Granisetron has superior control over postoperative nausea and vomiting than ondansetron in gynecological surgeries: a placebo controlled double-blind clinical study

A Wadaskar, N Swarnkar, A Yadav

Citation

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Abstract

Introduction: The aim of the study was to compare 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. Methods: Ninety patients (ASA I and II) undergoing gynecological laparoscopic surgeries under general anaesthesia were randomly allocated into three groups; Group A (n=30) received 40mcg/kg granisetron intravenously, group B (n=30) received 80mcg/kg ondansetron intravenously and group C (n=30) received 5 ml of normal saline by the same route 2 minutes before induction of general anaesthesia. Anesthetic procedure was standardized for all patients. Data was collected and analyzed statistically. Results: The incidence of nausea and vomiting over a period of 24 hour were found in 20% of 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, 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. At the same time it was observed that, in group A, 8 patients (20%) had to be administered rescue antiemetics; while in group B, 18 patients (45%) and in group C, 31 patients (77.5%) received antiemetics. Conclusion: It was concluded that granisetron is more effective than ondansetron and placebo in controlling postoperative nausea & vomiting after laparoscopic gynecological surgery.

INTRODUCTION

Postoperative nausea and vomiting (PONV) are distressing and common occurrences after operative procedures requiring general anesthesia, more so following laparoscopic surgeries. The incidence of nausea and vomiting after gynecological laparoscopic surgeries is high (40-77%) [1234]. The most important post-operative concerns frequently listed by most of the patients are pain, nausea and vomiting. PONV could be particularly distressing to the patient especially in day care surgeries not only delaying discharge but lengthening hospital stay & increasing bed occupancy leading to financial burden on the hospital. The causes of nausea and vomiting are believed to be high intra-abdominal pressure, rapid peritoneal distention, stretching of peritoneum by insufflation and diffusion of CO_2 into bowel leading to bowel distention[5]. The patients who are at risk are young females, 20-40 years and those undergoing laparoscopic gynecological procedures with residual pneumoperitoneum, use of nitrous oxide, opioid anesthesia, past history of nausea, vomiting and motion sickness[678]. Commonly used older, traditional antiemetics for PONV were known to cause adverse effects such as dry mouth, dysphoria, sedation, hypotension, tachycardia, extra-pyramidal reactions, dystonic effects and restlessness leading to patient dissatisfaction[22]. The newer antiemetics used for the prevention and treatment of PONV are $5HT_3$ receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron) are devoid of these side effects. The use of these $5\text{-}HT_3$ receptor antagonists have been shown to improve patients' satisfaction, decrease recovery and discharge times and reduced an unanticipated hospital admission especially when they are used prophylactically[2526].This prospective, randomized, double blind placebo controlled study was undertaken to compare the efficacy of granisetron and ondansetron in prevention PONV in patients undergoing gynecological laparoscopic surgeries.

METHODS

After the approval from the Institutional Ethical Committee, 120 consenting female patients of ASA I-II between 20-40 years undergoing diagnostic laparoscopy and laparoscopic tubal ligation were randomly allocated in to three groups of 40 each. These patients received 40 g/kg granisetron in group A, Ondansetron (80 g/kg) in group B and 0.9% saline in group C two minutes prior to induction of anesthesia. Exclusion criteria included a history of allergy to drug(s), pregnancy & lactation, menstruation, vomiting or retching within 24 h before the operation, administration of antiemetic or psychoactive medication within 24 h before surgery, active alcohol or drug abuse. Thorough history, clinical examination and routine investigations including any special investigation, if required were carried out. At the pre-anesthetic interview the patients were familiarized with a post-operative questionnaire and postoperative nausea and vomiting score, described as: 0 = No nausea or vomiting. 1 = Mild nausea (not requiring rescue antiemetic) 2 = Severe nausea (requiring rescue antiemetic) 3 = Mild vomiting (< 2 vomiting episodes), requiring rescue antiemetic 4 = Severe vomiting (> 2 vomiting episodes), requiring rescue antiemetic.

The study was kept double blind by one anesthetist preparing the drug(s) and putting code on the syringes while drug(s) were administered by anesthetist who was not part of the study team. Data and proformas were collected by resident anesthetist blinded to the study and handed over to the investigator. Decoding of the patients was done at the end of the study.

Premedication was given in preoperative room with glycopyrrolate 0.004mg/kg IV, midazolam 0.02mg/kg IV and fentanyl 0.5mg/kg IV, and the study drug was given two minutes prior to induction of anesthesia. On arrival in operating room all the standard monitors were attached, intravenous line established and lactated ringers' solution started. All patients were preoxygeneted with 100% oxygen for three minutes. General anesthesia was induced with thiopentone sodium 5mg/kg IV and vecuronium 0.08 mg/kg. After ventilating for 3 minutes patients were intubated with cuffed endotracheal tube. Once tracheal placement was confirmed, anesthesia was maintained with oxygen, nitrous oxide in the 60:40 ratio and halothane @ 0.5%. Patients' stomach was emptied with nasogastric tube before commencing with the surgery. After completion of procedure, patients were reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.008mg/ kg. Patients were also given diclofenac 1 mg/kg IM. Patients were extubated after confirming adequate tone, power and verbal response. Patients were shifted to anesthesia recovery room. After surgery all patients were nursed in the recovery room during the first 24 hr. The ECG & SpO_2 was monitored continuously and blood pressure was noted every ten minutes during the first hour then every 30 min until discharge. Incidence of nausea and vomiting was observed by resident anesthetist from 0 minute (when patient responded to verbal commands) to 24 hours post operatively.

The efficacy of study medication was assessed in terms of number of emetic episodes, percentage of emesis free patients and percentage of nausea free patients for 24 hours post-operatively. Patient's, who were restless and uncomfortable with nausea, were labeled as having severe nausea. Patient with severe nausea and one or more episodes of vomiting were rescued with antiemetic metoclopramide 0.2 mg/kg IV.

RESULTS

In this study, 120 female patients of ASA I-II between 20-40 years, undergoing diagnostic laparoscopy and laparoscopic tubal ligation were randomly distributed in three groups of 40 each. In this study, the treatment groups were similar with regards to age, weight and type of surgical procedures. The duration of anesthesia was also comparable in all the three groups (p>0.05) (Table 1).

Figure 1

Table 1: demographics, type of surgery and duration of anesthesia

Type of surgery	Group A	Group B	Group C	Significance
Age (yrs)	30.35 ± 6.53	28.72 ± 4.21	29.00 ± 5.17	NS
Weight (kg)	47.37±4.67	46.77±3.95	46.32±3.54	
DL/ LTL	27/13	21/19	23/17	
Duration of anaesthesia (min)	55.57±6.99	53.52±7.47	53.95±7.18	

Data presented as no. of patients and mean±SD. NS = Not significant as p>0.05, DL = Diagnostic laparoscopy , LTL = Laparoscopic tubal ligation

During the first six hours postoperatively, only eight patients (20%) in group A had episodes of nausea/vomiting as compared to fifteen patients (37.5%) in group B and thirty

eight patients (90%) in group C. The difference in frequencies was found to be significant between group A and group C (p = 0.005) and also between group B and group C (p = 0.0009). Although the incidence of PONV was recorded in more number of patients in group B within first six hours as compared to group A (eight versus fifteen) but the difference was found to be insignificant statistically (p = 0.59) (Table 2).

Figure 2

Table 2: Number of patients showing nausea and vomiting during first 6 hours

Degree of PONV	Groups			p-value		
	A	B	C	A Vs C	B Vs C	A Vs B
Mild nausea	3	4	22	0.005 S p<0.05	0.0009 HS p<0.05	0.59 NS p>0.05
Severe nausea	5	8	2			
Mild vomiting	0	1	3			
Severe vomiting	0	2	11			

Data presented as no. of patients. PONV = postoperative nausea and vomiting. S = significant, HS = highly significant, NS = non significant

During next eighteen hours postoperatively, only three patients (7.5%) in group A had episodes of nausea/vomiting as compared to nineteen patients (47.5%) in group B and thirty patients (75%) in group C. The difference was found to be significant when group A was compared with group B & C (p = 0.008 and 0.006 respectively). But when comparison in frequency of PONV was made between group B and C, the difference was not significant (p>0.05) (Table 3).

Figure 3

Table 3: Number of patients showing nausea and vomiting during 7-24 hours

Degree of PONV	Groups			p-value		
	A	B	C	A Vs C	B Vs C	A Vs B
Mild nausea	0	12	15	0.006 S p<0.05	0.84 NS p>0.05	0.008 S p<0.05
Severe nausea	3	2	4			
Mild vomiting	0	4	9			
Severe vomiting	0	1	2			

Data presented as no. of patients. PONV = postoperative nausea and vomiting. S = significant, NS = non significant

The total incidence of PONV in 24 hours was only 27.5% in group A as compared to 45% and 77.5% in group B & C respectively (p<0.001). But when groups were compared with regard to PONV episodes after 12 hours, there was no significant difference (p = 0.62) (table 4).

Figure 4

Table 4: Percentage incidence of postoperative nausea and vomiting in 24 hours

Time(hrs)	Group A	Group B	Group C	*P* value
0-6	20	27.5	40.00	0.0001 S
7-12	5.0	17.5	37.5	0.0001 S
13-18	2.5	0	0	0.62 NS
19-24	0	0	0	NA

Data presented as percentage of patients. S = significant, NS = non significant, NA = not applicable.

As it is evident in table 5, 80% of patients in group A did not require rescue antiemetic whereas corresponding figures in group B & C were only 55% and 22.5% respectively. There was significant difference in requirement of rescue antiemetic when group A was compared with group B & C (p = 0.03 & 0.0001 respectively).

Figure 5

Table 5: Patients who received rescue antiemetic

Rescue antiemetic given	groups			*P* value		
	A	B	C	A Vs C	B Vs C	A Vs B
Once	20	45	77.5	0.0001 **HS**	0.005 **S**	0.03 **S**
Not Given	80	55	22.5			

Data presented as percentage of patients. S = significant

Figure 6

Figure 1: No. of patients who received rescue antiemetic among three groups

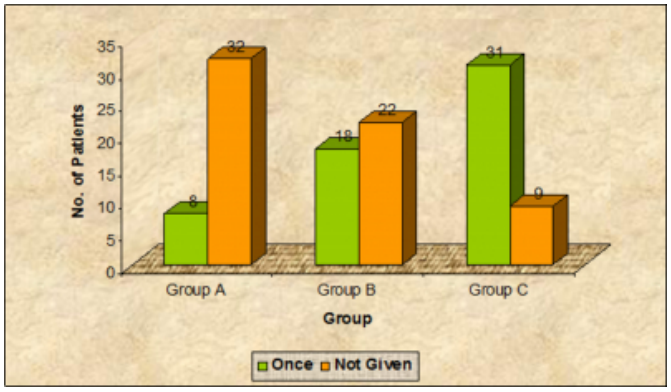
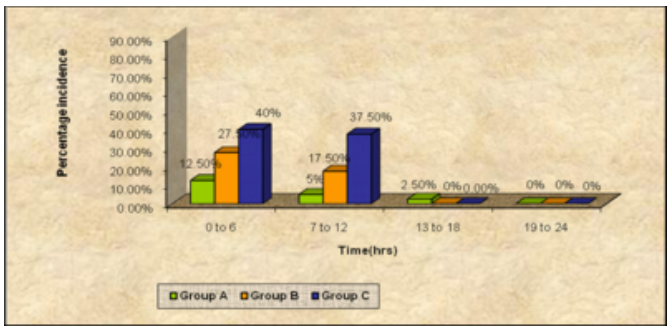


Figure 7

Figure 2: Percentage incidence of postoperative nausea and vomiting in 24 hours



DISCUSSION

Postoperative nausea and vomiting are common sequel after general anesthesia in patients undergoing gynecological laparoscopic surgeries. The incidence of nausea and vomiting after gynecological laparoscopic surgeries is high and found to be around 40-77%[2,3,4] The causes of nausea and vomiting in laparoscopic surgery are believed to be; rapid peritoneal distention, high intra-abdominal pressure, stretching of peritoneum by rapid insufflation of CO_2 and diffusion of CO_2 into bowel leading to bowel distention[5].

Various methods to reduce postoperative nausea and vomiting have been tried along the years, which include physical maneuvers like 'nothing per os' regimens, pre-anesthetic suctioning of gastric contents, application of cricoid cartilage pressure, avoiding inflation of stomach during positive pressure ventilation by mask ventilation, pharmacological agents such as administration of anticholinergics, antihistaminics and dopamine antagonists[21]. Acupuncture has also been tried to reduce postoperative nausea and vomiting. However, none of these techniques, alone or in combinations were entirely successful in reducing PONV. There are several types of antiemetics used in the management of PONV. Gastro-intestinal prokinetic drugs with anti-dopaminergic actions are metoclopramide, domperidone. Phenothiazines, for example prochlorperazine, perphenazine and butyrophenones for eg, droperidol also have antiemetic effect resulting from anti-dopaminergic actions. Central anticholinergic action is associated with antiemetic activity and this is seen not only in classical anticholinergic drugs such as hyoscine and atropine, but also in some anti-histamine receptor type I antagonists; eg, cyclizine. It may be seen that the anticholinergic effects of these drugs are responsible for their antiemetic activity. These traditional antiemetic drugs currently in use are associated with side-effects such as sedation, restlessness, hypotension, dysphoria and extrapyramidal symptoms[23].

$5HT_3$ receptor antagonists include ondansetron, granisetron, dolasetron and tropisetron. Currently introduced $5HT_3$ receptor antagonists include ramosetron, polanosetron. All the $5HT_3$ receptor antagonists have the same basic double nitrogen ring backbone for their chemical structure. This may be the chemical site of action of the $5HT_3$ receptor antagonists on serotonin, which is a six and five ring nitrogen based structure [21]. The use of these $5HT_3$ receptor antagonists has been shown to improve patients' satisfaction, decrease recovery time, discharge time and reduce an unanticipated hospital admission[1123]. Granisetron has higher selectivity and anti-emetic effect, more potent and long-lasting action than that of ondansetron. Granisetron has been reported to be effective in the treatment of vomiting in patients receiving cytotoxic drugs (cisplatin) [24]. It has also recently been demonstrated that this drug is effective in the prevention of postoperative nausea and vomiting after gynecological surgeries[14] and laparoscopies[111424].

In this study, we assessed postoperative nausea and vomiting by using PONV score[20]. This scale was preferred because of the ease of its understanding by the patients, feasibility of its application and evaluation. Patients, who were restless and uncomfortable with nausea, were labeled as having severe nausea.

Various factors are known to affect the incidence of postoperative nausea and vomiting, such as patients' age, weight and sex, history of motion sickness, phase of menstrual cycle, duration of surgery and duration of anesthesia. In our study, we analyzed the data in terms of age, weight, type and duration of surgeries and duration of

anesthesia, to find a correlation in respect of contribution towards the same. In our study, all these factors were well-balanced between the groups. All the patients underwent the same pre-operative fasting and premedication; same standardized balanced general anesthesia and postoperative analgesic. Therefore, the difference in the incidence of postoperative nausea and vomiting among the groups could be attributed to the agents used in this study.

The main objective in our study was to compare antiemetic effects of prophylactic single-dose of 40μg/kg granisetron and 80μg/kg ondansetron administered intravenously in a double-blind placebo controlled manner for prevention of nausea and vomiting in early postoperative period in patients undergoing gynecological laparoscopic surgeries under general anesthesia. 40μg/kg of granisetron was chosen in the study as it was found to be optimal dose for prevention of post operative nausea and vomiting. Fujii et al in 1994 revealed that granisetron in an i.v. dose as low as 0.04 mg/kg is effective in the prevention of PONV. In his study, granisetron 40 μg /kg was as effective as 60 μg/ kg and both resulted in reduction of the scores compared with placebo and granisetron 20 μg /kg[17] . 80μg/kg of ondansetron was chosen as it was found to be effective for prevention of nausea and vomiting as mentioned in different studies [21252627].

The incidence of nausea and vomiting over a period of 24 hour were found in 20% of 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, 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. At the same time it was observed that, in group A, 8 patients (20%) had to be administered rescue antiemetics; while in group B, 18 patients (45%) and in group C, 31 patients (77.5%) received antiemetics. Other workers have also produced similar results [22]. Gigilo et al in their study to prevent nausea and vomiting following cancer chemotherapy concluded that both ondansetron and granisetron have similar antiemetic efficacy but dose of granisetron is much less than ondansetron. 2 mg of granisetron IV is equivalent to 8-16 mg of ondansetron IV [28]. Granisetron is also more selective 5HT3 receptor antagonist than ondansetron [2930]. As the elimination half-life of granisetron is 9 hrs, which is 2.5 times longer than that of ondansetron it requires less frequent dosing [30].

Therefore, it was concluded that granisetron 40μg/kg intravenously is a safe, cost effective and efficient antiemetic agent than ondansetron and placebo, for prevention of postoperative nausea and vomiting in patients undergoing gynecological laparoscopic surgeries under general anesthesia.

CORRESPONDENCE TO

Dr Abhishek Wadaskar Address: M5GD-4, Meghdoot Apartments, JNMC campus, Datta Meghe Institute of Medical Sciences, Sawangi, Wardha-442001, MH, India. Phone: 91-7152-287701-06 ext-340 Fax: 91-7152-287714 Email: drabhi1118@gmail.com

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Author Information

Abhishek Wadaskar, MD Anesthesiology
Assistant Professor, Department of Anesthesiology and Intensive care, Datta Meghe Institute of Medical Sciences

Nikhil Swarnkar, MD Anesthesiology
Assistant Professor, Department of Anesthesiology and Intensive care, Datta Meghe Institute of Medical Sciences

Anshul Yadav
Resident anesthesiologist, Department of Anesthesiology and Intensive care, Datta Meghe Institute of Medical Sciences