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Study of intavenous granisetron on haemodynamic changes and motor and sensory blockade in spinal anesthesia with hyperbaric bupivacaine in patient undergoing infraumblical surgery

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Abstract
Objective: The aim of this study is to examine the effects of granisetron on the sensory and motor block and haemodynamic changes resulting from subarachnoid block using hyperbaric bupivacaine.
Methods: Forty ASA I and II adult patients undergoing infraumblical surgery under spinal anesthesia were included in this prospective, randomised, double blind study. They wrere randomly divided into two groups.Using computer generated random numbers, patients were allocated to one of two groups:
Control Group: Patients of this group received normal saline.
Granisetron Group: Patients of this group received 1mg Granisetron. Patients of both groups received heavy 0.5% Bupivacaine intrathecally.
Result: All the demographic parameters were comparable**.**19 patients (67.8%) in saline group while 13 patients (46.4%) in granisetron group had hypotension which was treated with IV ephedrine. Saline group had more than three episodes of hypotension while none of the patients in granisetron group had hypotensive episodes more than two.The maximum cephalad spread of sensory block was similar (P = 0.13).T Patients who received granisetron had significantly faster sensory regression times by two segments from T12 - S1. However motor regression is similar in both group. There were no significant differences between the two groups in haemodynamic variables.
Conclusion: IV administration of granisetron, in a dose of 1 mg, before intrathecal bupivacaine results in a faster recovery of sensory block in adult patients. There is also less incidence of hypotension in Granisetron group.

Keywords: Spinal anaesthesia, bupivacaine, granisetron, normal saline

Introduction
Hypotension is one of the main side effect of spinal anaesthesia and its incidence is about 80% [1]. Blockade of sympathetic efferent is one of the main mechanism by which produces cardiovascular side effects [2]. There are several way to minimize hypotension after subarachnoid block like preloading or co-loading of intravenous fluid, positioning, use of vasopressors and compression devices [3, 4, 5]. The decrease in preload may initiate vagally mediated cardiodepressor reflexes, the Bezold Jarisch Reflex which may be mediated by peripheral serotonin receptors (5-HT3 type) [6] However only few studies have shown the role of ondansetron and granisetron in the prevention of the Bezold-Jarisch reflex, [7, 8]. Granisetron is a highly selective 5-HT3 receptor antagonist [9]. It is not metabolized by the cytochrome P450 (CYP) 2D6 pathway therefore is associated with less variation in patient response due to factors such as pharmacogenomic differences.[10] The 5-HT3 binding sites are numerous at the the superficial laminae and substantia gelatinosa of the spinal cord.[13,14] Although, the spinal serotonergic mechanisms in pain modulation are complex. In rats, intrathecal injection of the selective 5-HT3 receptor agonist, 2-methyl-serotonin, revealed an antinociceptive activity. This effect was antagonized by the selective 5-HT3 receptor antagonists [17]. In humans, the cerebrospinal fluid serotonin levels increased three-fold after spinal bupivacaine administration [18] In addition, ondansetron antagonized the sensory blockade of spinal lidocaine [19]. The aim of this study is to examine the effects of granisetron on the sensory and motor block and hamodymanic changes resulting from subarachnoid block using hyperbaric bupivacaine.

Material and Methods

Ethics Statement

The study was approved by Institute Ethics Committee and was registered with Clinical Trials Registry-India at www.Ctri.nic.in (CTRI/2019/05/019193). Written consent was obtained after informing the participants about the risks, the nature and scope of study.

Duration and type of study

This study was conducted in department of Anesthesia in Indira Gandhi Institute of Medical sciences, Patna, Bihar, India between May 2019 and December 2019. Forty consenting adult patients were included in this double-blind, randomized, comparative study. The sampling type was randomized cluster sampling.

Inclusion criteria: The patients who give informed written consent, Age group 20-40 years of any sex, ASA grade I and II, Height more than 140 cms, Weight less than 90 kgs, and BMI less than 38.

Exclusion criteria: Patients who refuse to provide informed consent., Patient with contraindication to Spinal Anesthesia, Known Cardiovascular Disease, Haematocrit less than 30%, Hepatic/ Renal failure, Any degree of heart block, Beta blocker use.

Preanesthesia

Pre-anesthesia evaluation of all patients was done before admission to the ward. All patients were pre-medicated with Tab Rantidine 150 mg & Tab Alprazolam 0.25 mg the night before surgery. All patients were kept fasting for 6 h prior to undergoing surgery.

Intervention plan

On the arrival in operation theatre, routine monitoring in the form of electrocardiography, non-invasive blood pressure, pulse oximetry, and respiration were done and baseline values were noted. Intravenous access was established with an 18G intravenous catheter on dorsum of non-dominant hand.

Using computer generated random numbers, patients were allocated to one of two groups: Patients were randomly allocated into two equal groups (20 patients each) to receive either granisetron (granisetron group) or saline (control group). The granisetron group received IV 1 mg granisetron and The control group received an equal volume of 0.9% normal saline on arrival to the operating room.

Preload with Ringer's Solution 20ml/kg just prior to spinal anaesthesia and infusion is continued at 5 ml/kg/h after spinal injection until the end of surgery. 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 anesthesia. Under aseptic precautions lumbar puncture was performed with 25 gauze spinal needle (Quincke's needle) through midline approach with patient in sitting position at L3-L4 or L4-L5 position.

Patients were placed in the supine position. Baseline all parameter recorded and then at 5-min intervals up to 20 min, followed by 10 min intervals until the end of surgery. Upper sensory levels were assessed twice at 5-min intervals with cold sensation and the level of motor blockade was assessed according to the Modified Bromage scale.Unwanted effects like nausea, vomiting, shivering were noted in remarks.

- Cephalad sensory level by loss of cold sensation bilaterally at the mid-clavicular line using a spirit soaked cotton swab at every 2 minutes until the sensory block remained at the same level at two consecutive times and was recorded as maximal sensory block. Thereafter, the patients were evaluated every 15 min until sensory level regression to S1.
- Motor block every 2 min until maximal motor blockade, then every 15 min until complete motor recovery, on described Modified Bromage scale as follows:

1. Complete Block, (Unable to move feet, knees, hip)
2. Almost complete block (able to move feet)
3. Partial block (just able to move knee)
4. Detectable weakness of hip flexion while supine, (full flexion of knee)
5. No detectable weakness of hip flexion while supine(full flexion of knee)
6. Able to perform partial knee bend

Assessed the following variables at time intervals after spinal injection:

1. Maximum sensory block
2. Regression of sensory level by two dermatomes
3. Regression of sensory level to T12
4. Regression of sensory level to S1
5. Maximum motor block
6. Motor recovery by one level
7. Complete motor recovery (modified Bromage scale)

Blinding

The study drugs were prepared and administered by the independent anesthesiologist not involved in the study. The anesthesiologist giving spinal anesthesia and observing the patient was blinded to the treatment group. Neither the patient nor the attending anesthesiologist who collected the data was unaware of group allocation.

Rescue interventions

Decrease of systolic blood pressure to <100mm of Hg or more than 20% of baseline is treated with Ephedrine 5 mg iv; HR <50 beats/min is treated with titreted dose of iv atropine 0.6 mg. Shivering is treated with 100 mg tramadol in i.v. drip. Nausea and vomiting was treated with iv Ondenseteron 4 mg. When ephedrine or atropine were necessary, only values obtained before these medications were analyzed. Pain after spinal anaesthesia is treated with iv Fentanyl 100 mcg, but if persisted was considered as failed spinal anaesthesia & convert in general anaesthesia, and the patient excluded from the study. If blood loss exceeds allowable loss, blood transfusion started and case excluded from the study.

Statistical Analysis

At the completion of data were analyzed by using Microsoft Excel SPSS 21 software. Data were expressed as mean, standard deviation & confidence interval. Fischer's exact tests were used if more than 25% of cell frequency had expected value less than five. Students t test for continuous independent variables was used for comparing results. Chi square test was used for categorical variable. The 'p-value' calculated were considered statistically significant if value less than 0.05.

Results

There were no significant differences between the two groups with regard of age, weight, height, gender, and duration of surgery (Table 1).

Table 1: Demographic parameters

	Control Group	Granisetron Group	p-Value
Age in years (mean± SD)	27.07±3.934	27.14±4.395	0.949
Gender (male/female)	18/2	19/1	1.01
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
Duration of surgery (min)	57.5 ± 12.1	52.8 ± 13.0	1.01
BMI(kg/m2)	25.069±2.6414	24.116±2.3036	0.156

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%) in saline group while 13 patients (46.4%) in granisetron group had hypotension which was treated with IV ephedrine. When comparing between groups, saline group had more than three episodes of hypotension while none of the patients in granisetron group had hypotensive episodes more than two. The maximum cephalad spread of sensory block was similar (P = 0.13), since it was T4-5 (range, T2–8) in the control group and T5 (range, T3–9) in the granisetron group. The time course of spinal block in both groups is summarized in Table 2, which shows that patients who received granisetron had significantly faster sensory regression times by two segments from T12 - S1. There were no significant differences between the two groups in hemodynamic variables. One patient in each group required 10 mg of ephedrine to treat hypotension. Atropine was never given, and neither anesthetic failure nor complications related to spinal anesthesia were observed. 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 2: Time Course of Spinal Block

	Control Group (n = 20)	Granisetron group (n = 20)
Time to maximum sensory block (min)	10.2 ± 2.8	10.1 ± 2.0
Time to regression of sensory level by two dermatomes (min)	88.0 ± 27.8	69.8 ± 25.5*
Time to regression of sensory level to T12 (min)	127.0 ± 30.5	105.5 ± 25.1*
Time to regression of sensory level to S1 (min)	189.8 ± 39.8	162.8 ± 41.1*
Time to maximum motor block (min)	8.9 ± 2.1	9.3 ± 2.7
Time to motor recovery by one level (min)	117.0 ± 17.3	103.5 ± 32.3
Time to complete motor recovery (min)	160.8 ± 35.3	148.3 ± 44.6

Data are mean _ SD. * P_0.05.

Table 3: Baseline hemodynamic parameters and duration of surgery

Variable	Control Group (n=28)	Granisetron Group (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 of Hg) 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

Table 4: 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 5: Incidence of other side effects of the spinal anaesthesia in two groups

Variables	Group A	Group B	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 in spinal anesthesia are due to a decrease in systemic vascular resistance, central venous pressure, sympathetic block, and blood redistribution. The bradycardia is due to blockade of the sympathetic cardio accelerator fibers from T1-4 spinal segments is often suggested more common with high blocks. Diminished venous return has been another cause of bradycardia. Intracardiac stretch receptors have been reflexively decrease heart rate when filling pressures [18]. Another mechanism is hypovolaemic stimulation of cardiac sensory receptors in the left ventricle induces the Bezold Jarisch reflex (BJR).The Bezold-Jarisch Reflex is a cardio inhibitory 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 [14, 19]. The finding in our study was the significant decrease in use of vasopressors in patient who were given IV granisetron prior to of spinal anesthesia. The reduction in use of vasopressors is useful for risk population such as elderly and pregnant women. There are other methods for the prevention of hypotension are pre & co-loading of IV fluid, use of vasopressors, left lateral tilt [11, 12, 13]. But none of these techniques alone was sufficient in eliminating hypotension [19].This study prophylaxtic use of intravenous granisetron is effective 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 [20]. *Radoslaw et al.* found that 8 mg intravenous ondansetron (5-HT3 antagonist), attenuates the SBP and MAP drop in spinal anesthesia [21]. 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 [22]. 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.[23]The incidence of hypotension in our study was 57.1% which was comparable to previous data [15, 18]. 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 [24]. 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.

The important finding in this study is that IV Granisetron before spinal anaesthesia faster recovery of the sensory blockade. While motor blockade was similar in both groups. Fassoulaki *et al.* who reported that IV ondansetron caused a faster regression of the sensory block after spinal lidocaine [19]. In addition of that ondansetron and tramadol decreased its analgesic potency on postoperative pain [21]. In rats, intrathecal injection of serotonin antagonists significantly reduced the nociceptive threshold to both inflammatory and thermal pain [22]. No previous study examined the concomitant administration of IV Granisetron and spinal bupivacaine in humans. Granisetron, in contrast to ondansetron, which acts on mixed receptors, strongly and selectively binds to the 5-HT3 receptors with minimal or no affinity for other 5-HT receptors, or dopaminergic, adrenergic, histaminic, and opioid receptors [23]. Additionally, it has minimal adverse effects and possible drug interactions [9, 11].

The potential mechanisms are not clear. However, electrophysiologic and antinociceptive mechanisms of the descending serotonergic system at the spinal cord level [14, 24]. It directly hyperpolarizes the membrane of substantia gelatinosa neurons, inhibits the excitatory transmitter, glutamate, release from A and C afferent fibers presynaptically and increases the inhibitory transmitters release including aminobutyric acid and glycine from the interneurons [24]. The role of 5-HT3 receptors in pain modulation is could be excitatory and inhibitory effects, depending on the concentration of 5-HT3 or the state (sensitized/desensitized) of the spinal cord [25]. On the peripheral part, 5-HT3 receptors that mediate the inflammatory pain may be effectively inhibited through the local administration of granisetron and tropisetron [26, 28] Collection of the sensory and motor regression data at 15-min intervals is a limitation of our methodology. The dose of granisetron used in our study was 1 mg as per Food and Drug Administration (FDA) and the prescribing information of the drug for treatment of postoperative nausea and vomiting (PONV). *Fujii* and *Tanaka* found that the effective dose of granisetron for treatment of PONV in women was 20 mcg/kg body weight in a prospective, randomized, doubleblind, placebo-controlled study [29]. Although most studies have demonstrated granisetron's efficacy at 1 mg dose for prophylaxis of PONV, other researchers showed that substantially lower doses (0.1–0.35 mg) of granisetron have been effectively used as a prophylaxis and/or treatment of PONV [30, 10]. The effect of lower doses of granisetron on the sensory level regression time after spinal bupivacaine remains unknown. This study raises several concerns that need to be further investigated. Should the dose of bupivacaine for spinal anesthesia be adjusted whenever Granisetron is concomitantly used. The potential for Granisetron to reverse perioperative analgesia also requires further investigation. In addition, other studies are required to determine whether patients with intractable pain who are treated by granisetron demonstrate resistance to neuraxial analgesia.

Conclusion

IV administration of granisetron, in a dose of 1 mg, before intrathecal bupivacaine results in a faster recovery of sensory block in adult patients. There is also less incidence of hypotension in Granisetron group.

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