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ONDANSETRON VERSUS GRANISETRON EFFECTS ON HEMODYNAMIC INSTABILITY DURING SPINAL ANESTHESIA FOR CESAREAN SECTION

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ABSTRACT

Background: Spinal anesthesia avoids the risks involved in managing the airway of the parturient. Hypotension, shivering, nausea and vomiting are frequent risks in patients undergoing cesarean delivery under spinal anesthesia, Prophylactic intravenous administration of serotonin receptor antagonists such as ondansetron and granisetron has been used to overcome this problems. **Objective:** This study evaluated the efficacy of intravenous ondansetron and granisetron on hemodynamics, shivering and motor & sensory block in female undergoing elective cesarean section under spinal anesthesia. **Patient and Method:** Seventy five patients were assigned to three equal groups: group O received 4 mg Ondansetron, group G received 1 mg Granisetron and group S received 10 ml normal saline 5 min before spinal anesthesia. The incidence of hypotension, bradycardia, SaO2 changes, shivering, nausea and vomiting were recorded at baseline monitoring, intraoperative and postoperative. Also propagation and regression of motor and sensory block were assessed. **Results:** There was significant difference as regard decrease in mean arterial blood pressure and presence of shivering, nausea and vomiting between group S and both groups O and G, also there was significant difference as regard faster time to regression of sensory block between group G and both groups O and S. **Conclusion:** Prophylactic intravenous administration of 4 mg ondansetron or 1 mg granisetron 5 min before induction of spinal anesthesia in cesarean section can significantly reduces the severity of spinal-induced hypotension, reduce the incidence of nausea, vomiting and shivering. Regression of sensory block was faster with granisetron more than ondansetron and normal saline.

KEYWORDS: Cesarean section, granisetron, ondansetron, spinal anesthesia.

INTRODUCTION

Spinal anesthesia is a popular technique for cesarean delivery as it is easy to perform and provides a rapid-onset, dense surgical block. It is not associated with maternal or fetal risk for toxicity to local anesthetics **(Nag et al., 2015)**, but it is associated with hypotension and bradycardia, which may be deleterious to both parturient and baby **(Hajian et al., 2017)**. Fetal oxygenation depends on maternal oxygen carrying capacity, maternal cardiac output, and uteroplacental perfusion. Therefore, any interventions that compromise these factors may lead to fetal asphyxia **(Puvanesarajah et al., 2016)**.

There are several methods to minimize maternal hypotension after spinal anesthesia like fluids, medications, and physical methods like positioning, leg bindings, etc. **(Cyna et al., 2006).**

This study concentrated on two medications, which can minimize the occurrence of maternal hypotension after spinal anesthesia. They are ondansetron and granisetron selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists. These receptors are located peripherally as cardiac chemoreceptors on the cardiac vagal afferent and centrally in the chemoreceptor trigger zone **(Martinek, 2004).** Moreover, 5-HT3 receptors are present also in the spine and have antinociceptive effect, which can be antagonized by selective 5-HT3 receptor antagonist **(El Khouly & Meligy, 2016)**.

On the other hand, previous studies proved that the level of serotonin increased significantly in cerebrospinal fluid after intrathecal bupivacaine, and the sensory block of intrathecal lidocaine was antagonized by ondansetron **(Fassoulaki et al., 2005; Obasuyi et al., 2013; Marashi et al., 2014; Mattoo and Thosani, 2017**).

The aim of this study was to compare the effects of the two serotonin receptor antagonists' ondansetron and granisetron on the spinal induced hypotension, bradycardia, sensory, and motor block after spinal anesthesia in women undergoing cesarean sections.

PATIENTS AND METHODS

After approval of the medical ethics committee and obtaining written consent from each patient, this comparative study was conducted from June 15, 2016 through February 22, 2017 at Al Azhar University hospitals. S pregnant women aged between 20 to 40 years, with an ASA physical status of I–II, with GCS 15 were eligible if they were scheduled for elective cesarean section under spinal anesthesia were included in this study. Patients were excluded if they have any contraindications to subarachnoid block, history of hypersensitivity to studied drugs, hypertensive disorders with pregnancy or those receiving selective serotonin reuptake inhibitors or migraine medications or refused to participate.

Patients were randomly assigned to receive Ondansetron 4mg (Group O), Granisetron 1mg (Group G) or normal saline (Group S), each group contain 25 parturients. Study medications were prepared, presented as identical 10ml filled syringes and injected 5min before spinal anesthesia.

For eligible patients, demographic information was collected and a physical examination was performed. A standardized anesthesia regimen was followed. Age, weight, height, duration of surgery and ASA (I/II) were recorded and analyzed.

In the preoperative preparation room, nearly 500 ml crystalloid (lactated ringer's or normal saline 0.9%) given IV after insertion of IV 18 gauge cannula in non-dominant hand. On arrival in the operating room, patients monitored for mean arterial blood pressure MAP, electrocardiogram & pulse oximeter and this become baseline monitoring. After sterilization of the back, spinal anesthesia was induced at L3–L4, with the patient in the sitting position, with 2ml (10mg) of 0.5% hyperbaric bupivacaine plus 0.5ml (25µg) fentanyl after confirmation of free flow of cerebrospinal fluid through a 25-G Quincke spinal needle. The patients were then placed in the supine position with 15° left tilt.

Supplemental oxygen was administered via facemask at 4L/min. Maintenance fluids (10 ml/kg in the first one hour and 5ml/kg in the subsequent hours) were given at room temperature. Oxytocin was given following delivery of the fetus.

Hemodynamic data [mean arterial pressure (MAP), heart rate, oxygen saturation SaO2 and ECG changes] were recorded at 2-min interval in the first 15-min and then every 15-min until the end of procedure.

Rescue i.v. bolus doses of 9 mg ephedrine were given if the parturient became hypotensive (hypotension was defined as a decrease in MAP more than 20% from the baseline). Decrease in HR to less than 50 beat/min was treated with 0.5 mg atropine intravenous.

Rescue i.v. 10 mg metoclopramide for vomiting episode and i.v. 25mg pethidine for shivering episode. Pain was treated with i.v. 50µg fentanyl, but if persisted, it was considered failed spinal anesthesia, and patient anesthetized generally and excluded from the study.

The height of sensory blockade was assessed as the highest dermatome with loss of fine pinprick sensation at two consecutive times and this is the maximum sensory level; then, the patients were evaluated every 15 min till sensory level regression to S1. The time to upper sensory block, two-segment regression and sensory regression to T10 and S1 were recorded and analyzed.

Also, motor block was assessed every 2 min by the modified Bromage scale till the complete motor block then every 15 min till complete motor recovery.

Modified Bromage scale **(Ziyaeifard et al., 2014)**.

- Grade 0= able to move hip, knee, ankle, and toes.
- Grade 1= unable to move hip, able to move knee, ankle, and toes.
- Grade 2= unable to move hip and knee, able to move ankle and toes.
- Grade 3= unable to move hip, knee and ankle, able to move toes.

Sensory and motor recovery time will be noted, attacks of nausea, vomiting, shivering and hemodynamic monitoring (MAP, HR and SaO2) will be recorded 30 min, 2, 4, 6, 12 and 24 hours postoperative.

Statistical analysis

The Statistical Program SPSS (SPSS Inc., Chicago, Illinois, USA) for Windows, version 20, was used for data entry and analysis. Quantitative data were presented as mean and SD, whereas qualitative data were presented as frequency distribution. Analysis of variance was used to compare the means between groups, followed by post-hoc analysis. The $\chi 2$-test and Fisher's exact test were used to compare between proportions.

RESULTS

In the present study, there were no significant differences between the three groups as regard demographic data (age, weight and height), procedure duration and ASA I/II.

As regards the decrease in MAP, there were significant differences between group S and both groups O and G at 4, 6, 8, 10, 12 and 60 min, P value 0.035, 0.003, 0.006, 0.005, 0.011 and 0.042 respectively. While there were no differences between groups O and G (figure 1).

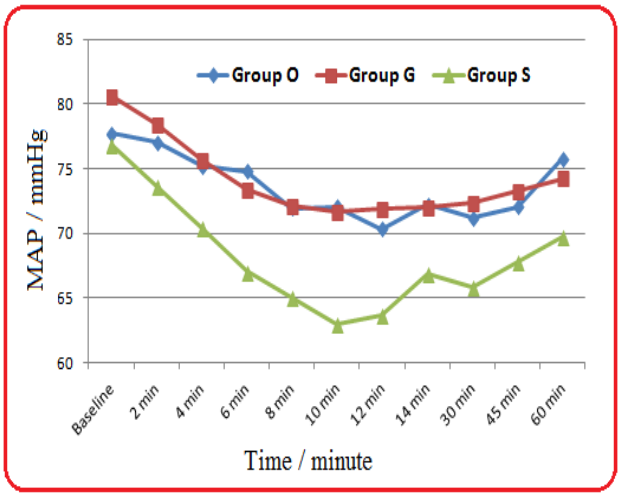

Figure (1): Changes in Mean Arterial Pressure (MAP) in studied groups.

As regard to heart rate and **oxygen saturation** there were no significant differences among the three groups (figure 2, 3).

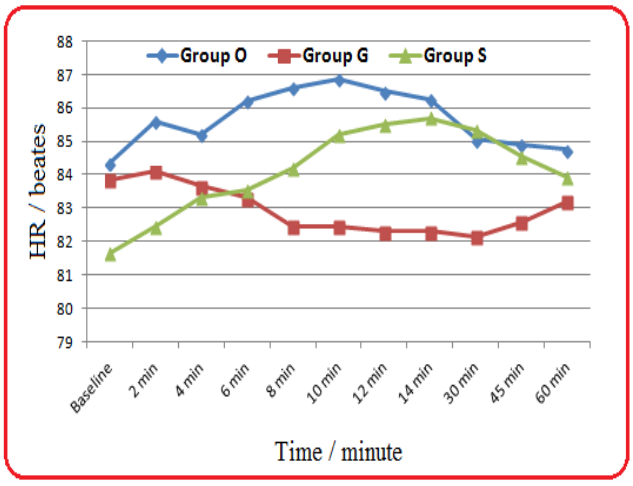

Figure (2): Changes in heart rate (HR) in studied groups.

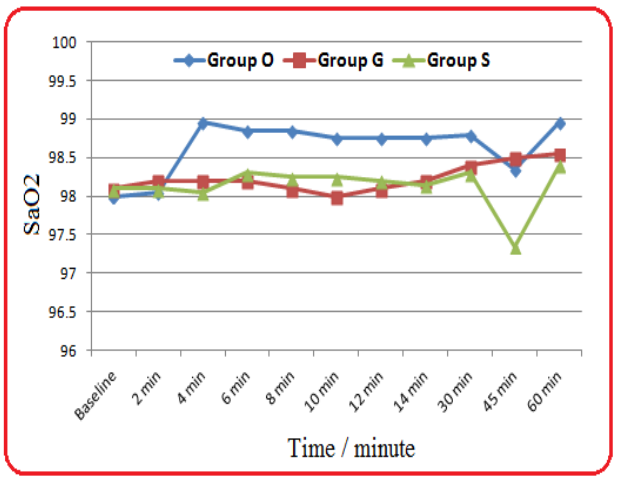

Figure (3): Changes in oxygen saturation (SaO2) in studied groups.

As regard sensory block, the maximum cephalad spread of sensory block in three groups there were no significant differences. At 60 min intraoperative there was significant regression in sensory block in group G faster than both groups O and S, p value <0.001. At 1:30hr, 2:00hr and 4:00hr there were significant regression in sensory block in group G faster than both groups O and S, p value <0.001 (Table 2).

On the other hand, there were significant difference as regard time to two segment regression and regression to T10, and S1 were faster in group G than groups O and S, p value <0.05, but no significant differences found between groups O and S (table 1).

As regard motor block, there were no significant differences among the three groups in the time to maximum motor block, time to motor recovery by one level, and the time to complete motor recovery (table 1).

As regard postoperative side effects of the spinal anesthesia: There was significant increase in the number of cases experienced nausea in group S more than groups G and O (30% vs 5% and 5%, respectively; p<0.05), but no significant differences found between groups G and O. **As regard vomiting**, there were three cases suffering from vomiting in group S versus to one case in groups O with no cases in group G (p<0.01).

As regard shivering, there were three cases suffering from episode of shivering in group S versus to no cases in groups O or G (p<0.01) (table 3).

Table (1): Demographic data, procedure duration and time to motor and sensory block among groups of study.

	Group O (Ondansetron) (N0.=20)	Group G (Granisetron) (N0.=20)	Group S (Normal saline) (N0.=20)	One way ANOVA	
	Mean + SD	Mean + SD	Mean + SD	F/X^2*	P-value
Age (year)	30.30+6.49	29.55+6.27	29.45+5.90	0.110	0.896
Weight (kg)	79.0+10.11	75.00+11.67	74.0+13.0	2.780	0.430
Height (cm)	167.0+5.0	165.0+5.20	167.0+6.0	2.903	0.450
Procedure duration (min)	63.20+7.11	63.98+8.75	60.81+8.23	3.810	0.470
ASA levels I II	14 (70%) 6 (30%)	13 (65%) 7 (35%)	14 (70%) 6 (30%)	0.476*	0.179
Time to modified Bromage scale grade 4	10.22+1.2	10.0+0.8	9.88+0.9	2.80	0.460
Time to sensory regression to T6 (min)	35.45+22.03	28.94+19.93	35.33+21.74	0.49	<0.05
Time to sensory regression to T8 (min)	50.85+43.55	38.11+30.67	51.06+42.91	0.45	<0.05
Time to sensory regression to T10 (min)	62.51+29.75	47.9+25.57	61.22+39.75	0.42	<0.05
Time to sensory regression to S1 (min)	198.4+31.63	132.4+36.94	197.5+32.74	0.56	<0.05

Table (2): Levels of sensory block at 60min and postoperative monitoring in studied groups.

Sensory block		Group O (Ondansetron) (N0.=20)		Group G (Granisetron) (N0.=20)		Group S (Normal saline) (N0.=20)		Chi square test	
		No	%	No	%	No	%	X^2	P-value
60 min	T4 T5 T6 T7 T8	11 6 8 0 0	45.0% 20.0% 35.0% 0.00% 0.00%	0 1 8 8 8	0.00% 5.00% 35.0% 30.0% 30.0%	9 7 9 0 0	35.0% 30.0% 35.0% 0.00% 0.00%	35.83	<0.001
1:30 hr	T10 T5 T6 T8	0 0 4 21	0.00% 0.00% 10.0% 90.0%	22 0 0 3	95.0% 0.00% 0.00% 5.00%	0 3 0 22	0.00% 5.00% 0.00% 95.0%	60.158	<0.001
2:00 hr	S1 T10 T12	0 25 0	0.00% 100.% 0.00%	21 2 2	90.0% 5.00% 5.00%	0 25 0	0.00% 100.% 0.00%	55.610	<0.001
4:00 hr	Recovery S1	0 25	0.00% 100.%	22 3	90.0% 10.0%	0 25	0.00% 100.%	51.429	<0.001

Table (3): Incidence of side effects of the spinal anesthesia in studied groups.

Side effect		Group O (Ondansetron) (N0.=20)		Group G (Granisetron) (N0.=20)		Group S (Normal saline) (N0.=20)		Chi square test	
		No.	%	No.	%	No.	%	X^2	P-value
Nausea	No Yes	23 2	92.0% 8.00%	23 2	92.0% 8.00%	18 7	72.0% 28.0%	8.077	0.017
Vomiting	No Yes	23 2	92.0% 8.00%	25 0	100.0% 0.00%	18 7	72.0% 28.0%	11.03	0.002
Shivering	No Yes	25 0	100.0% 0.00%	25 0	100.0% 0.00%	21 4	84.0% 16.0%	6.316	0.043

DISCUSSION

In the present study, two 5-HT3 antagonists, ondansetron and granisetron, as they block the Bezold–Jarisch reflex (BJR) and may successfully treat postspinal hypotension, this randomized controlled study was designed to test the effectiveness of pretreatment with intravenous

ondansetron or granisetron for the prevention of spinal anesthesia induced hypotension and bradycardia (**Heesen et al. 2016)**.

The important finding in this study is that, despite the reduction in mean arterial blood pressure (MAP) in the two therapeutic groups, it still less than that in group S, with significant difference recorded, with the least reduction in MAP detected in group O and the greatest in group S. Although nonsignificant differences in heart rate were observed between the groups at any time of study duration with higher rates noticed in groups O and G. Oxygen saturation (SaO2) and HR were closely similar in three groups with nonsignificant differences in all studied groups.

Eldaba and Amr, (2015) showed that administration of 1 mg of granisetron at 5 minutes before spinal anesthesia can reduce significantly the incidence of hypotension in these patients in comparison with placebo (normal saline). Moreover, they also reported that the dosages of ephedrine and atropine in the granisetron group were significantly lower than those of the placebo group.

Also **Abbas et al. (2014)** obtained same results in their study, intravenous administration of 4mg ondansetron 5min prior to subarachnoid block, is effective in decreasing frequency of hypotension.

Trabelsi et al. (2015) showed in their study that prophylactic ondansetron had a significant effect on the incidence of hypotension in healthy parturients undergoing spinal anesthesia with bupivacaine and sufentanil for elective caesarean delivery.

In study done to evaluate role of granisetron in postspinal hypotension by **Saberi, (2016)**, he showed that intravenous administration of 3 mg of granisetron immediately before spinal anesthesia in parturients (ASA Class I) undergoing non-emergency cesarean surgery had no effect on spinal anesthesia-induced hypotension compared with placebo. But he recommended that, regarding the results of his study and other similar studies on the effect of granisetron and ondansetron in prevention of spinal anesthesia-induced hypotension in cesarean section as well as different findings for the ondansetron effect, and very few studies about the effect of granisetron, it seems that further studies are required before a definite statement can be made.

Jarineshin et al. (2016) believed that their findings show the preventive effect of ondansetron on serotonin-induced BJR, reduction of vasodilation, and improvement of venous return, leading to less reduction in DBP and MAP. The blockade of 5-HT3 receptors inhibits serotonin-induced BJR.

Further, in the study **Arivumani and Ushadevi, (2016)** administration of intravenous Ondansetron 4mg given 5 minutes prior to spinal anesthesia significantly reduces the hypotension. The episodes of bradycardia as well as the requirement of vasopressors in parturients were low in ondansetron group, which was found to be statistically insignificant, may be due to less number of study population.

In contrast to the present study, **Mowafi et al. (2008)** found that i.v. granisetron administration had no effect on hemodynamic variables. In addition, the study by **Ortiz-Gómez et al. (2014)** showed that prophylactic ondansetron at 2, 4, or 8 mg i.v. had little effect on the incidence of hypotension in healthy parturients undergoing spinal anesthesia with bupivacaine and fentanyl for elective cesarean delivery. **Shrestha et al. (2015)** concluded that 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 anesthesia.

As regard motor and sensory block, we found that IV granisetron administration before spinal bupivacaine results in a faster recovery of the sensory blockade. On the contrary, the offset of motor blockade was similar in all groups.

These findings agree with prior studies by **Mowafi et al. (2008)**, **Rashad and Farmawy, (2013), and Khalifa, (2015)** as they concluded that i.v. granisetron facilitated the recovery of sensory block after bupivacaine subarachnoid anesthesia and resulted in a statistically faster sensory regression and earlier home discharge from the day-surgery unit.

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 **(Lummis & Thompson, 2013)**. Additionally, it has minimal adverse effects and possible drug interactions **(Aapro, 2004)**.

Kasem, (2016) found that administration of 1mg of granisetron before spinal anesthesia in ambulatory surgeries resulted in a statistically faster sensory regression and earlier home discharge from the day-surgery unit.

Against our study, **Marashi et al. (2014)** did not observe any significant changes in sensory block on using two different doses of ondansetron. Further, **Samra et al. (2011)** concluded that i.v. ondansetron does not affect the intensity or duration of sensory and motor block after spinal anesthesia with hyperbaric bupivacaine.

As regard to incidence of side effects of the spinal anesthesia in our study, there was significant decrease in incidence of nausea, vomiting and shivering in both ondansetron and granisetron groups compared to saline

group.

As granisetron and ondansetron are used primarily for prophylaxis or treatment of postoperative nausea and vomiting, many studies support our results in this aspect, **Schwartzberg et al. (2014)** concluded that both granisetron and ondansetron have similar antiemetic efficacy for prophylaxis of chemotherapy-induced nausea and vomiting and **Gupta et al. (2007)** found that both granisetron and ondansetron are superior to metoclopramide for prophylactic therapy for postoperative nausea and vomiting (PONV).

Janelsins et al. (2013) found that both ondansetron and granisetron have similar antiemetic efficacy but dose of granisetron is much less than ondansetron.

Marashi et al. (2014) observed that the administration of two different doses of intravenous ondansetron, 6 mg and 12 mg, significantly attenuates spinal induced hypotension, bradycardia and shivering compared to the control saline group. However, the hemodynamic profiles and shivering in experimental groups were not statistically different.

Babu and Penchalaiah, (2015) in their study concluded that injection of Granisetron in a dose of 1 mg. I.V. is much more effective in minimizing severe nausea, vomiting and shivering than ondansetron in a dose of 4 mg. I.V. and is free from the side effect headache which is a drawback of ondansetron. The use of granisetron as prophylactic antiemetic for high risk group may be recommended. Granisetron seems to be useful alternative and relatively safe drug for effective anti-emetic prophylaxis.

Makker et al. (2017) concluded that in the early postoperative period both Ondansetron and Granisetron are equally effective in preventing postoperative nausea, vomiting and shivering in patients undergoing gynecological surgery under spinal anesthesia. Granisetron is better than Ondansetron in the late postoperative period of up to 24 hrs.

George et al. (2009) found that prophylactic 5-HT3 receptor antagonists were significantly reduced the severity of the incidence of postoperative nausea and vomiting, and the need for rescue antiemetic therapy in parturients who received intrathecal morphine for cesarean delivery.

Ondansetron and granisetron, which are 5-HT3-receptor antagonists, have been used effectively to decrease postanesthetic shivering. The mechanism for 5-HT3-receptor antagonists is still unclear but is thought to be related to inhibition of serotonin reuptake on the preoptic anterior hypothalamic region **(Kim et al., 2010)**.

Our results were also similar to the findings of **Shakya et al. (2010)** who suggested that the prophylactic administration of low dose ketamine 0.25mg/kg and ondansetron 4mg produces significant antishivering effect in comparison with placebo in patients undergoing spinal anesthesia and that ketamine 0.25 mg/kg is significantly more effective than ondansetron (4 mg).

In a prospective double-blinded study by **Chagaleti and Athuru, (2015)** on 90 American Society of Anesthesiologists I-II patients undergoing elective cesarean section were randomly assigned to one of the three equal groups. Group T received 1 mg/kg tramadol; Group G received 40 μg/kg granisetron, Group M received 0.4 mg/kg meperidine, and Group P received saline 0.9% as placebo. They found that prophylactic use of granisetron 40 μg/kg is as effective as meperidine (0.4 mg/kg) and tramadol (0.1 mg/kg) in preventing postanesthetic shivering without prolonging the emergence time from anesthesia.

Abotaleb et al. (2016) in study compared between dexmedetomidine and granisetron for the management of postspinal shivering and found granisetron 2mg effectively reduce postspinal shivering without any major adverse effects.

Also our results matched with that of **Zhou et al. (2016)** who obtained 5-HT3 receptor antagonists appear to prevent postoperative shivering, with a broadly comparable efficacy to meperidine.

In contrast, **Jabalameli et al. (2012)** concluded that the most effective method for prevention of hypotension was administration of crystalloid preload plus ephedrine, but there was no significant effect on the severity of nausea or vomiting. Also **Sayed and Ezzat, (2014)** in their study showed that preoperative intravenous granisetron did not significantly reduce the incidence or severity of shivering in women undergoing cesarean section under spinal anesthesia.

CONCLUSION

Our study concluded that, prophylactic intravenous administration of 4mg ondansetron or 1mg granisetron 5min before induction of spinal anesthesia is significantly reduces the severity of spinal-induced hypotension with lower incidence of nausea, vomiting and shivering. There was significant faster recovery of sensory block was noticed with granisetron compared to both the ondansetron and saline groups, with no significant differences between the latter two groups, so granisetron may be useful in day case surgery and faster departure of patients.

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