Prophylactic efficacy of intravenous ondansetron in prevention of spinal anaesthesia induced hypotension: Randomized, double blinded, placebo controlled study

Shivika Nath
Assistant Professor, Department of Anesthesiology, School of Medical Sciences and Research, Sharda University, Greater Noida, India
Corresponding author email: doc.shivi45@gmail.com

Nupur Aggarwal
Post-graduate Trainee, Department of Anesthesiology, School of Medical Sciences and Research, Sharda University, Greater Noida, India

Ambhrin Saha
Post-graduate Trainee, Department of Anesthesiology, School of Medical Sciences and Research, Sharda University, Greater Noida, India

Aarti Srivatsava
Professor and Head, Department of Anesthesiology, School of Medical Sciences and Research, Sharda University, Greater Noida, India

Abstract---Background: Spinal anesthesia is used in wide range of surgical procedures, but it is associated with potential complications such as hypotension and shivering. Thus the present study was aimed to compare the effect of 6mg ondansetron and placebo 10 minutes before spinal anesthesia for prevention of hypotension and shivering in patients undergoing non-obstetric surgeries. Methods: A double blinded randomized placebo control trial was conducted in 50 patients. Patients were randomized into ondansetron group (n=25) and placebo group (n=25). The primary outcome was the measurement of SBP(Systolic Blood Pressure), DBP(Diastolic Blood Pressure), MAP(Mean Arterial Pressure) and HR(Heart Rate) at baseline, 5, 10, 15 and 30 minutes after subarachnoid block. Results: There was a significant mean difference in SBP and DBP at 5, 10, 15 and 30 minutes after subarachnoid block (SAB) between the groups (p<0.05). Further, significant decreased MAP was observed at 5,10,15 and 30 minutes after SAB in placebo as compared to ondansetron group (p<0.05). Further 30 minutes after SAB, 28% of patients in placebo
group and 4% of patients in ondansetron group had shivering (p=0.04). Conclusion: The present study shows that ondansetron is a suitable agent for the mitigation of spinal anesthesia-induced hypotension and shivering during non-obstetric surgeries.

Keywords---spinal block, hypotension, shivering, ondansetron.

Introduction

Spinal anaesthesia is a routinely employed anaesthetic method for elective surgeries encompassing lower abdomen, perineum and lower limbs as well during caesarean delivery. This method is easy to perform and elicits fast intraoperative anesthesia with minimal respiratory complications, thus enhancing a rapid and favorable recovery. Meanwhile, the clinical utility of spinal anaesthesia has various potential adverse effects such as hypotension, bradycardia, nausea, vomiting and dysrhythmia. The incidence of spinal anesthesia induced hypotension may vary according to the surgical procedure, with 40% in non-obstetric patients and 80% in obstetric patients. Arterial hypotension causes reduction in blood flow and cardiac output and thus leads to systemic hypoperfusion. Spinal anaesthesia induced hypotension is due to the decrease in systemic vascular resistance as a result of blockade of sympathetic fibers and enhanced vagal tone. The reduced venous return stimulates the Von Bezold-Jarisch (BJ)reflex, mediated by serotonin (5-HT3) receptors leading to elevated efferent vagal signaling and bradycardia, and induces the hypotension. So, the bradycardia must be properly managed, otherwise the hypotension may lead to cardiac arrest. Thus, proper treatment protocols must be followed to prevent the risk of hypotension after spinal anesthesia.

Shivering is one of the frequently encountered side effects in patients undergoing surgery under neuraxial anesthesia with a reported incidence of 40–70%. Spinal anesthesia blocks the tonic vasoconstriction which leads to redistribution of core heat from the trunk to the peripheral tissues and thus imposes hypothermia and shivering to patients. Shivering also induces artifacts in intraoperative monitoring especially with electrocardiogram (ECG), noninvasive blood pressure monitoring, and pulse oximetry. Serotonin, present in the brain and spinal cord orchestrate a vital role in the thermoregulation. Various therapeutic strategies has been used to reduce the incidence of hypotension, including administration of colloids, crystalloids, ephedrine, phenylephrine and glycopyrrolate but their effectiveness continues to be debated.

Ondansetron, a widely used agent in the prophylaxis of post operative nausea and vomiting and its action is mediated through the selective inhibition 5-HT3 receptors. Thus, ondansetron blocks the BJ reflex and it is used as a therapeutic modality in the prevention of hypotension in patients undergoing spinal anesthesia. Till date mounting studies evaluated the effect of ondansetron on prevention of hypotension and shivering in obstetric patients few trials are conducted in non-obstetric surgeries scheduled under spinal anaesthesia.
Thus the primary objective of this study was to evaluate the effect of intravenous ondansetron in preventing spinal anaesthesia induced hypotension in non-obstetric patients. Secondary objective was to assess for shivering and bradycardia.

**Methods and Materials**

The study was a prospective, double blinded, and randomized placebo-controlled study conducted in August 2021 to November 2021 at the department of Anaesthesia among the patients who underwent abdominal and lower limb surgeries. The protocol was approved by the Institutional Ethical Committee and registered at clinical trials registry (XXXXXX). Written informed consent was obtained from all subjects.

**Inclusion criteria**

All ASA I and II patients who underwent non-obstetric surgeries

**Exclusion criteria**

Patients who were unable to attend the spinal anesthesia, allergy to ondansetron, with hypertension and coronary artery disease and patients who were on selective serotonin reuptake inhibitors were excluded from the study.

**Study design**

Fifty patients were recruited for the study. The patients were randomized according to the computer-generated random numbers. The consort flow chart of study participants was shown in Figure 1. All patients were subjected to a thorough pre-anaesthetic checkup prior to surgery. On arrival to the preoperative area, demographic data such as age, sex, body mass index were recorded. In the operating theatre, baseline values of non-invasive systolic blood pressure (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) were obtained. In addition, heart rate (HR) and pulse oximetry (SpO₂) were recorded, and intravenous cannula was secured in each patient. Patients were randomized into the following 2 groups: the ondansetron group (n=25), received 3 mL of IV (intravenous) ondansetron (2mg/mL) i.e 6mg and placebo group received 3 mL of IV normal saline 10 minutes before subarachnoid block. All patients were preloaded with 500 ml of lactated Ringer's solution.

Under aseptic technique, the patients were positioned to sit and subarachnoid block (of L3-L4 or L4-L5) was performed by administering 2.8 mL of 0.5% hyperbaric bupivacaine through a 25-gauge Quincke's spinal needle. After that sensory block levels was assessed using modified Bromage scale.\(^{16}\) SBP, DBP, MBP, HR and SPO₂ were measured at 5, 10, 15 and 30 minutes after spinal block by Blinded anesthesiologists. Hypotension was defined as drop in MAP ≥20% of the baseline value. The hypotension was treated by increasing rate of crystalloids infusion and IV(intravenous) mephentermine 6mg and the patients whose HR drop by 20% of baseline value or less than 45 BPM(beats per minute) was defined as bradycardia and received atropine 0.6 mg IV.
During surgery, shivering score were recorded at 5, 10, 15 and 30 minutes after spinal block by blinded anesthesiologists. Shivering was graded using a scale similar to that validated by Crossley and Mahajan. in which Grade 0: no shivering, Grade 1: piloerection or peripheral vasoconstriction but no visible shivering, Grade 2: muscular activity in only one muscle group, Grade 3: muscular activity in more than one muscle group but not generalized and Grade 4: shivering involving the whole body. Continuous shivering ≥ grade 3 for 15 min was considered as significant side effect of intrathecal block. Rescue dose of 1 mg / kg tramadol IV was administered to control shivering. Intraoperative nausea and vomiting were recorded

**Outcomes**

Primary Outcome: To evaluate the effect of intravenous ondansetron in preventing spinal anaesthesia induced hypotension in non-obstetric patients.
Secondary Outcome: To evaluate the effect of intravenous ondansetron in preventing spinal anaesthesia induced shivering and bradycardia.

**Statistical Analysis**

The minimum patient in each group was calculated based on pilot study encompassing 12 patients, in which the MAP drop (difference between the initial and final value calculated 20 minutes after the block) was 17±9 and the same methodology was applied to the placebo group. MAP drop of 25% in the intergroup differences were assumed to be significant. Based on this assumption, a 80% test power and level of 0.05, each study group required a minimum of 25 patients.

Statistical analysis was done using SPSS v 21. Continuous variables were shown as mean± SD and non-normally distributed variables were represented as mean. Categorical variables were shown as frequencies and percentages. Student’s t test was used to compare the normally distributed continuous variables between the groups. Chi-square test was applied for the comparison of categorical data. A p <0.05 was found to be statistically significant.

**Results**

From August 2021 through November 2021, we screened a total of 60 patients for eligibility. Of these, 50 met all inclusion criteria and were randomized (25 per group). There was no significant difference among the two groups with regard to age, gender, BMI, ASA status and type of surgery (p value >0.05) as displayed in Table 1.

**Comparison of perioperative systolic and diastolic blood pressure between ondansetron and placebo group**

The means differences of perioperative of SBP and DBP between groups were analyzed by using unpaired t-test. Significant mean difference in SBP after subarachnoid block, was observed only at 10 min (117.2±13.6 mmHg in ondansetron group vs. 97.8±12.3; p<0.001), 15 min (119.3±11.9 in ondansetron
Comparison of perioperative mean arterial pressure between ondansetron and placebo groups

The means differences of perioperative of mean arterial pressure (MAP) between groups were analyzed by using unpaired t-test. The MAP was significantly lower in placebo group as compared to ondansetron group after subarachnoid block at 5 mins (82.6±9.5mmHg vs 89.9±7.2 mmHg; p=0.003), 10 mins (75.4±9.2mmHg vs 88.4±8.2mmHg; p<0.001), 15 mins (75.6±8.7 mmHg vs 90.4±6.9mmHg; p<0.001) and 30 mins (81.6±8.6mmHg vs 90.5±6.8mmHg; p<0.001). The results were shown in Figure 3.

Comparison of perioperative heart rate and oxygen saturation between ondansetron and placebo groups

The means differences of perioperative of heart rate and oxygen saturation (SPO$_2$) between groups were analyzed by using unpaired t-test. In this study, there was no significant difference in the heart rate and SPO$_2$ between placebo and ondansetron group (p>0.05). The results were displayed in Figure 4.

Comparison of perioperative shivering between ondansetron and placebo groups

The shivering among the groups was compared using chi-square test. There was no significant difference in the shivering at 5, 10, and 15 mins after subarachnoid block (p>0.05). However, at 30 mins 28% of the patients had grade 3 shivering in placebo group as compared to ondansetron group only 4% of the patients had grade 3 shivering and it was found to be significant (p=0.04). The results were shown in table 2.

Comparison of side effects between ondansetron and placebo groups

In this the study the incidence of hypotension was 4% in ondansetron group and 52% in placebo group and it was significant (p<0.001). The incidence of shivering was 8% in ondansetron group and 28% in placebo groups but was not significant (p=0.066). None of the cases in ondansetron group had bradycardia and only 8% of the cases in placebo group had bradycardia (p=0.149). The results were shown in table 3.
Table 1: Demographics and characteristics of the patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ondansetron group (n=25)</th>
<th>Placebo group (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>36.6±9.8</td>
<td>41.4±12.2</td>
<td>0.125@</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>22 (88%)</td>
<td>18 (72%)</td>
<td>0.157*</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>3(12%)</td>
<td>7 (28%)</td>
<td></td>
</tr>
<tr>
<td>BMI, Kg/m² (mean±SD)</td>
<td>25.5±3.4</td>
<td>23.9±3.4</td>
<td>0.104@</td>
</tr>
<tr>
<td>ASA physical status (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (68%)</td>
<td>12 (48%)</td>
<td>0.264#</td>
</tr>
<tr>
<td>II</td>
<td>8 (32%)</td>
<td>12 (48%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Type of Surgery (n.%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal surgeries</td>
<td>18 (72%)</td>
<td>16 (64%)</td>
<td>0.830*</td>
</tr>
<tr>
<td>Lower limb surgeries</td>
<td>4 (16%)</td>
<td>5 (20%)</td>
<td></td>
</tr>
<tr>
<td>Gynecological surgeries</td>
<td>3 (12%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>Duration of Surgery (mins)</td>
<td>158.0±40.0</td>
<td>160.4±39.4</td>
<td>0.832@</td>
</tr>
</tbody>
</table>

The data were shown as mean ±SD and n, %.@ denotes Unpaired T Test; # denotes Chi square test. P value <0.05 was considered as statistically significant.

Table 2: Comparison of shivering grade between the groups

<table>
<thead>
<tr>
<th>Shivering Grade</th>
<th>Ondansetron Group</th>
<th>Placebo group</th>
<th>Chi-square Test P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Mins After SAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>23</td>
<td>20</td>
<td>0.221</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10 mins after SAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>19</td>
<td>16</td>
<td>0.381</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>15 mins after SAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>18</td>
<td>13</td>
<td>0.098</td>
</tr>
<tr>
<td>Grade 1</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>30 mins after SAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>18</td>
<td>13</td>
<td>0.040</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Comparison of side effects between the groups

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Ondansetron Group</th>
<th>Placebo group</th>
<th>Chi-square Test P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shivering</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>7</td>
<td>0.066</td>
</tr>
<tr>
<td>No</td>
<td>23</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Bradycardia</th>
<th>No</th>
<th>24</th>
<th>96.0%</th>
<th>12</th>
<th>48.0%</th>
<th>0.149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0</td>
<td>0.0%</td>
<td></td>
<td>2</td>
<td>8.0%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>100.0%</td>
<td>23</td>
<td>92.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Assessed for eligibility (n = 70)**
  - Excluded (n = 20)
    - Not meeting inclusion criteria (n = 14)
    - Refused to participate (n = 6)
- **Randomized (n = 50)**
  - Ondansetron group (n=25)
    - Received Ondansetron IV 6mg
    - Received allocated intervention (n = 25)
  - Placebo group (n=25)
    - Received normal saline, 3ml IV
    - Received allocated intervention (n = 25)
- **Follow up**
  - Excluded from the study (n=0)
  - Lost to follow up (n = 0)
  - Excluded from the study (n=0)
  - Lost to follow up (n = 0)
- **Analysis**
  - Analyzed (n = 25)
  - Analyzed (n = 25)

Figure 1: Consort flow chart of the study participants

Figure 2: Comparison of perioperative systolic and diastolic blood pressure between ondansetron and placebo group
Discussion

In this randomized, double-blind placebo controlled trial, in patients undergoing emergency or elective surgeries of various departments, the i.v administration of ondansetron for prophylactic use displayed marked decreased hypotension rate during spinal anesthesia as that of the placebo. Albeit, spinal anesthesia is a safe and effective procedure, it produces hypotension and bradycardia. Earlier reports shows that the rate of hypotension and bradycardia post subarachnoid block is more frequent with a range between 10% - 80%.\textsuperscript{18,19} Spinal anesthesia provoked hypotension is activated by the Bezold-Jarisch (BJ) reflex, as a result of activation of 5-HT3 receptors. This receptor are present in ventricular walls, with afferent and efferent pathways include non-myelinated vagal C-fibers to the medulla and profound vagal activity and blockade of sympathetic outflow and thus leads to vasodilation, bradycardia, and hypotension. The alternate mechanism involved in the spinal anesthesia induced hypotension is the reverse Bainbridge reflex. In the event of high and low spinal anesthesia the amount of bradycardia is associated with fall in BP.\textsuperscript{20}
In the present study ondansetron at the dose of 6mg (IV) was administered 10 mins before spinal anesthesia and its effects on blood pressure, heart rate and shivering were monitored and there was a significant decrease in the incidence of hypotension. The results of this trial is in corroboration Owczuk et al. study in which 71 patients who underwent surgeries under subarachnoid block with ondansetron 8 mg, IV and there was a significant difference between MAP and SBP between study and control group and no significant variation in the HR. Previous studies conducted on obstetric patients shows that administration of 4 mg of ondansetron before subarachnoid block displayed low incidence of hypotension and vasopressor requirement.

In a recent systematic review and meta-analysis conducted by Tubog et al. analysis of thirteen trials encompassing 1166 patients undergoing spinal anesthesia for non-obstetric surgeries reveals that, prophylactic ondansetron significantly reduced the incidence of hypotension and bradycardia. Gao et al. performed a meta-analysis using 10 randomized controlled trials with 863 patients and the results showed that ondansetron decreased the incidence of hypotension and vasopressor consumption. Thus, mounting meta-analysis has been done in obstetric cases and only few studies are done on non-obstetric cases and further limited studies are reported on the efficacy 6mg ondansetron. So the present study is unique, since the efficacy of 6mg ondansetron in the prevention of hypotension in non obstetric is reported, with only few literatures have been reported.

In the present study, grade 3 shivering was significantly higher in patients receiving placebo as compared to ondansetron 30min after subarachnoid block. Shivering is one of the most prevalent complications as a result of post-anesthesia hypothermia. Spinal anesthesia mediated shivering is mainly due to increased heat owing to vasodilatation. The complications of shivering include arterial hypoxia and myocardial ischemia as a result of increased oxygen consumption. A previous meta-analysis which included six trials of 533 subjects, shows that compared with placebo, ondansetron was associated with a significant reduction of post anesthesia shivering without imposing a risk of bradycardia. In another, recent systemic review and meta-analysis done by Tubog et al. ondansetron significantly reduced the incidence of shivering (p=0.003) and also the need of rescue treatment for shivering (p=0.009) as compared to the placebo.

Finally, the outcome of the present study were in partial corroboration according to the study done by Wang et al. where the prophylactic efficacy 2, 4, 6 and 8 mg of ondansetron were evaluated in the prevention of hypotension in parturients underwent cesarean section under spinal anesthesia. They showed that the incidence of hypotension was 60% in the saline group 48.3% (2mg), 30% (4mg), 31% (6mg) and 40% (8mg) doses of ondansetron, respectively. Further, they also confirmed that ondansetron at the dose of 4 and 6mg were effective in the prevention of maternal hypotension, however their protocol was different as compared to the present study and they considered hypotension as >20% reduction in SBP, but we stated >20% reduction in mean arterial blood pressure.
Limitations

- First, we did not evaluate the clinical efficacy of ondansetron at the postoperative area; so it not possible to substantiate whether iv administration of ondansetron before subarachnoid block may elicit good clinical outcome post surgery.
- Second, post operative nausea and vomiting (PONV) were not evaluated since the efficacy of ondansetron in the mitigation of PONV has been widely reported.
- Third, in this study the efficacy of ondansetron at the dose of 6mg was not evaluated on elderly patients since the present study were done only on adult subjects.

Finally, future trials are warranted to evaluate the preventive role of ondansetron in spinal anesthesia induced hypotension and shivering using large sample size.

Conclusion

The present study supports the hypothesis that 6mg ondansetron, administered intravenously 10 mins before the injection of local anaesthetic into the subarachnoid space, mitigates the spinal anesthesia induced hypotension, bradycardia during abdominal, lower limb and gynecological surgeries particularly in adult patients.

Ethical considerations

The procedures followed in the study were in accordance with the ethical standards on human experimentation.

Previous presentation in conferences
Not applicable

Conflict of interest
None to declare

Funding sources
Nil

Acknowledgments
Nil

IRB number
Ref No: SU/SMS&R/76-A/2021/96

Clinical trial registration number
CTRI/2021/08/035388
References

16. Rashad MM, Farmawy MS. Effects of intravenous ondansetron and...


