

A COMPARATIVE STUDY ON EFFICACY OF ONDANSETRON AND GRANISETRON IN PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA

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ABSTRACT

BACKGROUND

Postoperative nausea and vomiting is one of the many side effects of patients undergoing laparoscopic surgeries under general anaesthesia. Its prevention is major concern of anaesthesiologist managing the case. To this effect, many drugs have been used and use of serotonin (5-HT₃) receptor antagonists like ondansetron, granisetron, tropisetron and dolasetron has been compared in many studies. This study was undertaken to study the efficacy of ondansetron, granisetron and their side effects.

MATERIALS AND METHODS

Patients were allocated into two groups, each group consisting of 50 patients. Group O received ondansetron 4 mg IV before induction. Group G received granisetron 1 mg IV before induction. The incidences of PONV were recorded within the first 24 hours after surgery at intervals of 0-2 hours, 3 hours, 6 hours, 12 hours and 24 hours. Episodes of PONV were identified by spontaneous complaints by the patients or by direct questioning.

RESULTS

In present study, incidence of nausea at different intervals in granisetron group is less than in the ondansetron group, which is statistically significant ($p < 0.05$). The incidence of nausea was 36% in Group O and 12% in Group G, which was significantly low. The incidence of retching was 22% in Group O and it was less in Group G that is 2%. Greater percentage of patients in Group O (16%) experienced vomiting compared to Group G (2%).

CONCLUSION

The overall frequency of Postoperative Nausea and Vomiting (PONV) was less in Group G than Group O.

KEYWORDS

Laparoscopic Surgeries, PONV, Ondansetron, Granisetron.

HOW TO CITE THIS ARTICLE: Upendranath I, Rupa Kumari A, Himani A, et al. A comparative study on efficacy of ondansetron and granisetron in prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anaesthesia. *J. Evid. Based Med. Healthc.* 2016; 3(83), 4479-4485. DOI: 10.18410/jebmh/2016/951

BACKGROUND

Nausea and vomiting have been associated for many years with the use of general anaesthetics for surgical procedures. The study was done by John Snow, published in 1848, within 18 months of the introduction of anaesthesia into Britain. He observed that vomiting was more likely to occur if the patient had eaten recently. There has been a general trend towards a decrease in the incidence and intensity of the problem because of the following;

1. Use of less emetic anaesthetic agents.
2. Improved pre- and post-anaesthetic medications (e.g. analgesics).
3. Refinement of operative technique, and
4. Identification of patient predictive factors.

With the introduction of newer techniques and medication, nausea and vomiting still occur with surgery and anaesthesia and the description of it as "the big little problem" encapsulates much of the general perception.¹

The various detrimental effects of PONV are:

Physical: Retching and vomiting are fairly violent acts and may place considerable stress upon certain structures leading to oesophageal tears resulting in haemorrhage (Mallory-Weiss syndrome) and rupture of the oesophagus (Boerhaave syndrome), rib fracture, gastric herniation, muscular strain and fatigue. Vomiting may cause wound dehiscence, intraocular bleeding and bleeding of skin flaps

Financial or Other, Competing Interest: None.

Submission 23-09-2016, Peer Review 01-10-2016,

Acceptance 13-10-2016, Published 15-10-2016.

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DOI: 10.18410/jebmh/2016/951



in the upper body after plastic surgery. The major problem associated with vomiting in the postoperative period is aspiration of vomitus, respiratory obstruction and aspiration pneumonia.

Metabolic: The metabolic effects include anorexia, dehydration and alkalemia.

Psychological: Nausea is a very aversive stimulus and if induced by operative experience may cause lifelong aversion to surgery.²

Over the years, numerous approaches have been used in the management of PONV. Phenothiazines were synthesised originally in the late 19th century. In the late 1930s, promethazine was found to have antiemetic property. Charpentier synthesised chlorpromazine in 1949, but sedation and hypotension were limiting side effects.³

Various drugs have been used for prevention of nausea and vomiting. Like:

- The traditional antiemetics include anticholinergics (scopolamine),
- Dopamine receptor antagonists, which include the phenothiazines (promethazine),
- Benzamides (metoclopramide),
- Butyrophenones (droperidol) and benzodiazepines (midazolam and lorazepam).

The nontraditional antiemetics include ephedrine, propofol and corticosteroids.

The introduction serotonin (5-HT₃) receptor antagonists like ondansetron, granisetron, tropisetron and dolasetron as antiemetics met with good acceptance. These medications do not have adverse effects of older traditional antiemetics.^{3,4}

MATERIALS AND METHODS

In the present study, intravenous ondansetron and granisetron are being compared in the prevention of postoperative nausea and vomiting. The present clinical study was conducted at Kamineni Institute of Medical Sciences, Narketpally, Nalgonda District, Telangana, during the period October 2013 to September 2015. After obtaining approval from Institutional Ethics Committee, the present study was undertaken to evaluate the efficacy of intravenous ondansetron vs. granisetron on postoperative nausea and vomiting following laparoscopic surgeries done under general anaesthesia. It was a prospective study done on 100 patients undergoing elective laparoscopic surgeries under GA.

Inclusion Criteria

- ASA grade I and II patients.
- Age between 20-60 years of either gender.
- Elective laparoscopic surgeries posted under GA.

Exclusion Criteria

- Patients belonging to ASA Grade III and above.
- Pregnancy, hyperemesis gravidarum.
- Patients with motion sickness.

- Allergic to study drugs.
- Patients who have received antiemetics 48 hrs. before surgery.
- Patients with BMI >30.

After a thorough clinical examination and relevant laboratory investigations of all patients, an informed, valid, written consent was obtained both for conduct of the study as well as for the administration of GA. All patients were kept nil by mouth from 8 hrs. before surgery and tablet alprazolam (0.01 mg/kg body weight) was administered per orally at bedtime the day before surgery. Tablet ranitidine (150 mg) was administered orally in the morning at 6 a.m. on the day of surgery.

All the patients were re-examined, assessed and weighed preoperatively on the day of surgery. Intravenous access was established with an 18G intravenous cannula and baseline haemodynamic parameters, i.e., HR, SBP, DBP, MAP were noted. Anaesthesia machine and accessories were checked. Drugs including emergency drugs were kept ready. Also, monitoring equipment like pulse oximeter, noninvasive blood pressure, ECG and EtCO₂ monitors were checked and applied to each patient on arrival to the operating room.

All the patients were allocated into two groups, each group consisting of 50 patients.

Group O received ondansetron 4 mg IV before induction.

Group G received granisetron 1 mg IV before induction.

Induction of anaesthesia was done with Inj. Thiopentone sodium 5 mg/kg, Inj. Succinylcholine 2 mg/kg was used as muscle relaxant for intubation with appropriate size endotracheal tube. Inj. Fentanyl 1 µg/kg IV was used for analgesia and inj. vecuronium 0.08 mg/kg IV were used to provide muscle relaxation during surgery depending on the type and duration of the procedure.

Maintenance of anaesthesia was with nitrous oxide (66%) and oxygen (33%) with halothane using controlled ventilation. Haemodynamic parameters (HR, SBP, DBP, MAP) and EtCO₂ were recorded at 0 mins., 3 mins., 5 mins., 10 mins., 15 mins. and for every 15 mins. during the intraoperative period till the end of surgery. On completion of surgery, the residual paralysis was reversed with Inj. Neostigmine 0.05 mg/kg IV and glycopyrrolate 0.01 mg/kg IV. Patients were transported to the recovery room and later to the ward after confirming an adequate level of consciousness and intact reflexes. Postoperative analgesia was given with paracetamol infusion 6th hourly.

The incidences of PONV were recorded within the first 24 hours after surgery at intervals of 0-2 hours, 3 hours, 6 hours, 12 hours and 24 hours. Episodes of PONV were identified by spontaneous complaints by the patients or by direct questioning. "Complete response" was defined as the absence of nausea, retching or vomiting and no need for rescue antiemetic during the 24-hour observation period. Rescue antiemetic was provided with Inj. Metoclopramide 10 mg IV in the event of 1 or more episodes of vomiting depending on the observer's discretion.

Observation and results were evaluated and compared between the two groups:

STATISTICS

Mean: The mean of a collection of numbers is their arithmetic average, computed by adding them up and dividing by their number.

Standard Deviation (SD): It is a statistical measure of spread or variability.

In the present study, student’s unpaired t-test (HR, SBP, DBP, MAP and EtCO₂) and chi-square test (nausea, vomiting, retching and rescue antiemetic) was used for measuring the statistically significance between both the groups. These were used because two sets of population were compared, which were independent and identically distributed.

‘p’ value: It indicates the probability of error and a value less than 0.05 is considered statistically significant.

OBSERVATION AND RESULTS

Following is the observation and result of the present study.

The demographic profile of age-wise distribution, gender-wise distribution, weight-wise distribution and mean duration of surgery was comparable in both the groups.

Duration	Group O (Ondansetron)	Group G (Granisetron)	P value
	No. of Cases (Percent)	No. of Cases (Percent)	
0-2 hours	9 (18%)	2 (4%)	0.04
3 hrs.	1 (2%)	1 (2%)	>0.9
6 hrs.	1 (2%)	2 (4%)	0.56
12 hrs.	3 (6%)	1 (2%)	0.32
24 hrs.	4 (8%)	0 (0%)	0.041
Total	18 (36%)	6 (12%)	0.0027

Table 1: Distribution of Cases According to the Occurrence of Nausea in the Postoperative Period in Groups O and G (n=100)

Nausea: It’s a sensation of unease or discomfort in the upper stomach with an involuntary urge to vomit. P-value <0.05 was taken as significant.

Above table shows the occurrence of nausea during the first 24-hours postoperative period. During the 0-2 hours interval, out of 50 patients, 9 (18%) patients in Group O had nausea while only 2 patients (4%) in Group G had nausea. This was found to be statistically significant (P<0.05). In the 3-hour, 6-hour and 12-hour intervals, 1 (2%), 1 (2%) and 3 (6%) patients of Group O had nausea while 1 (2%), 2 (4%) and 1 (2%) patients belonging to Group G had nausea, respectively. These results were found to be statistically nonsignificant. However, in the 24-hour interval, 4 out of 50 (8%) Group O patients complained of nausea while no Group G patients had similar complaints. This was found to be statistically significant (P <0.041).

Overall, 18 (36%) patients out of 50 in Group O had nausea while only 6 (12%) out of 50 in Group G had nausea.

Group O patients were found to have significantly higher occurrence of nausea compared to patients in Group G (P <0.005).

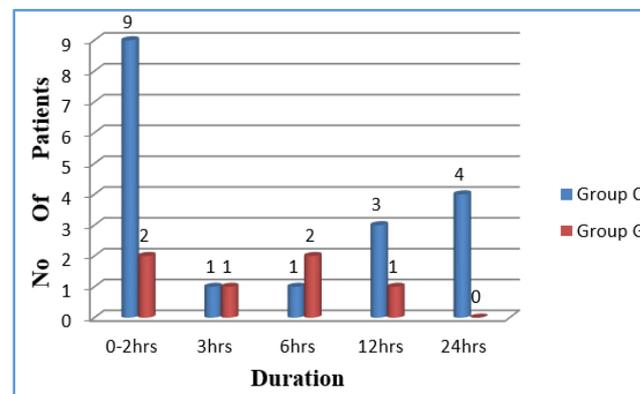


Fig. 1: Distribution of Cases According to the Occurrence of Nausea in the Postoperative Period in Groups O and G

Duration	Group O (n=50)	Group G (n=50)	P-Value
	No. of Cases (Percent)	No. of Cases (Percent)	
0-2 hours	5 (10%)	0 (0%)	0.028
3 hrs.	1 (2%)	0 (0%)	0.31
6 hrs.	1 (2%)	1 (2%)	>0.9
12 hrs.	2 (4%)	0 (0%)	0.16
24 hrs.	2 (4%)	0 (0%)	0.16
Total	11 (22%)	1 (2%)	0.006

Table 2: Distribution of Cases According to the Occurrence of Retching in the Postoperative Period in Groups O and G. (n=100)

Retching: It is the reverse movement of stomach and oesophagus without vomiting.

P-value <0.05 was taken as significant.

Table 2 shows the occurrence of retching during the first 24-hour postoperative period. During the 0-2 hour interval, 5 (10%) patients out of 50 in Group O had retching, while none in Group G had retching. This analysis was found to be statistically significant (P <0.028).

In the 3-hour, 6-hour, 12-hour and 24-hour intervals, 1 (2%), 1 (2%), 2 (4%) and 2 (4%) Group O patients had retching, respectively.

Duration	No. of Episodes	Group O (n=50)	Group G (n=50)	P-Value
		No. of Cases (Percent)	No. of Cases (Percent)	
0-2 hours	1	4 (8%)	0 (0%)	0.028
	2	1 (2%)	0 (0%)	
3 hrs.	1	1 (2%)	0 (0%)	0.32
	2	0 (0%)	0 (0%)	
6 hrs.	1	1 (2%)	1 (2%)	>0.9
	2	0 (0%)	0 (0%)	
12 hrs.	1	2 (4%)	0 (0%)	0.16
	2	0 (0%)	0 (0%)	
24 hrs.	1	1 (2%)	0 (0%)	0.32

	2	0 (0%)	0 (0%)	
Total		10 (20%)	1 (2%)	0.025

Table 3: Distribution of Cases According to the Occurrence of Vomiting in the Postoperative Period in Groups O and G (n=100)

Vomiting: It means to eject a part or all of the contents of the stomach through mouth.

P-value <0.05 was taken as significant.

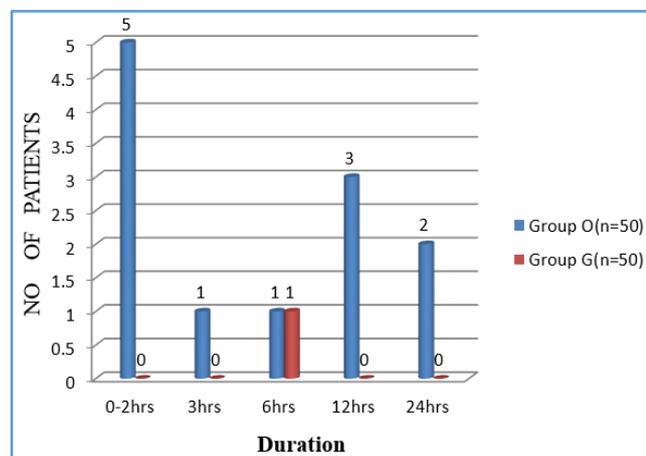


Fig. 2

Fig. 2: In the 0-2 hour interval, 4 (8%) out of 50 patients in Group O vomited once and 1 (2%) out of 50 vomited twice. However, none of the 50 Group G patients had any episodes of vomiting during this interval. This analysis was found to be statistically significant. In the 3-hour and 6-hour intervals, 1 (2%) and 1 (2%) patient of Group O had vomiting, respectively.

Rescue Antiemetic	Groups		P value
	Group O (n=50) (Ondansetron)	Group G (n=50) (Granisetron)	
Given	10 (20%)	1 (2%)	0.0098
Not given	40 (80%)	49 (98%)	

Table 4: Group Wise Distribution of Patients who Required Administration of Rescue Antiemetic (n=100)

In present study, Inj. Metoclopramide 10 mg IV was used as rescue antiemetic in both the groups. In Group O, 10 (20%) patients received Inj. Metoclopramide 10 mg IV in the 24-hour postoperative period. However, in Group G only 1 (2%) out of 50 patients needed rescue antiemetic. This analysis was found to be statistically significant (P<0.05).

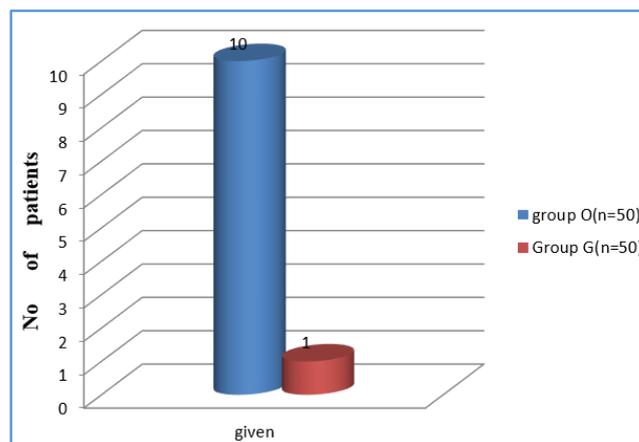


Fig. 3: Group Wise Distribution of Patients who required Administration of Rescue Antiemetic

	Group O (n=50)	Group G (n=50)	P-value
Overall PONV	18 (36%)	6 (12%)	0.0271

Table 5: Comparison of Overall Frequency of Occurrence of Postoperative Nausea and Vomiting (PONV) in Both the Groups (n=100)

The occurrence of overall Postoperative Nausea and Vomiting (PONV) was lower in Group G 6 (12%) when compared to Group O 18 (36%). These findings are statistically significant (P value 0.0271).

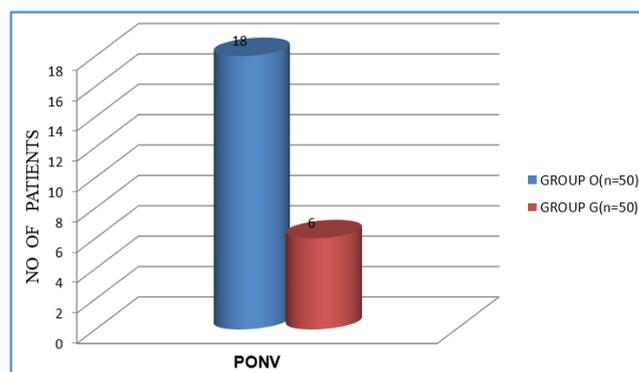


Fig. 4: Distribution of the Sample by the Overall Occurrence of Postoperative Nausea and Vomiting (PONV) in Groups O and G

Adverse Effects	Groups		P Value
	Group O No. of Cases (Percent)	Group G No. of Cases (Percent)	
Headache	6 (12%)	2 (4%)	0.17
Dizziness	1 (2%)	0 (0%)	0.31
Rashes and Allergic Reactions	0(0%)	0 (0%)	

Table 6: Group Wise Distribution of Cases with Adverse Effects (n=100)

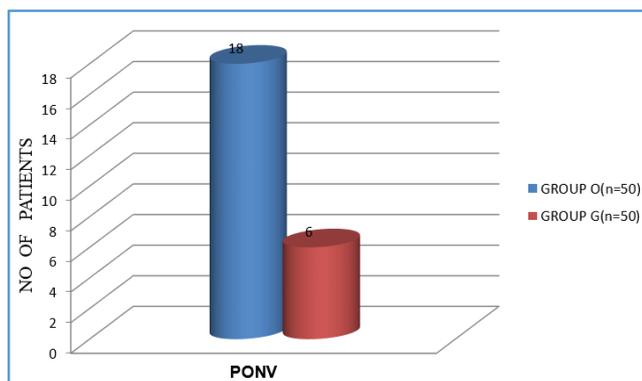


Fig. 5

The above table and figure shows the incidence of adverse effects in both the groups. In Group O, 6 (12%) patients had headache, while in Group G, headache was reported in only 2 (4%) patients. Dizziness was reported in 1 (2%) patient in Group O, whereas no patients in Group G had similar complaints. Rashes and allergic reactions were not reported in the entire study population. This analysis was found to be statistically nonsignificant ($p > 0.05$).

DISCUSSION

For many procedures due to its associated advantages of reduced morbidity and a shorter hospital stay, surgeries are being carried out through laparoscopy.^{5,6} Patients undergoing laparoscopic surgeries under general anaesthesia have a high incidence of PONV, the aetiology being multifactorial.

The present study observed the incidence of PONV in patients undergoing laparoscopic surgeries and compared the incidence of PONV in patients who received different preoperative antiemetic regimens like ondansetron and granisetron. As PONV is a recognised complication of laparoscopic procedures, it was considered unethical to include a placebo group. Hence, placebo group was not included in the present study.

The mechanism of action of 5HT₃ (serotonin) receptor antagonists like ondansetron and granisetron is by binding to the receptor at the Chemoreceptor Trigger Zone (CTZ) and at vagal afferents in the gastrointestinal tracts.⁷ Granisetron is highly selective in its ability to bind the 5HT₃ receptors 1000:1 compared to other receptors such as (5HT_{1A}, 5HT_{1B}, 5HT_{1C}, 5HT₁, 5HT₂) or α 1 and α 2 adrenergic, dopamine D₂, histamine H₁, benzodiazepine, β adrenergic and opioid receptors while the selectivity for ondansetron is only 250-400:1.

The anaesthetic technique was standardised (general anaesthesia with controlled ventilation) in all patients. Since the opioid analgesics are associated with increased incidence of PONV, intravenous paracetamol was administered every 6th hourly for postoperative analgesia. Hence the incidence of PONV in both the groups can be attributed alone to the study drugs used.

In the present study, the dosage selection of ondansetron (4 mg) was based on the previous studies done by Naguib M. et al⁸ in 1996, Rajeeva V. et al⁹ in 1999, Argiriadou H. et al¹⁰ in 2002 and Yuksek M.S. et al¹¹ in 2003. The dosage selection of granisetron (1 mg) was based upon

the work done by Wilson J et al¹² in the year 1996. They conducted a dose-ranging study and concluded that the optimum dose as prophylactic therapy for PONV was 1 mg.

It was decided to administer the study drugs two minutes before the induction of anaesthesia on the basis of previous studies done by Honkavaara P¹³ in 1996, Biswas BN et al¹⁴ in 2003 and Bhattacharya D and Banerjee A¹⁵ in 2003.

Rajeeva et al⁹ considered nausea and vomiting occurring within 2 hours as early onset nausea and vomiting, whereas delayed vomiting consisted of vomiting over 2-24 hours. Biswas BN et al (2003)¹⁴ and Yuksek M et al (2003)¹¹ considered the overall incidence of PONV in the first 24 hours by evaluating the incidence at periodic intervals. They did not specifically classify them into early or delayed onset nausea and vomiting. Similarly, in this study, the overall incidence of PONV has been taken into consideration and the episodes of PONV have been evaluated at intervals of 0-2 hours, 3 hours, 6 hours, 12 hours and 24 hours.

All the patients were observed for nausea, retching and vomiting episodes postoperatively for 24 hrs. The patients with nausea, retching and vomiting in the study were tabulated at 0-2 hrs., 3 hrs., 6 hrs., 12 hrs. and 24 hrs. in postoperative period. Any side effects appreciated were also recorded.

The incidence of nausea in the present study at different intervals in granisetron group is less than in the ondansetron group, which is statistically significant ($p < 0.05$).

The incidence of nausea in the postoperative 24 hrs. in the present study is in accordance with the incidence of nausea in the studies of Saha S and Chatterjee S (2014) and Bendre R et al (2015). However, in a time interval, the incidence of nausea is more in ondansetron group in Saha S study compared to the present study, which could not be attributed to any particular reason.

Incidence of retching at different intervals in granisetron group were lesser than in the ondansetron group, which was statistically significant ($p < 0.05$).

The incidence of retching in the postoperative 24 hrs. in the present study was in accordance with the incidence of retching in Bendre et al (2015).

The incidence of retching was less in the study by Gauchan et al (2014), which can be attributed to usage of higher dose of granisetron, i.e. 40 μ g/kg in Gauchan study when compared to 1 mg in present study and administration of drugs at the end of surgery in the present study. The study drugs were administered 2 mins. before induction.

In the present study, incidence of vomiting at different intervals in granisetron group were less than in the ondansetron group, which was statistically significant ($p < 0.05$).

In the postoperative 24 hrs., incidence of vomiting in the present study was in accordance with the incidence of vomiting in Bendre R et al (2015).

In few time intervals, the incidence of vomiting was more in the studies of Saha S study (2014) and Ommid M et al (2013), which could not be attributed to any particular reason.

The incidence of requirement of rescue antiemetic in the present study is in accordance with study conducted by Ommid M et al (2013).

The postoperative nausea and vomiting was less in the group who received granisetron when compared with the group of subjects who received ondansetron just before the induction of anaesthesia. During 24 hrs. after recovery from anaesthesia, the frequencies of PONV and the need for rescue antiemetic in patients who received granisetron were significantly lower than those in patients who received ondansetron.

The incidence of adverse affects is not significantly different between both the groups in the present study. Findings in the present study are in accordance with Saha S and Chatterjee S (2014)¹⁶ and Bendre R et al (2015).

In Bendre et al¹⁷ (2015), prospective randomised double-blind study in postoperative period only 3 patients out of 30 (10%) in group with granisetron had nausea while 8 (26.7%) patients in group with ondansetron had nausea. This was found to be statistically significant ($P < 0.10$). Vomiting was observed in 16% of Group O and 3% of Group G, which was also statistically significant. This study has concluded that the overall postoperative nausea and vomiting is less with granisetron compared to ondansetron.

Bhattacharya D and Banerjee A¹⁵ in 2003 compared the antiemetic effects of intravenous ondansetron 4 mg (2 mL) and granisetron 2 mg (2 mL) in a study and they concluded that granisetron is much more effective than ondansetron to prevent PONV following daycare gynaecological laparoscopy. The incidence of PONV in Battacharya study was lesser than the present study because the study was conducted in laparoscopic tubal ligation, which is a short duration surgery and less no. of cases was included in their study.

SUMMARY

Observations were tabulated and analysed using chi-square test and 'student's unpaired t-test.'

1. The demographic profile (age, age wise distribution; gender, gender-wise distribution; weight, weight-wise distribution; and mean duration of surgery) was comparable in both the groups.
2. Haemodynamic parameters (heart rate, systolic, diastolic blood pressure and mean arterial pressure) were comparable in both the groups.
3. The incidence of nausea was 36% in Group O and 12% in Group G, which was significantly low.
4. The incidence of retching was 22% in Group O and it was less in Group G that is 2%.
5. Greater percentage of patients in Group O (16%) experienced vomiting compared to Group G (2%).
6. The overall frequency of Postoperative Nausea and Vomiting (PONV) was less in Group G (12%) than Group O (36%).
7. The frequency of need of overall rescue antiemetics were more in Group O (20%) when compared to Group G (2%).

8. No significant side effects were noted in both the groups. In Group O, six patients (12%) developed headache and in Group G 2 patients (4%) developed headache and 1 patient in Group O developed dizziness and these side effects were not worrisome.

CONCLUSION

From the present study, it is concluded that both the drugs are haemodynamically stable and IV administration of granisetron in the dosage of 1 mg preoperatively for laparoscopic surgeries done under GA has the following advantages over ondansetron.

- It has significantly lower incidence of nausea, retching and vomiting in postoperative period.
- It was not associated with any worrisome adverse effects and hence can be used as an alternative to ondansetron.

It is clear from the present study that patients at high risk for PONV who are treated prophylactically with granisetron are overall less likely to require rescue antiemetics than if treated with ondansetron.

In conclusion, granisetron is better than ondansetron as a prophylaxis against PONV following laparoscopic procedures.

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