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The Effect of Intravenous Granisetron on the Sensory and Motor Blockade produced by Intrathecal Bupivacaine

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Abstract:
Background: *Granisetron, a potent antiemetic and a highly selective $5HT_3$(serotonin)receptor antagonist shows action on peripheral as well as central receptors. Since serotonin has an important role in pain modulation, premedication with such serotonin antagonists could influence the subarachnoid block produced by spinal anaesthesia .*
Study design: *prospective randomized double blind study.*
Patients & Method: *Eighty unpremedicated patients undergoing pelvic or lower limb surgeries were randomly taken into two equal groups. Study group received 1mg i.v.granisetron and control group received same volume of normal saline five minutes prior to spinal anaesthesia. The maximum sensory and motor block achieved and the time to achieve it was recorded.Two segment regression of sensory block, regression of sensory level to T_{12}, regression of sensory level to S_1 and motor recovery were documented*
Results: *Demographic data showed insignificant difference in the two groups. The time of onset of sensory block as well as the maximum sensory level achieved was similar in both the groups. However the time to two segment regression of sensory blockwas significantly faster in granisetron group. There was no difference with respect to onset and regression of motor block in the two groups.*
Conclusion: *Administration of 1mg intravenous granisetron five minutes prior to spinal anaesthesia with 0.5% hyperbaric bupivacaine without any additives in unpremedicated patients causes faster regression of sensory level without affecting the speed of onset of sensory or motor block.*
Keywords: *$5HT_3$ receptor antagonists, granisetron, spinal anaesthesia, sensory and motor blockade, intravenous premedication*

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I. Introduction

An anaesthesiologist administers various drugs in the perioperative period. This includes anaesthetic drugs as well as non-anaesthetic agentsadministered by different routes. This polypharmacy can result in pharmacokinetic and pharmacodynamics interactions between drugs. These interactions and their implications need to be studied.Spinal anaesthesia i.e. subarachnoid block is unparalleled in the way a small mass of drug, virtually devoid of systemic pharmacologic effects, can produce profound surgical anaesthesia. The main reasons for the popularity ofsubarachnoid block are that the block has well-defined endpoints and the anaesthesiologist can produce the block reliably with a single injection. The versatility of subarachnoid block is afforded by a wide range of local anaesthetics and additives that allow control over the level, the time of onset and the duration of spinal anaesthesia. Spinal anaesthesia with hyperbaric bupivacaine 0.5% is a popular method for abdominal, pelvic or lower limb surgeries.Bupivacaine has a reasonably rapid onset of action and anaesthesia is satisfactorily long.

Prophylactic administration of anti-emetics is routinely practised by anaesthesiologists to prevent occurrence of nausea and vomiting in the perioperative period. Various classes of anti-emetics commonly used include dopamine antagonists, pro-kinetics, antihistamines, anticholinergics, and 5-HT_3 receptor antagonists. Other drugs like steroids and anaesthetic agents like propofol also have anti-emetic property.

Granisetron is a highly selective 5-HT_3(5-hydroxytryptamine) receptor antagonist. It is a potent anti-emetic and is commonly used to prevent or treat perioperative and chemotherapy/radiotherapy induced nausea and vomiting. The serotonergic (5-HT_3) receptors play an important role in pain modulation. While the peripheral 5-HT_3 receptors subserve mechanisms of nociception and contribute to secondary inflammation, central 5-HT_3 system is a critical substrate in analgesia[1]. Simultaneous use of a drug like granisetron which modulates pain pathways could affect the duration of action of bupivacaine. The aim of this study was to

examine the effects of granisetron on the sensory and motor block resulting from subarachnoid anaesthesia using hyperbaric bupivacaine.

II. Patientsand Method

After Ethics committee approval and written informed consent, 80 patients aged 18-60 years of ASA I-II scheduled for any pelvic or lower limb surgery were enrolled in this prospective randomized double-blind study done at our tertiary care teaching hospital over a period of one year.

Exclusion criteria were patients with difficulty in communication, chronic pain, neurological diseases, those receiving drugs such as opioids, α_2 agonists, calcium channel blockers, drugs acting on the serotonin receptors(e.g. Buspirone, sumatriptan, ketanserin, atypical antipsychotics) or affecting the level of serotonin in the body (e.g. selective serotonin reuptake inhibitors), pregnant or nursing women, patients having any contraindication to spinal anaesthesia and patient refusal.

Patients were randomly allocated into either of two groups, Granisetron group (n=40) or Control group (n=40).Randomization was done with computer-generated random coding. Double blinding was ensured such that the perioperative nursing staff, surgical team, patient and the anaesthesia team was unaware of the allocation. According to the randomization code, the study drug was prepared by an anaesthetist who was not involved in the study.No sedation or analgesic premedication was given.The coded syringe containing same volume of either drug was handed over to the anaesthesiologist.Granisetrongroup received 1mg intravenous granisetron five minutes prior to spinal anaesthesia. The patients in the Control group received an equal volume of intravenous0.9% normal saline at the same time.

In the operation theatre, non-invasive monitors including cardioscope, pulseoximeter, sphygmomanometerwere attached.Baseline pulse rate, respiratory rate, systolic and diastolic blood pressure, electrocardiogram (ECG) and peripheral oxygen saturation (SpO_2) were noted and regularly monitored until the end of the study. Intravenous access was secured using an 18G cannula and10mL /kg /hrRinger lactate solution was infused before spinal anaesthesia and infusion was continued at 5mL / kg /hr till the end of surgery. All patients received supplemental oxygen at 6 L / min using Hudson face mask until recovery. Under all aseptic precautions, spinal anaesthesia was performed with the patient in sitting position at the L3- L4 intervertebral space via midlineapproach , with 23G Quincke needle.After a free flow of cerebrospinal fluid was confirmed, 3ml of hyperbaric 0.5% bupivacaine was injected slowly in over 15 seconds without barbotage. After injection patient was kept in the supine position and maintained in the same throughout the surgery. In the operating room and recovery room following parameters were recorded:

1. Blood pressure and heart rate every 5 minutes for first 20 minutes after injection followed by every 15 minutes during the surgery.
2. Cephalad sensory level by loss of pinprick sensation bilaterally in the midclavicular line using a short bevelled 25G needle every 2 minutes from the time of injection until the level of sensory block remains constant three consecutive times and is recorded as maximum sensory block. Thereafter patients is evaluated every 15 minutes until the sensory level regresses to S1.
3. Motor block every 2 minutes until maximum motor blockade, then every 15 minutes till complete motor recovery on modified Bromage scale:

0 = able to move hip, knee, ankle and toes
1 = unable to move hips, able to move knees, ankle and toes
2 = unable tomove hips and knees, able to move ankle and toes
3 = unable to move hips, knees, ankle, able tomove toes
4 = unable to move hips, knees, ankles and toes

A more than 30% decrease in systolic blood pressure below baseline was treated with 10mg i.v.ephedrineand a decrease in heart rate more than 45 beats per minute was treated with 0.6 mg i.v. atropine.

From the recorded variables the time intervals to be assessed are the time elapsed from the spinal injection to:

1. Maximum sensory level
2. Two segment regression
3. Regression of the sensory level to T_{12}
4. Regression of the sensory level to S_1
5. Maximum motor block (Modified Bromage scale 4)
6. Motor recovery

III. Observation and Results

80 patients were divided randomly into two equal groups of 40 each and labelled as Control group and Granisetron group. The demographic and study parameters were compared and analysed using the Pearson chi-square test and independent sample t-test and the results were considered significant if $p \leq 0.05$.

1. Demographic parameter: Age

By Pearson chi-square test, p value was found to be 0.651. Since the p value is more than 0.05, the difference between the age of patients in the two groups is statistically insignificant.

Age group	Group		Total
	Control	Granisetron	
18 to 30 years	17	12	29
31 to 40 years	4	4	8
41 to 50 years	10	11	21
51 to 60 years	9	13	22
Total	40	40	80

Table no 1: shows comparison of age in years of patients in the Control group and the Granisetron group

2. Demographic parameter: Weight

By Pearson chi-square test, p value was found to be 0.269. Since the p value is more than 0.05, the difference between the weights of patients in Control group and Granisetron group is statistically insignificant

Weight	Group		Total
	Control	Granisetron	
50 to 60 kg	14	19	33
61 to 70 kg	15	16	31
71 to 80 kg	9	5	14
More than 80 kg	2	0	2
	40	40	80

Table no 2: showing comparison of weight in kilograms of patients in the Control group and the Granisetron group

3. Demographic parameter: Height

By Pearson chi-square test, p value was found to be 0.562. Since the p value is more than 0.05, the difference between the height of patients in the Control group and Granisetron group is statistically insignificant.

Height (cm)	Group		Total
	Control	Granisetron	
150 to 160 cm	25	24	49
161 to 170 cm	14	16	30
171 to 180 cm	1	0	1
Total	40	40	80

Table no 3: showing comparison of height of patients in centimeters in the Control group and Granisetron group

4. Demographic parameter: Gender distribution

By Pearson chi-square test, p value was found to be 0.22. Since the p value is more than 0.05, the two groups have statistically insignificant difference with respect to the gender distribution of the patients.

	Male	Female
Control group	27	13
Granisetron group	25	15

Table no 4: showing the gender distribution of patients in the Control group and Granisetron group

5. Maximum sensory level in Control and Granisetron group

By Pearson chi-square test the p value was found to be 0.111. Since the p value is more than 0.05, the two groups have statistically insignificant difference between the maximum sensory level attained by the patients.

	Max level T4	Max level T6	Max level T8
Control group	14	19	7
Granisetron group	15	19	6

Table no 5:showing maximum sensory level achieved by the Control group and Granisetron group

6. Time required for maximum sensory level

By independent sample t-test, p value was found to be 0.953. Since the p value is more than 0.05, the difference between the time required for maximum sensory level to be achieved in the two groups is statistically insignificant.

Group	Mean time for max sensory level (minutes)	Standard Deviation	SEmean
Control group	8.88	2.09	0.33
Granisetron group	8.9	1.692	0.267

Table no 6: showing mean time in minutes required for maximum sensory level in Control group and Granisetron group

7. Time required for two segment regression

By independent sample t-test, the p value was found to be 0.001. Since the p value is less than 0.05, the difference between the time required for two segment regression in the two groups is statistically significant, Thus, two segment regression occurred significantly faster in the Granisetron group as compared to the Control group.

Group	Mean time for two segment regression (minutes)	Standard Deviation	SEmean
Control group	89.05	12.708	2.009
Granisetron group	70.83	12.838	2.03

Table no 7: showing the mean time in minutes required for two segment regression in the Control group and Granisetron group

8. Time required for sensory level to recede to T12

By independent sample t-test, the p value was found to be 0.001. Since the p value is less than 0.05, the difference between the mean time required for sensory level to recede to T12 in the two groups is statistically significant. Thus, regression of sensory level to T12 occurred significantly faster in the Granisetron group as compared to the Control group.

Group	Mean time for level to recede to T_{12} (minutes)	Standard Deviation	SEmean
Control group	130.15	14.44	2.28
Granisetron group	107.82	8.42	1.33

Table no 8: showing mean time required for sensory level to recede to T12 in the Control group and Granisetron groups

9. Time required for sensory level to recede to S1

By independent sample t-test, the p value was found to be 0.001. Since the p value is less than 0.05, the difference in the mean time required for regression of sensory level to S1 between the two groups is statistically significant. Thus, the regression of sensory level to S1 occurred significantly faster in the Granisetron group as compared to the Control group.

Group	Mean time for level to recede to S_1 (minutes)	Standard Deviation	SEmean
Control group	187.85	16.67	2.63
Granisetron group	156.45	9.79	1.54

Table no 9: showing the mean time required for sensory level to recede to S1in the Control group and Granisetron group

10. The time in minutes (mean) for the sequential regression of sensory level in Control group and Granisetron group is show in table no. 10.

Group	Mean time to max sensory level (minutes)	Mean time to 2 segment regression (minutes)	Mean time for sensory regression to T_{12} (minutes)	Mean time for sensory regression to S_1 (minutes)
Control group	8.875	89.05	130.15	187.85
Granisetron group	8.9	70.825	107.83	156.45

Table no 10: showing sequential regression of sensory level in the Control group and Granisetron group

11. Time required for maximum motor blockade

By independent sample t-test, the p value was found to be 0.84. since the p value is more than 0.05, the difference in the time required for achieving maximum motor blockade in the Control group and the Granisetron group is statistically insignificant.

Group	Mean time for onset of maximum motor blockade(minutes)	Standard deviation	SE_{mean}
Control group	7.7	1.829	0.289
Granisetron group	7.78	1.387	0.219

Table no 11: showing the mean time required for maximum motor blockade in the Control group and Granisetron group

12. Time required for motor recovery by one level

By independent sample t-test, the p value was found to be 0.102. Since the p value is more than 0.05, the difference in the mean time required for motor recovery by one level in the Control group and the Granisetron group is statistically in significant.

Group	Mean duration of maximum motor blockade(minutes)	Standard deviation	SE_{mean}
Control group	114.85	10.07	1.59
Granisetron group	111.23	9.51	1.5

Table no 12: showing mean time required for motor recovery by one level in the Control group and Granisetron group

13. Time required for complete motor recovery

By independent sample t-test, the p value was found to be 0.164. Since the p value is more than 0.05, the difference in the time required for complete motor recovery between the Control group and Granisetron group is statistically insignificant.

Group	Mean time (min) for complete motor recovery	Standard deviation	SE_{mean}
Control group	145.23	9.17	1.45
Granisetron group	142.2	10.08	1.56

Table no13:showing mean time in minutes for complete motor recovery in the Control group and Ganisetron group

14. The time in minutes (mean) for the sequential regression of motor blockade in the Control group and the Granesetron group is shown in table no. 14.

	Max motor level(minutes)	Motor recovery by one level (minutes)	Complete motor recovery (minutes)
Control group	7.7	114.85	145.23
Granisetron group	7.8	111.23	142.2

Table no 14: showing sequential regression of motor blockade in the Control group and Granisetron group

15. Adverse effects.

There were no significant differences in the haemodynamic variables in both the groups. 3 patients in the Control group and 2 patients in the Granisetron group required i.v. ephedrine to treat hypotension. No patient had significant bradycardia requiring treatment. 4 patients in the Control group had nausea peri-operativelyand required treatment with intravenous metoclopramide 10 mg.

IV. Discussion

Spinal anaesthesia I sa popular form of regional anaesthesia devoid of the drawbacks of general anaesthesia like need for securing the airway ,nausea ,vomiting, excessive sedation etc.The most common reason for nausea and vomiting under spinal anaesthesia is hypotension and probably additives like opioids[2,3]. The practice of prophylactic administration ofantiemeticsinvolves polypharrmacy with different antiemetic agents administered by different routes in the perioperative period[4]. As a result there may be interactions between the various drugs which may have anaesthetic implications as well.

Serotonin is an essential central nociceptive-modulating neurotransmitter. Spinal serotonergic 5-HT_3 receptors mediate bulbospinal analgesia. These receptors seem to play a role in the antinococeptive effect of serotonin against a mechanicalacute noxious stimulus[1].

Since Granisetron belongs to the class of 5-HT_3 antagonists which are commonly administered as antiemetic drugs in the perioperative period, this study was undertaken to evaluate its effecton intrathecal bupivacaine mediated analgesia and motor block.

80 patients were randomly allocated into two groups of 40 patients each. While patients in the study group received 1mg intravenous Granisetron as premedication, the patients in the control group received equal volume of normal saline.

Demographic variables:

In our study, patients studied across both groups (Control group and Granisetron group) did not vary significantly with respect to age, height, weight and gender.

A study conducted by Praggeret al suggests that age, weight and height significantly correlate with the sensory level after spinal hyperbaric bupivacaine[5].Also a study byZaidi et al suggests slower regression of spinal level in elderly patients[6].

Thus although various patient characteristics especially age, height, weight may influence the onset and duration of subarachnoid block, these factors are not contributory to any statistically significant difference in the findings in our study.

Onset of sensory and motor block:

In our study the maximum sensory level was achieved in 8.8±2.09 minutes in the control group and in 8.9±minutes in the Granisetron group. The difference between the onset of maximum sensory level is statistically insignificant (p=0.953). Similarly, maximummotor block(modified Bromage scale 4) was achieved in 7.7±1.829 minutes in the control group and 7.8±1.387 minutes in the Granisetrongroup.The difference between the two groups is statistically insignificant(p=0.84)

As per a study conducted by ShashiKiran et al increasing doses of bupivacaine enhances the speed of onset of spinal anaesthesia[7]. A similar study by Bogra et al agreed with this finding and also showed that additives like opioids given intrathecally increased the speed of onset of sensory and motor block[8].In our study we have used 3ml of 0.5% bupivacaine in both groups without any additives and the maximum sensory level as well as the maximum motor block achieved was similar in both the groups.

Fassoulaki et al who studied the effect of intravenous ondansetron on the sensory and motor blockadebyintrathecal lignocaine alsofound there tobenoeffect on the onset of action[9].

In our study, comparing with those in the Control group, patients in the Granisetron grouphad significantly faster two segment sensory regression(89.05±12.708 min vs 70.83±12.838 min, $p < 0.01$), sensory regression to T_{12} (130.15±14.44min vs 107.83±8.42 min, $p < 0.01$)and sensory regression to S_1(187.85±16.67min vs 156.45±9.79 min, $p < 0.01$). In contrast there was statistically insignificant difference in the motor recovery by level 1 as per modified Bromage scale (114.85±10.07 min vs 111.23±9.51 min, p =

0.102).Also the time to complete motor recovery was similar in both the groups (145.23±9.17 min vs 142.2±10.0 min, p = 0.164).

Our finding agree with those of Mowafi et al who did a controlled study on the effects of granisetron on sensory and motor blockade produced by intrathecal bupivacaine in patients of elective knee arthroscopy[10].

MM Rashad and Farmawy compared the effects of ondansetron and granisetron on haemodynamic changes and sensory and motor blockade produced by spinal anaesthesia for elective caesarean section patients. They concluded that while intravenous ondansetron given before spinal anaesthesia decreased the incidence of hypotension, premedication with 1mg intravenous granesetron can cause faster recovery from the sensory blockproduced by spinal anaesthesia[11].

O Khalifa did a comparative study on the prophylactic use of intravenous granisetron, ondansetron and ephedrine in patients for caesarean section under spinal anaesthesia. Among other findings they concluded that there was faster recovery of sensory block with granisetron[12].

MostafaMegahed et al compared the clinical effects of intravenous ondansetron and granisetron in women given spinal anaesthesia for caesarean section and incidentally found significant faster recovery from the sensory block in granisetron group compared with ondansetron and saline groups[13].

A Kumar et al did a comparative evaluation of premedication with intravenous ondansetron or granisetron in patients posted for infra-umbilical surgeries given spinal anaesthesia. Their results note a statistically significant faster sensory block regression in ondansetron and granisetron group in comparison with the control group[14].

Various factors affect the regression of sensory and motor block. Astudy by Kooger et al showed that with the same dose of hyperbaric bupivacaine, the duration of subarachnoid block is longer in patients with restricted spread of the local anaesthetic[15]. Thus, maximum sensory level may affect the duration of analgesia. Both our Control and Granisetron groups had a maximum sensory level between T_4 to T_8. The statistical difference between the maximum sensory level of the two groups was insignificant (p = 0.111).

Moore JM et al showed additionof epinephrine to low dose intrathecal bupivacaine prolongs the duration of action[16]. Similarly, Singh H et al showed addition of intrathecal fentanyl prolongs the duration of sensory block of bupivacaine[17]. As per a study by Liu Spencer et al, oral or parenteral premedication with clonidine also prolongs the analgesic action of intrathecal local anaesthetics. Similarly, intrathecal clonidine prolongs the duration of sensory analgesia[18].In our study we used 3ml of plain hyperbaric bupivacaine without any additives in both the groups. No other premedication other than the study drug was given to the patients.

Perhaps the time duration between premedication with granisetron and spinal anaesthesia could influence the clinical effects observed. S Mohammadi et al evaluated the systemic effects of intravenous granisetron given fifteen minutes prior to spinal anaesthesia with hyperbaric bupivacaine in patients for cystoscopy and concluded that granisetron did not have any effect on duration of sensory or motor block produced by spinal anaesthesia[19].

Granisetron is a highly selective 5-hydroxytryptamine3 (5-HT_3) receptor antagonist[20]. In contrast to ondansetron, which acts on mixed receptors, granisetron strongly and selectively binds to the 5-HT_3 receptors with minimal or no affinity for other 5-HT receptors or dopaminergic, adrenergic, histaminic and opioid receptors[21].

The 5-HT_3 binding sites are abundant at the spinal level[22]. These receptors are located in the superficial laminae and substantiagelatinosa of the dorsal horn of the spinal cord[23]. Although the spinal serotonergic mechanisms in pain modulation are complex, several studies have confirmed the role of 5-HT_3 receptors in antinociception[24,25].

While spinal 5-HT_3 receptors appear to play a role in mediating bulbospinal analgesia, the peripheral 5-HT_3 receptors mediate a component of inflammatory pain. Thus, systemically administered 5-HT_3 antagonists will have anti-nociceptive effects at peripheral sites and pro-nociceptive effects at central receptors[23].

Thus, the faster regression of sensory level observed in the Granisetron group was probably due to its 5-HT_3 antagonist activity at the central receptors, which antagonised the sensory analgesia of the subarachnoid block.

Our concerns are that especially in prolonged surgeries or surgeries requiring a sensory level of T8 and above,

- Should the anti-emetic dose of granisetron be reduced to reduce effect on spinal sensory blockade?
- Should granisetron and other $5HT_3$antagonists be avoided in case of patients undergoing spinal anaesthesia?
- Should the dose of the intrathecal drugs be modified taking into consideration the effect of granisetron?

V. Conclusion

Our study shows that administration of 1mg intravenous granisetron just prior to spinal anaesthesia using3 mL hyperbaric 0.5% bupivacaine without any additives in unpremedicated patients causes faster regression of sensory level without affecting either the speed of onset of sensory or motor block or the duration of motor blockade.

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