Original Research Article

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Effects of Intravenous Ondansetron and Granisetron on Hemodynamic Changes and Blockade Characterestics Induced By Spinal Anesthesia: A Prospective Observational Study

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Abstract

Background: Spinal anaesthesia has many advantages for elective surgeries, but the undesired effect of hypotension is to be managed by different interventions. Induction of the Bezold Jarisch reflex in the setting of decreased blood volume, mediated through serotonin is hypothesised to be one of the factors contributing to hypotension. Recent studies suggested that ondansetron, a 5-hydroxytryptamine subtype 3 receptor antagonist, given prior to spinal anaesthesia may reduce the hemodynamic changes. *Aims:* To evaluate the effects of two serotonin receptor antagonists, ondansetron and granisetron in the spinal anaesthesia induced hypotension, bradycardia, sensory and motor blockade using hyperbaric bupivacaine in patients undergoing elective surgeries. *Methods:* A prospective observational study on 300 patients scheduled for elective surgery under spinal anaesthesia was donedividing them into 3 with 100 in each group, receiving intravenous ondansetron 4mg granisetron 1mg and saline 2mL respectively. Spinal anaesthesia was given using 3 ml 0.5% heavy bupivacaine. Mean arterial pressure, heart rate, vasopressor use, sensory and motor blockade, their regression were assessed. Chi-square test was used for analysing incidence of hypotension, ANOVA test for changes in mean arterial pressure, vasopressor use, motor and sensory blockade characteristics. p value<0.05 was considered statistically significant. *Results:* The ondansetron group, compared to granisetron and control groups showed a lower incidence of fall in mean arterial pressure, and vasopressor use [p< 0.05] No significant changes in heart rate, onset and regression ofsensory and motor blockade were noted among three groups. *Conclusion:* Intravenous ondansetron 4mg given before spinal anaesthesia in elective surgeries significantly decreased hypotension and vasopressor usage. There were no significant inter group differences in incidence of bradycardia, motor and sensory blockade.

Keywords: Spinal Anaesthesia; Ondansetron; Granisetron; Hemodynamic Changes; Motor and Sensory Blockade.

Inroduction

Orthopaedic procedures can be particularly challenging for anaesthesiologists. Patients ranging from an elderly patient with multiple comorbid conditions, to a youngdeceptively healthy trauma victim with associated injuries that can have significant impact on the type of anaesthetic administered would have to be dealt with. Spinal anaesthesia is usually preferred for elective lower limb surgeries due to many advantages like avoiding risks of general anaesthesia, better postoperative pain relief etc. It is a simple technique with low failure rate. But certain problems after giving spinal anaesthesia like hypotension, bradycardia and failure of block are the other side of the coin. The incidence of hypotension is about 13 to33%, which is the most frequent complication [1].

This study concentrated on two drugs, which can minimize the occurrence of hypotension after spinal anaesthesia namely ondansetron and granisetron, which are selective 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptor antagonist [2] These receptors are located peripherally as cardiac chemoreceptors on the cardiac vagal afferent, and centrally in the chemoreceptor trigger zone [3].

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Animal studies have demonstrated that serotonin (5-HT) could be associated with the induction of the Bezold–Jarisch reflex in the setting of decreased blood volume [4] Triggering of chemoreceptors sensitive to serotonin in the intra-cardiac wall by a reduction inblood volume due to decreased venous return may lead to increased vagal nerve activity, decreased sympathetic activity leading to bradycardia and vasodilatation [5]. This effect can be blocked at 5-HT_3 receptors. Recent studies suggestedthat ondansetron, and granisetron,

Five hydroxytryptamine subtype 3 (5-HT_3) receptor antagonists generally usedfor prophylaxis and treatment of nausea and vomiting, may also reduce the hemodynamic changes induced by spinal anaesthesia. The mechanism of action is believed to be inhibition of the Bezold-Jarisch reflex. Whether ondansetron can be used routinely to prevent spinal anaesthesia induced hemodynamicchanges is still unclear.

Moreover, 5-HT_3 receptors are present also in the dorsal horn of spinal cord, and serotonin have antinociceptive effect, which can be antagonized by selective 5-HT_3 receptor antagonist [6] So administration of intravenous 5HT_3 antagonists could affect the intensity or duration of sensory and motor block after spinal anaesthesia.

Our study was done to evaluate the effects ofondansetron and granisetron in spinal anaesthesia induced hypotension,bradycardia,sensory and motor blockade in patients undergoing elective lower limb surgeries.

Materials and Methods

After getting approval from The institutional Ethics Committee, a prospective observational cohort study was conducted in the elective operation theatre of Government Medical College, Kozhikode from January 2015 to February 2016, on 300 patients. ASA 1 and ASA 2 Patients scheduled for elective lower limb surgeries, of age 18 to 60 years with expected duration of surgery 1to 3 hours were selected for the surgery.

Patients who refused, those with contraindications for neuraxial block (coagulation defects, local infection) hypersensitivity to ondansetron and granisetron, uncontrolled hypertension, cardiovascular insufficiency were excluded.

After getting informedconsent, patients were randomly allocated into three groups using a random number table with 100 patients in each, named as group O, G and C, receiving intravenous ondansetron 4mg ie 2ml, granisetron 1mg with 1 ml normal saline, and normal saline 2 ml respectively. All patients received oral ranitidine150 mg and metoclopramide 10 mg on previous night of surgery and on morning of surgery. On the operation table, basal non-invasive BP, pulse rate and SpO_2 were recorded and patients were coloaded with 20 ml/kg of normal saline.

Five minutes before providing spinal anaesthesia, Group O patients received ondansetron 4 mg, Group G received granisetron 1 mgin 1ml saline and Group C received 2 ml normal saline intravenously. Spinal anaesthesia was given in the lateral position using 0.5% heavy bupivacaine at L3-L4 level through a 23 gauge Quincke needle.

The parameters assessed were mean arterial pressure, heart rate, vasopressor use, time for sensory and motor blockade and their regression.

Mean arterial pressure and heart rate were observed from starting of spinal anaesthesia at 2 min intervals for the initial 10 min, then at 15 minutes, 20 minutes, and then every 10 min till 60 minutes. Upper sensory level was assessed using a 26 gauge IM needle by bilateral loss of pinprick at the midclavicular line every 2 min till the fixation of the sensory level at 2 consecutive times and this was taken as the maximum sensory level. Then, the patients were evaluated every 15 minutes for two segment regression of sensory level.

The time to upper sensory block (defined as the time between intrathecal injection and achievement of the highest level of sensory blockade), two-segment regression (defined as the time between achievement of the highest level of sensory blockade and its regression to a level two segments lower) were recorded and analysed.

Modified Bromage scale

Grade	Criteria	Degree of block (%)
I	Free movement of legs and feet	Nil (0)
II	Just able to flex knees with freemovement of feet	Partial (33)
III	Unable to flex knees, but withfree movement of feet	Almost complete(66)
IV	Unable to move legs or feet	Complete (100)

Motor block was assessed every 2 min by the modified Bromage scale till the achievement of complete motor block, then every 15 minutes till complete motor recovery. Decrease in MAP more than 20% of baseline value was treated with 6mg mephentermine, decrease in heart rate less than 50/minute treated with atropine and shivering treated with 25 mg tramadol.

Data collected were entered into a master chart and necessary statistical tables were constructed. Statistical analysis was performed using SPSS programme version 18. Data was reported as mean ± SD. Chi-square test was used for the analysis of incidence ofhypotension & ANOVA test were employed for the analysis of changes in mean arterial pressure, vasopressor use, motor and sensory blockade characteristics. A p value<0.05 was considered statistically significant.

Observations and Results

The demographic data were analysed using student's t test. The study groups were comparable in terms of age, height and duration of surgery, as shown in Table 1. (p value =0.575, 0.159, 0.117 respectively).

Mean arterial pressure was assessed before giving spinal anaesthesia (Basal MAP), and at 2 min, 4 min, 6 min, 8 min,10 min 15 min, 20 min, 30 min, 40 min and 60 min. after giving spinal anaesthesia. (Shown in Table 2) There were no significant differences in basal MAP among three groups. Incidence of hypotension was analysed by Chi-square test.

Decrease in mean arterial pressure was significantly lower in Group O than Group G and Group C at 6 minutes, 8 minutes,15 minutes,30 minutes, 40 minutes and 60 minutes with a P value of 0.03, 0.038, at 6 and 8 minutes. 0.001, at 15, 30, 40 minutes, and 0.004 at 60 minutes respectively. A comparison of changes in mean arterial pressure among the three groups were done by Post Hoc test as shown in Table 3. It showed that the decrease in mean arterial pressure was significantly lower in group O than other two at 6, 8, 15, 30, 40 and 60 minutes.

Table 1: Demographic data

	Group O	Group G	Group C	P value
Age (years)*	43.1 ± 10.2	44.1 ± 10.3	44.6 ± 9.6	0.575
Height (centimeters)*	164.14 ± 6.5	163.9 ± 7.3	164.43 ± 7.9	0.159
Duration of surgery (minutes)*	91.8 ± 23.5	93.2 ± 24.9	91.7 ± 23.3	0.117

Table 2: Mean arterial pressure

	Group O Mean ± SD	Group G Mean ± SD	Group C Mean ± SD	P value
0 min	86.5 ± 7.8	84.4 ± 7.8	82.9 ± 8.5	0.12
2 min	74.9 ± 5.6	73.6 ± 6.8	74.3 ± 7.2	0.37
4 min	68.9 ± 7.3	69.63 ± 7.7	67.9 ± 7.4	0.27
6 min	70.4 ± 7.6	68.7 ± 6.8	67.8 ± 6.7	0.03*
8 min	73.2 ± 6.5	71.7 ± 6.9	70.7 ± 7.4	0.038*
10 min	72.6 ± 7.7	74.4 ± 7.5	73.6 ± 8.3	0.27
15 min	77.5 ± 7.6	74.5 ± 7.2	73 ± 7.5	0.001*
20 min	74.7 ± 5.9	75.7 ± 6.4	73.8 ± 8.1	0.124
30 min	80.4 ± 6.8	79.3 ± 6.9	74 ± 7.8	0.001*
40 min	83.3 ± 7.4	81.5 ± 7.7	77.8 ± 8.5	0.001*
60 min	83.9 ± 8.2	82.9 ± 8.9	80.3 ± 6.9	0.004*

Table 3: Comparison of fall in mean arterial pressure

Dependent variable	Group 1	Group 2	Mean difference	P value
6 min	Group O	Group C	2.6	0.03
8 min	Group O	Group C	2.5	0.001
15 min	Group O	Group C	4.1	0.001
15 min	Group O	Group G	3.4	0.02
30 min	Group O	Group C	6.1	0.001
30 min	Group O	Group G	2.1	0.03
40 min	Group O	Group C	6.3	0.001
60 min	Group O	Group C	4.2	0.004
60 min	Group O	Group G	2.3	0.02

Mean value of mean arterial pressure was charted as shown in Figure 1. It is seen that mean arterial pressure lies above 70 mm Hg throughout the observation period in the ondansetron group.

On comparing the need for mephentermine as a rescue vasopressor, significant difference was seen among the groups, with decreased amount of vasopressor needed in Group O with a mean value of 5.76 mg, (SD of 4.46); when compared to 7.08 mg in Group G (SD of 4.77) and 7.44 mg in Group G, (SD of 5.40) as shown in Figure 2. On statistical analysis, a significant P value of 0.03 was obtained among the three groups; as well as when tested between groups using Post-hoc test.

Heart rate less than 50 beats/minute was taken as bradycardia, and there were no significant difference in incidence of bradycardia among three groups, with a p value of 0.828.

Time taken for (in minutes) the attainment of upper sensory level and 2 segment regression was assessed and analysed statistically. There were no significant difference among three groups with a P value of 0.294 and 0.74 respectively (Figure 3).

Table 4: Time taken for the attainment of modified Bromage grade 3

	Group O	Group G	Group C	P value
Time for modified bromage 3 (minutes)	122	125	123	0.294

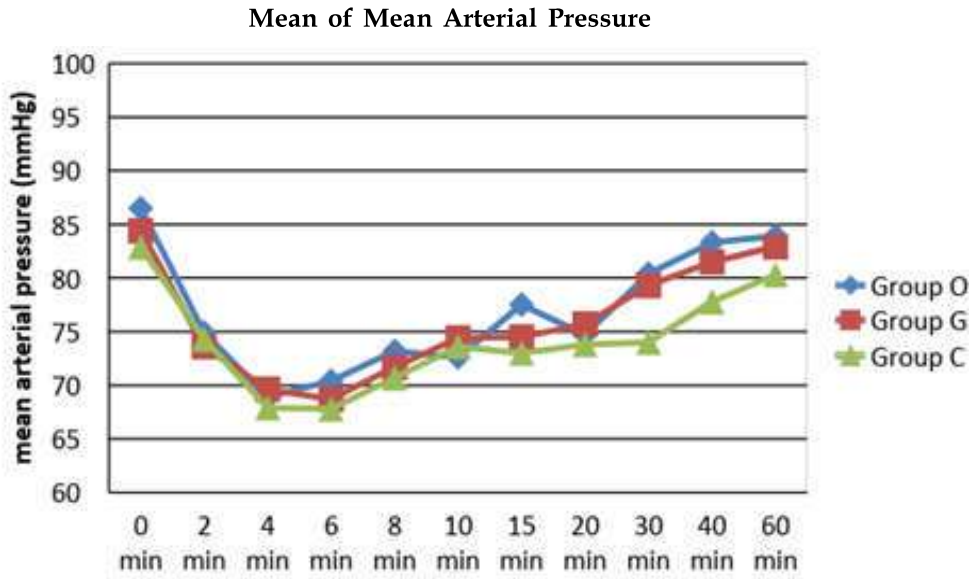

Fig. 1:

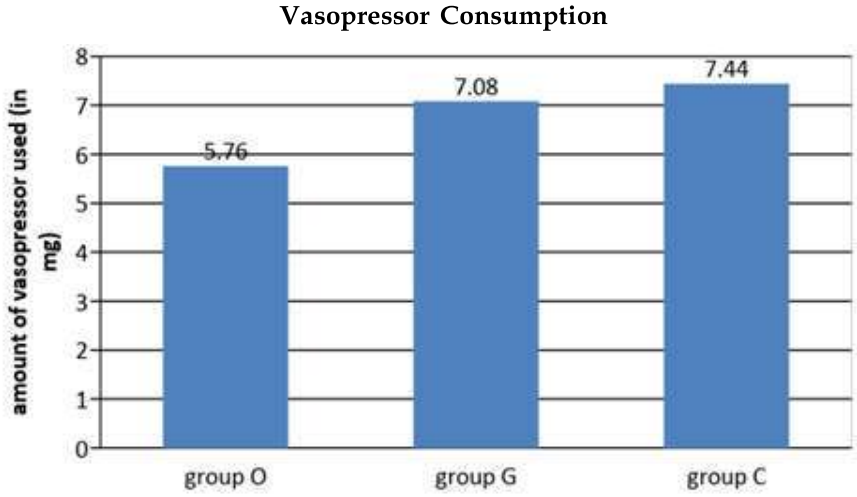

Fig. 2:

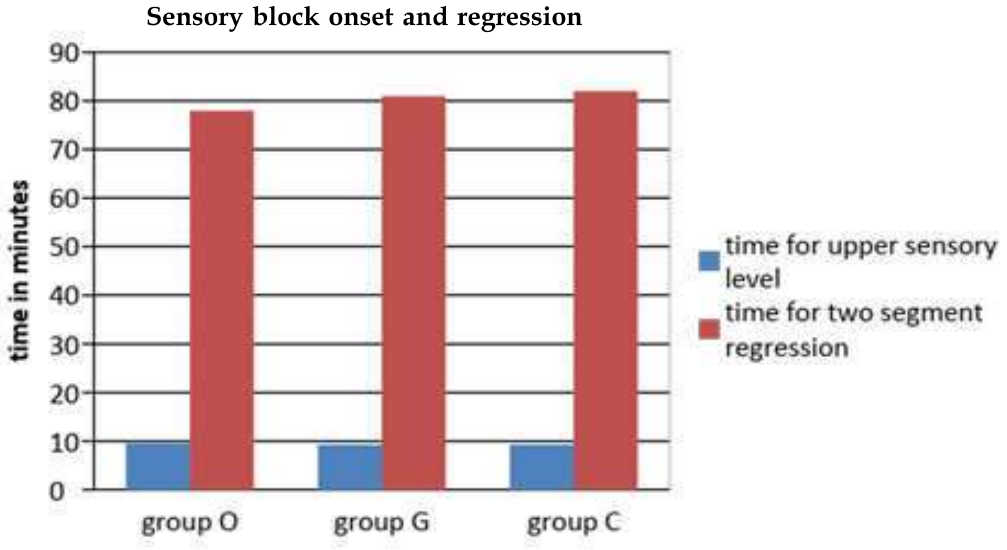

Fig. 3:

Timetaken (minutes) for the attainment of Modified Bromage scale was assessed.There was no significant difference among three groups with a P value of 0.294 (Table 4).

Discussion

Spinal anaesthesia is a simple, fast, reliable, and cost-effective technique which has emerged as the technique of choice for routine lower limb surgeries. It avoids the risk associated with general anaesthesia, but has some undesired effects associated with it, the most common being hypotension due to sympathetic block. Several studies were done in a trial to prevent undesired cardiovascular effects of spinal anaesthesia like hypotension, which in turn leads to multiorgan involvement.

Hypotension during subarachnoid block occurs due to a marked decrease in systemic vascular resistance by blockade of the sympathetic nerve fibres, which control vascular smooth muscle tone. The rate of onset and spread of the neuraxial blockade determines the extent of the sympathetic involvement and the severity of hypotension. Decreased stroke volume and heart rate is caused by blockade of the peripheral (T1-L2) and cardiac (T1-T4) sympathetic fibres as well as adrenal medullary secretion.

Bezold Jarisch reflex is also a cause of profound bradycardia and circulatory collapse after spinal anaesthesia, especially in the presence of hypovolemia. Mechanoreceptors of this reflex are located mainly in left ventricle.These receptors are activated by a rapid decrease in ventricular blood volume, induced by spinal anaesthesia, and gives feedback via the vagus nerve which triggers a vasodepressor response by increasing the activity of parasympathetic system. Systemic vasodilatation, hypotension and bradycardia occur as a consequence of this.

Serotonin can induce Bezold Jarisch reflex. The afferent limbis unmyelinated type C fibres that pass via the vagus nerve to the brainstem. 5-HT_3 receptors are mainly located in this infra cardiac afferent vagal and sympathetic neurons. $5HT_3$ receptors mediate the most dramatic cardiovascular effect of serotonin-The Bezold Jarisch reflex. Few seconds after intravenous administration of serotonin, a very strong bradycardia is observed followed by hypotension. These effects are due todepolarization and activation of afferent vagal nerve endings in the heart carrying $5HT_3$ receptors [8,9]. Direct stimulation of the cardiac 5-HT_3 chemoreceptors located on cardiac vagal afferents with serotonin or with 5-HT_3 agonists elicited BJR in several mammals [10,12]. Animal studies proved that intravenous or direct pericardial administration of $5HT_3$ antagonists completely abolished Bezold Jarisch reflex,induced by serotonin or $5HT_3$ agonists [4,7,11].

This study was designed to test the effectiveness of pre-treatment with intravenous granisetron and

ondansetron for the prevention of spinal anaesthesia induced hypotension and bradycardia due to Bezold Jarisch reflex. Current research in animals, obstetric and nonobstetric populations indicates that 5-HT3 antagonism may abolish the Bezold-Jarisch reflex.

We also attempted to study the effect of ondansetron and granisetron on sensory and motor blockade characteristics induced by spinal anaesthesia, sinceserotonin has got a definite role in antinociception. Serotonin acts as a neurotransmitter in the descending system that inhibits signals from peripheral nociceptors. 5-HT_3 receptors are present also in the dorsal horn of spinal cord and have antinociceptive effect, which can be antagonized by selective 5-HT_3 receptor antagonist [6].

Previous studies have concluded that $5HT_3$ receptor antagonists are effective in preventing spinal anaesthesia induced hemodynamic changes [13,14,19,20].

There have been only a few studies which assess the effectiveness of ondansetron and granisetron for prevention of hemodynamic changes induced by spinal anaesthesia as wellas motor and sensory blockade characteristics.

In our study, onanalysis of the incidence of fall in mean arterial pressure, we found that the drop in mean arterial pressure were less for ondansetron group compared with granisetron and control group, at many time intervals, and the difference was statistically significant. The total amount of mephentermine as the vasopressor used to correct hypotension was significantly lower in ondansetron group compared with granisetron and control group, with a mean value of 5.76 mg, 7.08mg and 7.44 mg in ondansetron, granisetron and control group respectively.

Ondansetron is one of the medications studied before by Sahoo et al. [14] and proved that it attenuated hypotension induced by spinal anaesthesiaif given intravenously in caesarean section patients beforespinal anaesthesia and our results agreewith it. Tsikouris et al. [16] in their study with granisetron found that, it decreased heart rate and BP changes occurring during the head-up tilt table test due to Bezold Jarisch Reflex. In our study, it was found that granisetron has no effects on the hemodynamic variables, and this is in agreement with the study of Mowafi et al [6].

Bradycardia was considered when heart rate was below 50 per minute. Analysingbradycardia, there were no significant difference in the incidence of bradycardia between three groups.This finding is comparable with those of Rashad MM et al. [18], who studied the effect of ondansetron and granisetron on hemodynamic changes induced by spinal anaesthesia inparturients undergoing caesarean section and found that there were no significant difference in the incidence of bradycardia among three groups.

Animal studies clarified that serotonin has antinociceptive effect at the spinal cord level by inhibiting the excitatory transmittersand increasing the inhibitory transmitters [21,22] Consequently, serotonin antagonists decrease the nociceptive threshold as proved by Giordano and Dyche [23].

When we studied the effects of ondansetron and granisetron on sensory regression and motor block of subarachnoid anaesthesia it was found that intravenous ondansetron and granisetron did not affect sensory or motor block of intrathecal bupivacaine, similar to the observation made by Samra et al. in their study [17].

They did the study in 60 patients for TURP surgery under spinal anaesthesia, and found thattime to attain peak sensory block,time to two segment regression ,regression to the S_1 dermatome, and mean duration of motor block did not significantly differ between the ondansetronand control group. But Sasaki M et al. [24] found that systemic ondansetron enhance the sensory block regression after intrathecal lidocaine.

These differences between the effects of ondansetron and granisetron, both of them being in the same category and mechanism of action, may be due to the action of ondansetron on mixed receptors and the high selectivity of granisetron on 5-HT_3 receptors than to other 5-HT receptors [25].

Conclusion

Prophylactic intravenous use of 4 mg ondansetron reduces the severity of spinal anaesthesia induced hypotension and the need for rescue vasopressor than with granisetron and control groups.

There were no significant differences in the incidence of bradycardia,sensory and motor blockade characteristics among groups.

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