

**EFFICACY OF GRANISETRON COMPARED TO ONDANSETRON AS PROPHYLACTIC ANTIEMETIC IN GENERAL ANAESTHESIA**Abhishek Kumar Barnwal<sup>1</sup>, Geeta Karki<sup>2</sup>, K. C. Sharma<sup>3</sup>, H. S. Nanda<sup>4</sup>**HOW TO CITE THIS ARTICLE:**

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**ABSTRACT: BACKGROUND:** Post-operative nausea and vomiting (PONV) is one of the most distressing and frequent adverse event occurring after general anaesthesia. **OBJECTIVES:** To compare the efficacy of Ondansetron with Granisetron in preventing post-operative nausea and vomiting (PONV) after general anaesthesia. **STUDY DESIGN:** The study was conducted over a period of 1.5 years in the Department of Anaesthesiology in SRMSIMS, Bareilly on patients undergoing elective surgeries under general anaesthesia. **MATERIAL AND METHODS:** 60 patients of American Society of Anaesthesiologists (ASA) status I and II were randomly divided into two groups. Group 1(n=30) Ondansetron 0.15 mg/kg i.v, Group 2(n=30) Granisetron 10 mcg/kg i.v. Incidence of nausea and vomiting was observed upto 24 hours post operatively after extubation. The efficacy was assessed in terms of number (percentage) of patients with mild nausea not requiring rescue antiemetic, number (percentage) of patients with severe nausea or vomiting requiring rescue antiemetic and number (percentage) of patients with no nausea or vomiting for 24 hours post operatively. **STATISTICAL ANALYSIS:** Data presented as number and percentages. Analysis done using ANOVA followed by Chi square, Unpaired 't-test'. **RESULTS:** The number (percentage) of patients with mild nausea not requiring rescue antiemetic in group 1 was 10(33.3%) and in group 2 was 2(6.6%). The number (percentage) of patients with severe nausea or vomiting requiring rescue antiemetic in group 1 was 12(40%) and in group 2 was 5(16.6%).The number (percentage) of patients with no nausea or vomiting in group 1 was 8(26.6%) and in group 2 was 23(76.6%). **CONCLUSION:** Granisetron is the better drug for prevention of postoperative nausea and vomiting than Ondansetron.

**KEYWORDS:** General anaesthesia, Post-operative nausea and vomiting (PONV), Antiemetic, Ondansetron, Granisetron.

**INTRODUCTION:** General Anaesthesia is defined as reversible, intentional, temporary, controlled, drug induced loss of consciousness. There are various complications of general anaesthesia out of which, post-operative nausea and vomiting (PONV) is one of the most distressing and frequent adverse event.<sup>1</sup> General anaesthesia using volatile anesthetic agents is associated with an average incidence of PONV ranging between 60% and 30%.

Incidence of PONV has decreased from 60% when ether and cyclopropane were used, to approximately 30% nowadays. Descriptions of these side effects induced by ether and chloroform were included in the earliest textbooks of pharmacology and therapeutics.<sup>2</sup> During the past decade, anaesthesiologists have been modifying their anaesthetic techniques to ensure a more rapid and smooth recovery. There has been a general trend towards decrease in the incidence of the problem of post-operative nausea and vomiting because of the use of lesser emetogenic anaesthetic agents,

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improved pre-operative and postoperative medications, refinement of operative technique and identification of patient predictive factors.<sup>3,4</sup>

However in spite of these advances, nausea and vomiting still occur with unacceptable frequency in association with surgery and anaesthesia, the description of it as “the big little problem”<sup>3</sup> encapsulates much of the general perception. Though several traditional antiemetic agents viz, metoclopramide, prochlorperazine, droperidol are available in the anaesthetic armamentarium, they are not in much use for the prophylaxis because of their relative ineffectiveness and higher incidence of serious side effects.

There are a number of drugs that are used to manage postoperative nausea vomiting (PONV). These drugs are generally antihistaminics, phenothiazine derivatives, anticholinergics and dopamine receptor antagonist with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia.<sup>5,6</sup> Recently introduced selective serotonin 5-hydroxytryptamine type 3 (5HT<sub>3</sub>) receptor antagonists (5HT<sub>3</sub>RA) are devoid of such side effects and are highly effective and thus the first line therapies in prevention of PONV.<sup>7,8</sup> These drugs include ondansetron, granisetron, dolasetron and tropisetron. Currently introduced 5HT<sub>3</sub> RA include ramosetron and palonosetron.

Most research on the 5HT<sub>3</sub>RA has been on ondansetron and its antiemetic efficacy has been well established in the prevention and treatment of PONV.<sup>7,8</sup> Granisetron is also effective in the prevention of post-operative nausea and vomiting after gynaecological surgeries<sup>9,10</sup> and laparoscopies.<sup>9,11,12</sup>

The present study was undertaken to compare the antiemetic efficacies of ondansetron and granisetron in preventing post-operative nausea and vomiting after general anaesthesia in terms of number (percentage) of patients with mild nausea not requiring rescue antiemetic, number (percentage) of patients with severe nausea or vomiting requiring rescue antiemetic and number (percentage) of patients with no nausea or vomiting for 24 hours post operatively.

**MATERIAL AND METHODS:** The study was conducted over a period of 1.5 years from November 2012 to May 2014 in the Department of Anaesthesiology in Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly on patients undergoing elective surgeries under general anaesthesia. After obtaining approval from institutional ethical committee (IEC) and informed written consent of patients, 60 patients of ASA grade I and II, aged between 12 to 58 years, both male and female sex undergoing various surgical procedures under general anaesthesia were selected for the study. Patients who had received antiemetic drug within the preceding 24 hours, with history of alcohol or drug abuse within last 3 months, allergic to any of the study medications, posted for ENT and obstetric surgeries, known case of GIT diseases like hiatus hernia, GERD, peptic ulcer disease, with history of motion sickness, with history of PONV in previous surgery were excluded from the study. All patients were subjected to thorough pre-anaesthetic evaluation and all other relevant laboratory investigations as per institution protocol. A standard anaesthetic protocol was used in both the groups of patients.

60 patients were divided randomly into two groups by computer generated random number list with 30 patients in each group. GROUP 1: patients in this group received inj ondansetron 0.15mg/kg i.v. three minutes before induction. GROUP 2: patients in this group received inj granisetron 10mcg/kg i.v. three minutes before induction.

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The incidence of nausea and vomiting was observed up to 24 hours post operatively after extubation. The episodes of post-operative nausea and vomiting were identified by spontaneous complaints by the patients.

### SCORE TABLE (WADASKAR ET AL, 2009):

0. No nausea.
1. Mild nausea.
2. Severe nausea.
3. Mild vomiting.
4. Severe vomiting.

“Complete response” was defined as the absence of nausea, retching or vomiting and no need for rescue antiemetic during the observation period. Rescue antiemetic was provided with Inj. Metoclopramide 0.3mg/kg iv for vomiting or persistent nausea.

**STATISTICAL CONSIDERATIONS:** Data are presented as number and percentages. The statistical analysis was pre-formed using SPSS version 20. Analysis of demographic data was done by Chi-square test. Unpaired or independent ‘t- test’ and ANOVA (Analysis of variance) was used to compare intergroup differences. A ‘p’ value of less than 0.05 was considered statistically significant.

**OBSERVATIONS ANE RESULTS:** The study was conducted in 60 patients undergoing elective surgery under general anaesthesia. The patients were randomly divided into two groups with 30 patients each.

The mean age of patients in group 1 (Ondansetron) was 33.06 ±7.96 years and in group 2 (Granisetron) was 35.36 ±8.37 years. (Table 1)

The duration of anaesthesia in group 1 was 108 ± 27.96 minutes and in group 2 was 111 ±26.30 minutes. No significant difference was found in both groups with respect to age and duration of anaesthesia (p> 0.05) (Table 1)

The number (percentage) of patients with mild nausea (PONV 1) not requiring rescue antiemetic in group 1 was 10(33.3%) and in group 2 were 2(6.6%). So, it was observed that mild nausea not requiring rescue antiemetic was significantly less (p=0.035) in granisetron group than ondansetron group. (Table 2)

The number (percentage) of patients with severe nausea or vomiting requiring rescue antiemetic in group 1 was 12(40%) and in group 2 was 5(16.6%). So, it was observed that severe nausea or vomiting requiring rescue antiemetic was significantly less (p=0.028) in granisetron group than ondansetron group. (Table 3)

The number (percentage) of patients with no nausea or vomiting for 24 hours postoperatively in group 1 was 8(26.6%) and in group 2 was 23(76.6%). So, it was observed that number (percentage) of patients with no nausea or vomiting was significantly more (p=0.018) in granisetron group than ondansetron group. (Table 4)

Out of 30 cases in Group 1, 4(13.33%) had headache and 2(6.67%) had dizziness. As compared with group 2 only 1(3.33%) had dizziness and 3(10%) had headache. The difference

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between the incidence of headache and dizziness between the 2 groups was statistically not significant ( $p>0.05$ ). (Table 5)

**DISCUSSION:** Postoperative nausea and vomiting (PONV) are common sequelae of general anaesthesia and a leading cause of delayed discharge of unanticipated hospital admission after ambulatory surgical procedure.<sup>13</sup> This is very frequent in abdominal surgeries leading to recommendation of routine prophylactic administration of antiemetics. The etiology of nausea and vomiting after abdominal surgeries under general anaesthesia are multifactorial in origin. Age, type of surgery, anaesthetic procedure and duration of surgery may influence PONV.<sup>14</sup>

The introduction of 5-HT<sub>3</sub> receptor antagonist in 1990 was heralded as a major advance of the treatment of PONV, because of absence of adverse effects that were observed with commonly used traditional antiemetics. The 5-HT<sub>3</sub> receptor antagonists produced no sedation, extrapyramidal reactions, adverse effects on vital signs or laboratory tests or drug interactions with other anaesthetic medications.

Updated guidelines for managing postoperative nausea and vomiting were recently announced at the 2006 annual meeting of the American Society of Anaesthesiologists in Chicago, Illinois, USA. Evaluating the current medical literature, they recommended the use of antiemetics, with an emphasis on the use of the 5HT<sub>3</sub> receptor antagonists.<sup>15</sup>

In our study, the incidence of mild nausea not requiring rescue antiemetic (PONV 1) was less in granisetron group than ondansetron group. This observation is supported by study conducted by Shobhana Gupta et al.<sup>16</sup> They compared efficacy of granisetron with that of ondansetron as prophylactic antiemetic in 90 patients undergoing laparoscopic surgeries. The patients were divided into three groups of 30 patients each. In group G, patients received granisetron 40 mcg/kg intravenously 3 min before induction. Group O patients received ondansetron 80 mcg/kg intravenously 3 min prior to induction while group C patients received 3 ml of 0.9% normal saline as control. All the patients were observed up to 12 hours postoperatively. In group G, only 3(10%) patients experienced nausea as compared to group O in which 9(30%) patients experienced nausea and in group C 12(40%) patients experienced nausea. So, in group G patients, incidence of nausea was comparatively less than groups of patients. The statistical analysis showed that granisetron is significantly efficient for prevention of post-operative nausea and vomiting (PONV) ( $p<0.05$ ) in comparison to ondansetron and is highly significant ( $p<0.01$ ) in comparison to control group.

In our study, the incidence of severe nausea or vomiting requiring rescue antiemetic (PONV 2, 3, 4) was less in granisetron group compared to that in ondansetron group. This observation is supported by various studies conducted in the past. Shobhana Gupta et al<sup>16</sup> observed that in patients who received granisetron, incidence of vomiting was comparatively less than in patients who received ondansetron. So, it was concluded that granisetron 40mcg/kg was superior to ondansetron 80 mcg/kg as a prophylactic antiemetic in laparoscopic surgeries in controlling PONV. Wadaskar Abhishek et al<sup>17</sup> compared the antiemetic effects of intravenous ondansetron 80 mcg/kg and granisetron 40 mcg/kg in a double blind placebo controlled manner for prevention of postoperative nausea and vomiting in patients undergoing gynecological laparoscopic surgeries.

It was observed that the incidence of nausea and vomiting over a period of 24 hour was 20% in patients who had received granisetron, 45% of patients who had received ondansetron and 77.5% of patients who had received placebo. It was also observed that in group A, 8(20%) patients had to be

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administered rescue antiemetic, in group B, 18 (45%) patients and in group C, 31(77.5%) patients received rescue antiemetic. So, it was concluded that granisetron was more effective than ondansetron in controlling postoperative nausea and vomiting after laparoscopic gynecological surgery. Dipasri Bhattacharya et al<sup>18</sup> compared the antiemetic effects of intravenous ondansetron 4 mg (2 ml) and granisetron 2 mg (2 ml) in a double blind placebo controlled manner for prevention of nausea and vomiting in early postoperative period in patients undergoing daycare laparoscopic tubal ligation. Emetic episodes were observed in 7% patients who had received intravenous granisetron (Group B), in 20% who had received ondansetron (Group A) and in 50% in patients who had received placebo (Group C). The result was both clinically and statistically significant ( $p < 0.05$ ). They concluded that minimal emetic episodes were observed in early postoperative period in patients who had received intravenous granisetron in comparison to those who had received intravenous ondansetron and placebo.

In our study, the number (Percentage) of nausea and vomiting free patients (PONV 0) was more in granisetron group than in ondansetron group comparable to the results of other studies. Abhishek Wadaskar et al<sup>17</sup> observed that 32 patients (80%) of group A and 22 patients (55%) in group B did not experience any nausea and vomiting, whereas only 9 patients (22.5%) of group C did not experience nausea and vomiting. So, it was concluded that granisetron was more effective than ondansetron in controlling postoperative nausea and vomiting after laparoscopic gynecological surgery. Dipasri Bhattacharya et al<sup>18</sup> observed that the percentage of patients who were postoperative nausea and vomiting free in group A (ondansetron) was 80%, in group B (granisetron) was 93% and in group C (placebo) was 50%. So, it was concluded that granisetron is much more effective than ondansetron to prevent PONV following daycare gynecological laparoscopic surgery. This is comparable with our study. Yoshitaka F et al<sup>19</sup> in another study showed that granisetron in a dosage of 40mcg/kg is an effective antiemetic agent compared to placebo in preventing PONV in children undergoing strabismus surgery and tonsillectomy under GA.

Naguib et al<sup>20</sup> demonstrated that the incidence of PONV after laparoscopic cholecystectomy in their placebo group was remarkably high (72%). The 5HT<sub>3</sub> receptor antagonist drug granisetron, which is more potent and long acting than ondansetron against emesis associated with chemotherapy, have been found to be very effective for preventing PONV after laparoscopic cholecystectomy. Wilson AJ et al<sup>21</sup> compared three doses (0.1 mg, 1.0 mg and 3.0 mg) of the 5-HT<sub>3</sub> receptor antagonist, granisetron as prophylactic therapy for the prevention of postoperative nausea and vomiting and found that the two higher doses of granisetron (1.0 mg and 3.0 mg) provided effective prophylaxis against vomiting, with 78% and 77% of patients, respectively, being free from vomiting in the first 6 h after surgery, and 63% and 62% in the first 24 hours. Study conducted by Sinha<sup>22</sup> concluded that prophylactic administration of i.v. ondansetron is safe and effective in preventing post-operative nausea and vomiting in females undergoing breast surgery.

The observations of our study show that granisetron is better than ondansetron as prophylactic antiemetic. This can be explained by the fact that granisetron is a more selective 5-HT<sub>3</sub> receptor antagonist and is more potent than ondansetron.

In our study, the incidence of side effects was higher in ondansetron group than granisetron group but not statistically significant ( $p > 0.05$ ). Similar results were obtained in the study conducted by Gupta S et al<sup>16</sup> who found that side effects like headache, dizziness, diplopia and shivering was significantly higher in ondansetron group.

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Chidambaram A et al<sup>22</sup> compared the effectiveness of ondansetron with that of granisetron for prevention of PONV after laparoscopic surgery. A complete response was achieved in 75% of the patients given ondansetron and 86% of the patients given granisetron ( $p < .05$ ). Thus study concluded that the prophylactic intravenous administration of granisetron is more effective drug than ondansetron for controlling postoperative nausea and vomiting with fewer incidences of side effects.

**CONCLUSION:** It can be concluded that granisetron is more effective drug than ondansetron for controlling postoperative nausea and vomiting with less incidence of side effects. We observed minimal emetic and nausea episodes in the postoperative period in patients who had received intravenous granisetron in comparison to intravenous ondansetron.

### REFERENCES:

1. Watcha MF, White PF: Post-operative nausea and vomiting: Its etiology, treatment and prevention. *Anesthesiology* 77: 162-184, 1992.
2. Kappor PA. The big Little problem. *Anaesth. Analag* 1991; 73: 243-5.
3. Wang JJ, Ho TS, Liu SH, Ho MC. Prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery *Br J Anaesth* 2000; 84 (4): 459-62.
4. Jimenez, FJ, Garcia-Ruiz PJ, Molina JA. Drug induced movement disorders. *Drug Safety* 1997; 16: 180-204.
5. Andrews PLR, Davis CJ, Bighanis DH, Honvthoin J, Mashell L. The abdominal visceral innervation and the emetic reflex, pathway and plasticity. *Can J Physiol Pharmacol* 1990: 68: 325-45.
6. Andrews PLR, Hawtorn J. The Neurophysiology of vomiting. *Clinical Gastroenterology* 1998; 2: 141-68.
7. Habib AS, GanTJ. Evidence based management of post-operative nausea and vomiting: A review. *Can. J. Anesth* 2004; 51: 326-41.
8. Candiotii KA. A randomized double blind study to evaluate the efficacy and safety of three different doses of Palanosetron versus placebo for preventing postoperative nausea and vomiting. *Anesth Analgesia* 2008; 107: 445 51.
9. Mathew B, Paul FW. Antiemetic efficacy of ondansetron after outpatient laparoscopy. *Anaesthesia Analgesia* 1991; 73: 250-4.
10. Fuji Y, Tanaka H, Toyooka H. Reduction of post-operative nausea and vomiting with granisetron *Can. J. Anesth*:1994; 41: 291-4.
11. Kovac A. Prophylactic Ondansetron in female outpatients undergoing gynaecological surgery: A multicentre dose comparison. *European Journal of Anaesthesia* 1992; 6: 37-47.
12. Lesser and Lip H. Prevention of PONV using Ondansetron. A new, selective 5 HT<sub>3</sub> receptor antagonist. *Anaesthesia Analgesia* 1991; 72: 751-5.
13. Gold BS, Kitz DS, Lecky JA, Neuhans JH. Unanticipated admission to the hospital following ambulatory surgery. *JAMA* 1989; 262: 3008-10.
14. Lerman J. Surgical and patient factors involved in post-operative nausea and vomiting. *Br J Anaesth* 1992; 69: 245-325.
15. New guidelines issued for PONV 2005-06 (cited on November 22, 2006).  
<http://www.anaesthesianow.com/news>

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16. S. Gupta, R.K. Choudhary: A Comparative Clinical Study Of Prevention Of Post-Operative Nausea And Vomiting Using Granisetron And Ondansetron In Laparoscopic Surgeries. The Internet Journal of Anesthesiology. 2010; 26; 1. DOI: 10.5580/4b4.
17. Wadaskar, N. Swarnkar, A. Yadav: Granisetron has superior control over postoperative nausea and vomiting than ondansetron in gynaecological surgeries: a placebo controlled double-blind clinical study. The Internet Journal of Anaesthesiology.2009; 20; 1. DOI: 10.5580/2069.
18. Bhattcharya D, Banerjee A. Comparison of Ondansetron and Granisetron for prevention of nausea and vomiting following day care gynecological laproscopy. Indian journal Anaesthesia 2003, 47 (4); 279-282.
19. Yoshitaka F, Hiroyoshi T, Hidenori T. Granisetron reduces vomiting after strabismus surgery and tonsillectomy in children. Can J Anaesth 1996; 43 (1): 35-8.
20. Naguib M, El Bakry AK, Khoshim MHB. Prophylactic antimetic therapy with Ondansetron, Tropisetron, Granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy. Can J Anaesth 1996; 43: 226-31.
21. Wilson AJ, Diemunsch P, Lindeque BG, Scheinin H, Helbo-Hansen HS, Kroeks MVAM, Kong KL. Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting. British Journal of Anaesthesia 1996; 76: 515–518.
22. Sinha Prabhat K, Sushil P. Ondansetron in prophylaxis of postoperative nausea and vomiting in patients undergoing breast surgery: A placebo-controlled double blind study. Journal Indian MED. ASSOC. vol 102, No.2, FEB 2004.
23. Chidambaram A, Bylappa K, Somasekaram P: A Comparative Study of Ondansetron and Granisetron for Prevention Of Nausea And Vomiting Following Laparoscopic Surgeries. The Internet Journal of Anesthesiology.2011; 29 (1) DOI: 10.5580/28c.

VARIABLES	GROUP 1	GROUP 2	p value (independent 't' test)
			1 Vs2
AGE (IN YRS.)	33.06 ± 7.96	35.36 ±8.37	.2804
DURATION OF ANAESTHESIA (IN MINUTES)	108.00 ± 27.96	111.00±26.30	.6703

**TABLE 1: DEMOGRAPHICS, AGE AND DURATION OF ANAESTHESIA**

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	<b>GROUP 1 (n=30)</b>	<b>GROUP 2 (n=30)</b>	<b>p value (ANOVA)</b>
NO. OF PATIENTS	10	2	0.035
PERCENTAGE OF PATIENTS	33.3%	6.6%	

**TABLE 2: NO. OF PATIENTS WITH MILD NAUSEA(PONV 1) NOT REQUIRING RESCUE ANTIEMETIC (IN 24 HOURS)**

	<b>GROUP 1 (n=30)</b>	<b>GROUP 2 (n=30)</b>	<b>p value (ANOVA)</b>
NO. OF PATIENTS	12	5	0.028
PERCENTAGE OF PATIENTS	40%	16.6%	

**TABLE 3: NO. OF PATIENTS WITH SEVERE NAUSEA OR VOMITING (PONV 2, 3 & 4) REQUIRING RESCUE ANTIEMETIC (IN 24 HOURS)**

	<b>GROUP 1 (n=30)</b>	<b>GROUP 2 (n=30)</b>	<b>p value (ANOVA)</b>
NO. OF PATIENTS	8	23	0.018
PERCENTAGE OF PATIENTS	26.6%	76.6%	

**TABLE 4: NO. OF PATIENTS WITH NO NAUSEA OR VOMITING (PONV 0) FOR 24 HOURS**

<b>Side effects</b>	<b>GROUP 1 (n=30)</b>	<b>GROUP 2 (n=30)</b>	<b>p value</b>
Dizziness	2 (6.67)	1 (3.33)	>0.05
Headache	4 (13.33)	3 (10)	>0.05

**TABLE 5: COMPARISON OF SIDE EFFECT IN STUDY GROUPS**



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