minutes before the procedure. Subarachnoid block (SAB) was performed with 25 G spinal needle (Quincke) at L3-L4 or L2-L3 space. After free flow of cerebrospinal fluid, 4 ml of 0.5% hyperbaric Bupivacaine was injected over 15 to 20 seconds. The time of completion of sub-arachnoid injection was recorded as 0 min. After SAB, heart rate, SBP, DBP and MAP were recorded every 2 minutes for the first 10 minutes and then every 5 min for the subsequent 20 minutes. The sensory and motor block achieved was tested every 5 minutes till 15 minutes. Sensory level achieved was defined as the loss of cold sensation to spirit swab. The motor block achieved was graded according to the Bromage scale. The highest sensory and motor block obtained in 15 minutes were recorded for the study.

Hypotension was defined as an absolute decrease in SBP <90 mmHg.\textsuperscript{1} If hypotension developed, it was first managed with fluid bolus of 4 ml/kg. If it was not corrected with this, Mephentermine 6 mg was given and was repeated after 3 minutes till it was corrected. Phenylephrine 50 µg IV was kept as rescue drug when more than 30 mg of Mephentermine was required. Bradycardia was defined as absolute decrease in HR less than 50/min.\textsuperscript{1} It was treated with bolus Atropine 0.6 mg and was repeated with similar dose subsequently till bradycardia was corrected. Total amount of IV fluid given in bolus, amount of vasopressor and Atropine required in first 30 minutes were recorded. Untoward effects like nausea, vomiting, shivering, restlessness or any significant hemodynamic changes till 4 hours from the time of administration of drugs (intraoperative, recovery, postoperative period) were noted in remarks.

Statistical Analysis

Data were recorded in preformed data collection Sheet. All data were entered in Microsoft office Excel worksheet 2007. For the analysis of the data, Statistical Package for the Social Sciences (SPSS) 17 was used. Sample size was calculated considering $\alpha = 0.05$, $\beta = 0.10$, Power = 90%, with confidence interval obtained from the study of Radoslaw et al.\textsuperscript{8} STATA 9.0 (statistical software) was used for sample size calculation. Independent t test was used for comparison between two groups. $p$ value less than 0.05 was considered significant.

Results

Sixty patients were enrolled in the study. There were no statistically significant differences between the groups with respect to demographic data (Table 1), baseline haemodynamic parameters, sensory and motor block obtained.

There was a trend of decrease in heart rate and systolic blood pressure in both groups after Sub-arachnoid Block. However, the difference in decrease was not statistically significant. There was statistically significant decrease in DBP in normal saline group in 10, 15, 20, 25 & 30 minutes as compared to baseline (Figure 1).

There was trend in decrease in MAP in both groups. However, significant decrease was seen in Group N at 30 minutes ($p = 0.03$). There was no significant difference in development of adverse events like hypotension, bradycardia, nausea, vomiting and shivering between the groups till 30 minutes of study period (Table 2). Three patients in group N developed hypotension with nausea at 35, 40 and 45 minutes while one in group G developed hypotension at 40 minutes intraoperatively. All were managed with fluid bolus and Mephentermine 6 mg IV bolus.
Two patients, one in each group developed shivering in recovery room after one hour of surgery. Both were managed with inj. Pethidine 25 mg IV stat.

### Table 1. Demographic profiles

<table>
<thead>
<tr>
<th></th>
<th>Group G (n = 30)</th>
<th>Group N (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>37 ± 11.0</td>
<td>35 ± 8.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>11/19</td>
<td>18/12</td>
<td>0.07</td>
</tr>
<tr>
<td>Weight (Mean ± SD)</td>
<td>53.3 ± 8.3</td>
<td>52.2 ± 8.2</td>
<td>0.36</td>
</tr>
<tr>
<td>ASA PS (I/II)</td>
<td>26/4</td>
<td>26/4</td>
<td>1</td>
</tr>
</tbody>
</table>

### Figure 1. Trends of mean DBP as compared to baseline

![Trends of mean DBP](image)

### Table 2. Adverse effects

<table>
<thead>
<tr>
<th></th>
<th>Group G (n=30)</th>
<th>Group N (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Shivering</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Discussion

Studies 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 and compression devices. However, a Cochrane review concluded that none of these techniques alone was sufficient in eliminating hypotension. This emphasized the need of the future research concerning other agents. This double blind randomized controlled study was designed to test the effectiveness of pretreatment with intravenous Granisetron for the prevention of spinal anaesthesia induced hypotension and bradycardia.

To prevent spinal anaesthesia induced hypotension and bradycardia, Granisetron, a 5-HT3 antagonist, was chosen in this study for following reasons: first, animal studies showed the effectiveness of Granisetron in the prevention of the Bezold Jarisch Reflex which also occurs following spinal anaesthesia due to severe decrease in preload. Second, Tsikouris et al found the role of Granisetron for the prevention of neurally mediated hypotension upon head upright tilt testing associated with systemic vasodilatation. Third, Radoslaw et al found that 8 mg intravenous Ondansetron, another 5-HT3 antagonist, attenuates the SBP and MAP drop in spinal anesthesia and emphasized the need for further studies. Forth, Yeasmeen et al found that Granisetron is more effective than Ondansetron in the prevention and treatment of postoperative nausea and vomiting. So Granisetron was preferred over Ondansetron. Regarding the dose of Granisetron, Kamanabrou et al found 40 µg/kg as the optimal dose of Granisetron for chemotherapy induced vomiting. Tsikouris et al also used 40 µg/kg of intravenous Granisetron in their study for prevention of neurally mediated hypotension upon head upright tilt testing. So we decided to use 40 µg/kg of Granisetron.

The results of our study showed that pretreatment with 40 µg/kg of intravenous Granisetron does not prevent the incidence of hypotension and bradycardia following spinal anaesthesia for lower abdominal surgery in ASA I and II patients. However, this study showed the decrease in HR, SBP, DBP and MAP in both groups till 30 minutes of...
observation after spinal anaesthesia. This decrease was explained with the sympathetic blockade following sub arachnoid block. The decrease was significant for DBP 10, 15, 20, 25 and 30 minutes in Normal Saline group. The decrease in MAP was statistically significant only at 30 minutes in placebo group.

In the study conducted by Radoslaw et al there was significant decrease in SBP and MAP in control group as compared to treatment group (receiving 8mg of intravenous Ondansetron) following spinal anaesthesia with 4 ml 0.5% hyperbaric Bupivacaine solution. Sahoo et al conducted a study using 4mg of intravenous Ondansetron in parturients undergoing caesarean section under spinal anaesthesia and found decrease in fall of SBP and MAP in treatment group. However, in our study, there was statistically significant decrease in reduction of DBP. The main difference between our study and studies of Radoslaw et al and Sahoo et al is the use of drug. Radoslaw et al and Sahoo et al used Ondansetron and we used Granisetron. This could be possible reason for the difference in results.

Regarding the limitations of the study, we used oscillatory method for noninvasive blood pressure measurements. Invasive blood pressure monitoring would have been used for more precise assessment of hemodynamic changes. Amount of blood loss was not recorded in this study. This can influence the hemodynamic profile of patients. The study was conducted in ASA PS I & II patients, low risk groups with stable hemodynamic. The result of this study may not be extrapolated to patients with high risk group. Absolute value was used in this study to define hypotension and bradycardia. Use of relative value (percentage reduction from baseline) in addition to absolute value may be more precise in defining hypotension and bradycardia when there is wide fluctuation in baseline values.

From this double blind, randomized, prospective study, it was concluded that Granisetron when given at 40 µg/kg intravenously 5 minutes before spinal anaesthesia does not decrease the incidence of hypotension and bradycardia. However, it attenuates the decrease in diastolic blood pressure.

References