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ORIGINAL ARTICLE

PROSPECTIVE, RANDOMIZED, DOUBLE BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF GRANISETRON VERSUS ONDANSETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY UNDER GENERAL ANAESTHESIA

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HOW TO CITE THIS ARTICLE:
D. Vijayalakshmi, Gedela Vasavi, R. Srinivasa Rao, P. S. Gopal. "Prospective, Randomized, Double Blind Study to Compare the Efficacy and Safety of Granisetron versus Ondansetron in Prevention of Post-Operative Nausea and Vomiting in Patients Undergoing Elective Laparoscopic Cholecystectomy under General Anaesthesia". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 75, September 17; Page: 13077-13087, DOI: 10.14260/jemds/2015/1883

ABSTRACT: OBJECTIVE: To compare the efficacy and safety of Granisetron versus Ondansetron in prevention of post-operative nausea and vomiting in patients undergoing elective Laparoscopic Cholecystectomy under general anaesthesia. **MATERIALS AND METHODS:** After the approval from IEC, the study was started and conducted over a period of two years i.e., from 2010-2012. Data was collected from 100 ASA I and II patients scheduled for laparoscopic cholecystectomy aged between 20-60 years at Government General Hospital, Kakinada. Both the study groups were selected from these patients. Written informed consent was taken from all patients. Preanesthetic medication was given with Ranitidine 150mg and Lorazepam 1mg, the night before and morning of surgery. Patients were randomly allocated into 2 groups. Group A - Received Inj. Ondansetron 8mg diluted in 5ml of normal saline. Group B - Received Inj. Granisetron 1mg diluted in 5ml of normal saline. INJ. Glycopyrolate 0.01mg/kg & INJ. Fentanyl (1-2µ/Kg) given intravenously 5min prior to induction of anaesthesia. All the vital data values recorded before & throughout surgery at 15 min interval for 2 hours. Patients were observed at 0-2hrs, 2-6hrs, 6-12hrs post operatively for episodes of PONV. **RESULTS:** At the end of the study, a complete response i.e., no PONV and no need for another rescue antiemetic was attained in 92% of patients who received Granisetron and 68% of patients who received Ondansetron. No differences in adverse events were observed in the two groups. **CONCLUSION:** The incidence of PONV after laparoscopic cholecystectomy is large. In view of the proven advantage of serotonin antagonists, we decided to study the antiemetic efficacy of Granisetron. After premedication, patients were administered the study drugs intravenously prior to the induction and balanced general anaesthesia was administered. Patients were observed for nausea and vomiting after the procedure at 0-2hrs, 2-6hrs, 6-12hrs post operatively. Granisetron was found to be better in attaining a complete response than Ondansetron. We conclude that Granisetron might be considered clinically relevant in a moderate risk setting.

KEYWORDS: Post-Operative Nausea vomiting, Granisetron, Odansetron.

INTRODUCTION: Nausea and vomiting have been associated for many years with the use of general Anaesthesia for surgical procedures induced by ether and chloroform. The incidence of postoperative Nausea and Vomiting in recent studies has been reported to be in the 20-30% range which is consistently lower than the 75-80% incidence reported during the "ether" era.[1]

The description of it as " THE BIG LITTLE PROBLEM" encapsulated much of the general population even though there has been less usage of antiemetic anesthetic agents, imported pre and

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post-operative medication, refinement of operative technique and identification of patient predictive factors. However, in spite of these advances, Nausea and vomiting still occur with unacceptable frequency rendering the description as "THE BIG LITTLE PROBLEM".[2]

Although anaesthetics have been used to facilitate surgical procedures for almost 150 years, the mechanism of nausea and Vomiting is unknown due to factors, like the complexity of the inadequate quantification, inadequate regimens and lack of suitable animal models.

Severe Nausea and Vomiting occur only in 0.1% (1 in 1000). Although frequently described as a minor post-operative complication, PONV may result in dehydration, electrolyte imbalance; tension in suture lines, venous hypertension, and increased length of stay in PACU & Delayed discharge times.[1]

Although Benzamide derivatives like Metoclopramide accelerates gastric emptying and increases lower oesophageal sphincter tone in non-pregnant patients, their efficacy in doing so is not clear in pregnant patients. And also is effective only in 30 to 70% of patients and only at doses which have been associated with extrapyramidal side effects in about 5% of patients.

As a result of this several selective 5HT3 antagonists have been developed for clinical use out of which ONDANSETRON was the first drug to reach market.

Subsequently newer drugs like GRANISETRON, DOLOSETRON, POLOSETRON, TROPISETRON, etc., have come into clinical practice. In this study, an effort has been made to compare the efficacy of "GRANISETRON VS ONDANSETRON" in preventing the incidence of post-operative nausea and Vomiting in patients undergoing elective Laparoscopic Cholecystectomy under general anaesthesia.

PATIENTS AND METHODS:

Sources of Data: Data was collected from 100 ASA I and II patients scheduled for laparoscopic cholecystectomy aged between 20-60 years at Government General Hospital, Kakinada. Both the study groups were selected from these patients. The study was conducted over a period of 2 years, 2010-12. The study was a prospective, randomized, double blinded one. Written informed consent was taken from all patients. Pre anaesthetic medication was given with Ranitidine 150mg and Lorazepam 1mg, the night before and morning of surgery. SpO2, NIBP, ECG monitors were attached. The base line values were recorded. IV access was established.

Patients were randomly allocated into 2 groups:

1. Those who receive Ondansetron 8mg diluted to a 5ml volume with normal saline.
2. Those who receive Granisetron 1mg diluted to a 5ml volume with normal saline.

INJ. Glycopyrolate 0.01mg/kg & INJ. Fentanyl (1-2μ/Kg) given intravenously 5min prior to induction of anaesthesia.

Prior to induction of anaesthesia, Boyle anaesthetics machine, appropriate sized, oral high volume and low pressure cuffed endotracheal tubes, styllete, and laryngoscope. Guedel's airway, a working suction apparatus and all emergency drugs were kept ready. Vital signs, arterial blood pressure, and heart rate, respiratory rate and SpO2, ETCO2, Tidal volume were monitored during the intra-operative period.

ANAESTHETIC TECHNIQUE:

- All patients were pre-oxygenated for 5 min with 100% O2 with a face mask using Maple son "A" circuit while monitors were applied.

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- The patients were soon induced with 4-5mg/Kg of Thiopentone sodium and 1.5mg/kg of Suxamethonium was given.
- After intubating the larynx with an appropriate sized high volume and low pressure cuffed endotracheal tube, the cuff was inflated and connected to closed circuit and IPPV was begun with 66% nitrous oxide and 33% oxygen.
- A non-depolarizing muscle relaxant viz., vecuronium 0.08-0.1mg/Kg was given to achieve muscle relaxation and increments were given subsequently.
- At the end of surgery, muscle relaxation was completely reversed with INJ. Glycopyrolate 0.4mg along with INJ. Neostigmine 0.05mg/Kg wt.

Patient were extubated after the recovery from neuromuscular blockade and shifted to the post-operative ward once the recovery was completed, as assessed by:

A. Sustained head lift for 5 seconds.
B. Adequate depth of tidal volume.
C. Regular rate of respiration.
D. Sustained hand lifting again gravity.
E. Ability to respond to vocal commands.
F. Hemodynamically stable.

MEASUREMENT OF DATA: Patients and their attendants were educated to report the incidence of nausea and occurrence of vomiting episodes in the postoperative ward regularly monitored every 30 min for the first 2hrs, and every 1 hour for the first 4hrs. Patients were specifically asked by anesthesiologist whether they had any symptoms of nausea and vomiting.

All the patients in both groups I & II were recorded for the incidence of nausea, occurrence of emetic episodes, vital signs and any adverse events.

Antiemetic efficacy was assessed by monitoring the incidences of nausea and vomiting (Emesis or retching), as well as the need for "Rescue" antiemetic medication. An emetic episode was defined as either a single episode or repeated episodes of vomiting or retching occurring within 1 min of each other. If the patient complained of feeling nauseated for more than 5 min, it was considered to be an episode of nausea. Rescue antiemetic therapy (i.v Metoclopramide 10mg) was administered if the patients experienced >2 emetic episodes or intractable nausea. Complete responses referred to incidence when no emesis (Vomiting/Retching) and no rescue antiemetic drugs were required.

RESULTS: there is no significant difference in SBP, DBP, Heart rate, SPO2, ETCO2, tidal volume, maximum airway pressure in both groups.

	Group –I n=50(%) Granisetron	**Group – II n=50(%) Ondansetron**	**χ^2**	**p**
No. of patients who experienced nausea	0(0%)	4(8%)	6.5104	0.01
No. of patients who experienced vomiting	0(0%)	4(8%)	6.5104	0.01

Table 1: Incidence of nausea and vomiting in 0-2 hrs. post operatively

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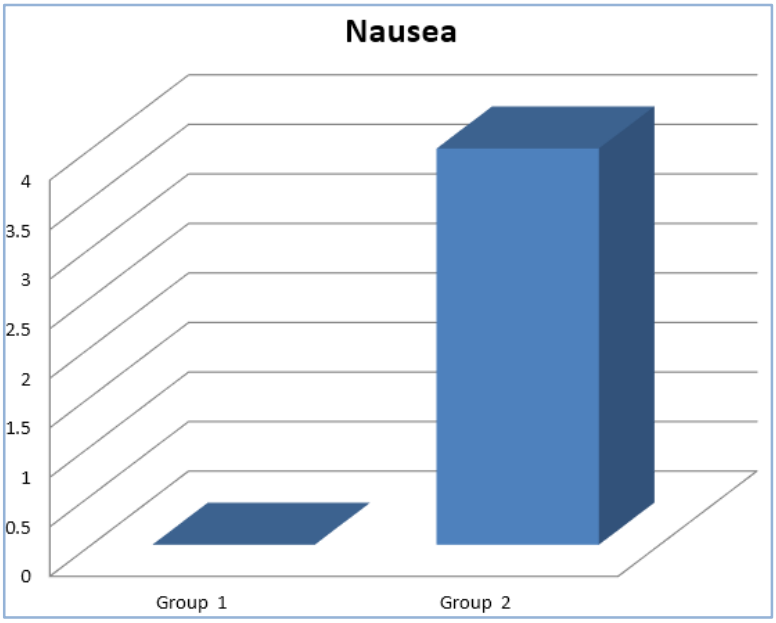

Fig. 1: Graphic representation of incidence of nausea in 0-2 hrs. Post-operatively

Group I (Granisetron)
Group II (Ondansetron)

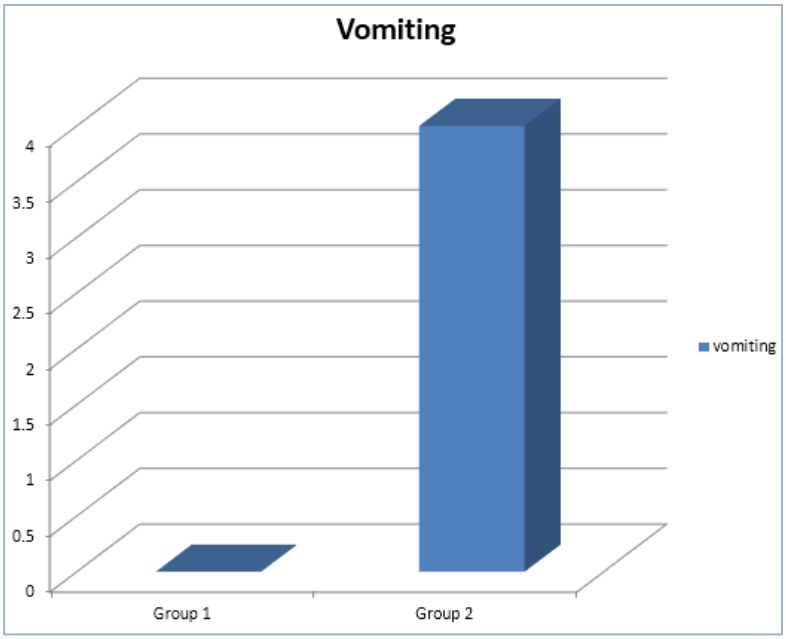

Fig. 2: Graphic representation of incidence of vomiting in 0-2 hrs. Post operatively

Group I (Granisetron)
Group II (Ondansetron)

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	Group I n=50(%) Granisetron	Group II n= 50(%) Ondansetron	χ^2	p
No. of patients who experienced nausea	4(8%)	10(20%)	4.069	0.02
No. of patients who experienced vomiting	2(4%)	6(12%)	3.396	0.05

Table 2: Incidence of nausea & vomiting in 2-6hrs post operatively

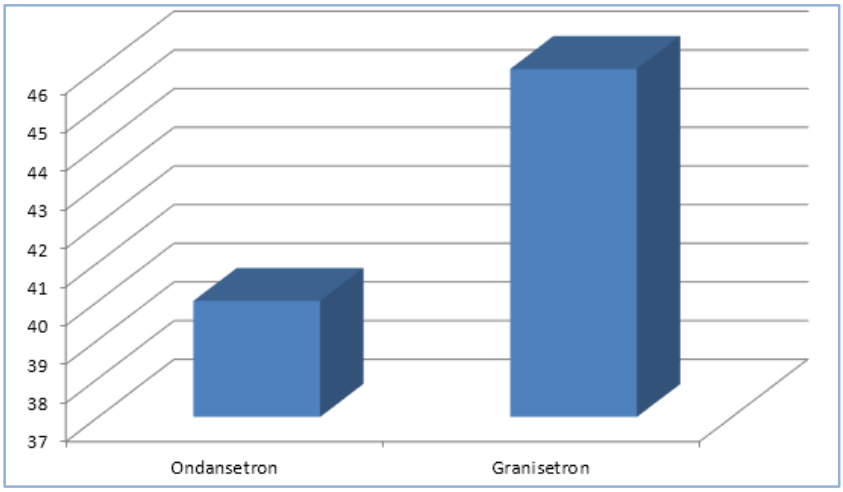

Fig. 3: Graphic representation of incidence of nausea in 2-6 hrs. Post operatively

Group I (Granisetron)
Group II (Ondansetron)

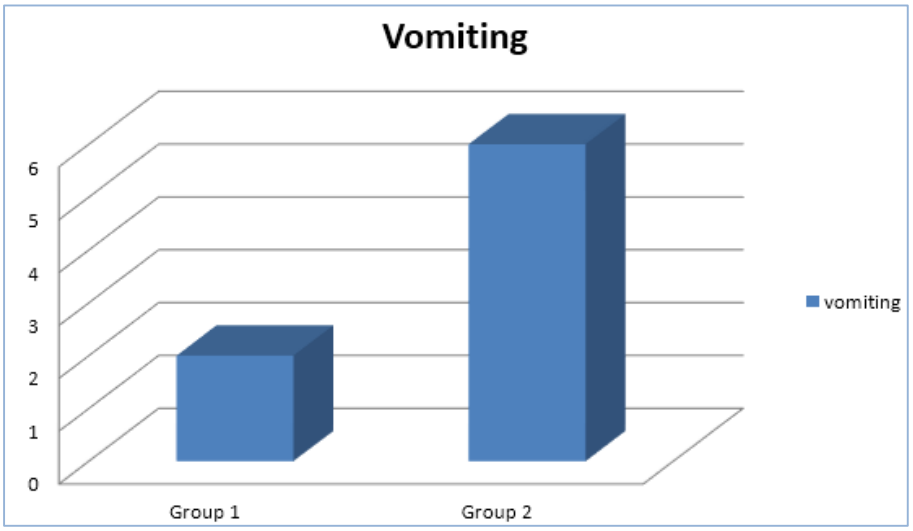

Fig. 4: Graphic representation of incidence of vomiting in 2-6hrs postoperatively

Group I (Granisetron)
Group II (Ondansetron)

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	Group – I N=50(%) Granisetron	Group – II N=50(%) Ondansetron
no. of patients who experienced nausea	0(0%)	0(0%)
No. of patients who experienced vomiting	0(0%)	0(0%)

Table 3: Incidence of nausea & vomiting in 6-12 hrs. postoperatively

	Ondansetron	Granisetron	$\varkappa^2$	p
Number of patients who experienced complete response from nausea with single dose	46	50	6.51	0.01
Number of patients who experienced complete response from Vomiting with single dose	46	50	6.51	0.01

Table 4: Complete response from nausea and vomiting 0-2 hrs. Post-operatively

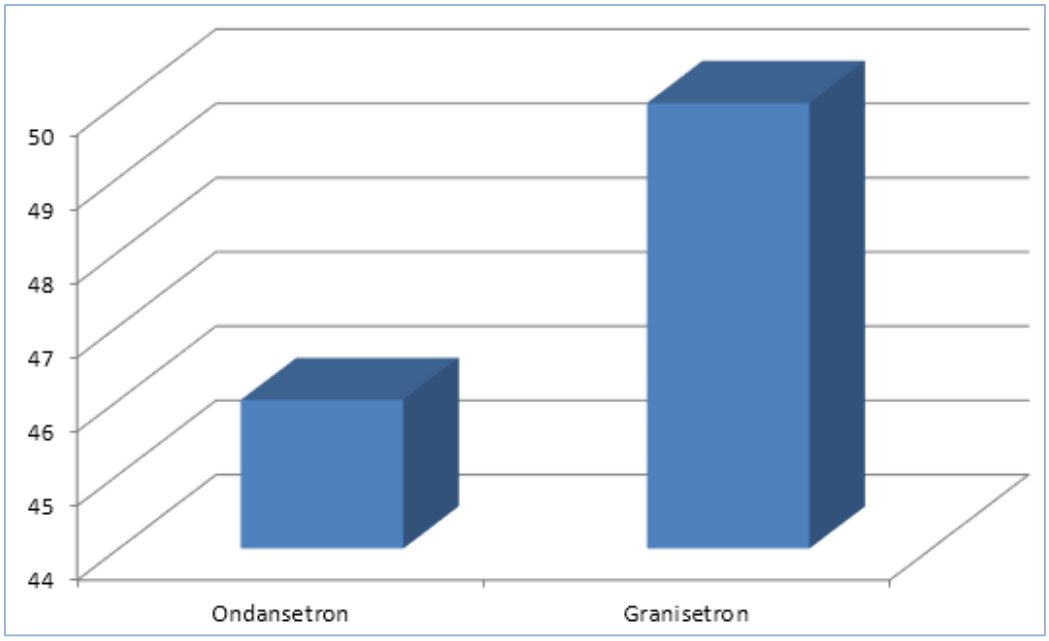

Fig. 5: Complete response from nausea 0-2 hrs. Post-operatively

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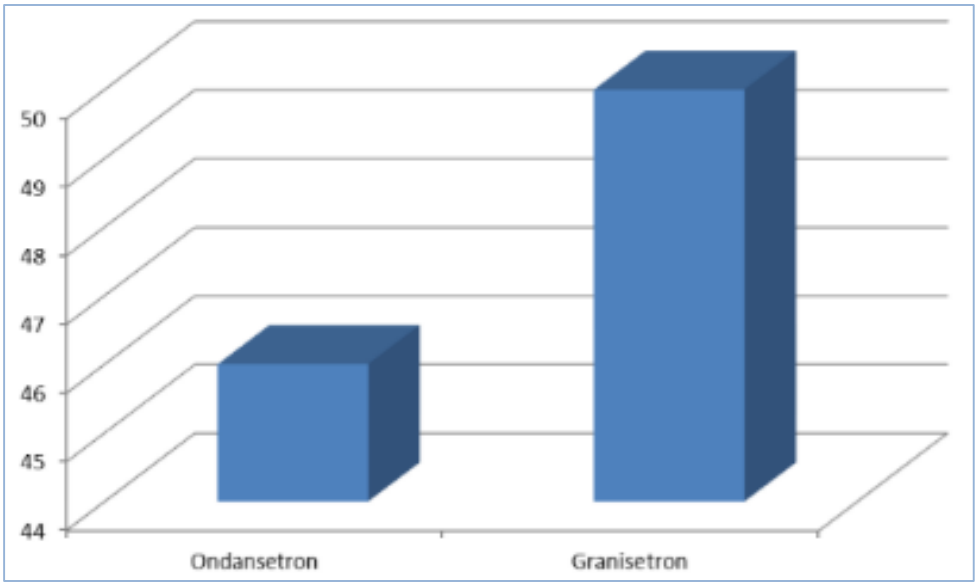

Fig. 6: Complete response from Vomiting 0-2 hrs. Post-operatively

	Ondansetron	Granisetron	$\varkappa^2$	p
Number of patients who experienced complete response from nausea with single dose	40	46	6.271	0.01
Number of patients who experienced complete response from Vomiting with single dose	44	48	6.271	0.01

Table 5: Complete response from nausea and vomiting 2-6 hrs. Post-operatively

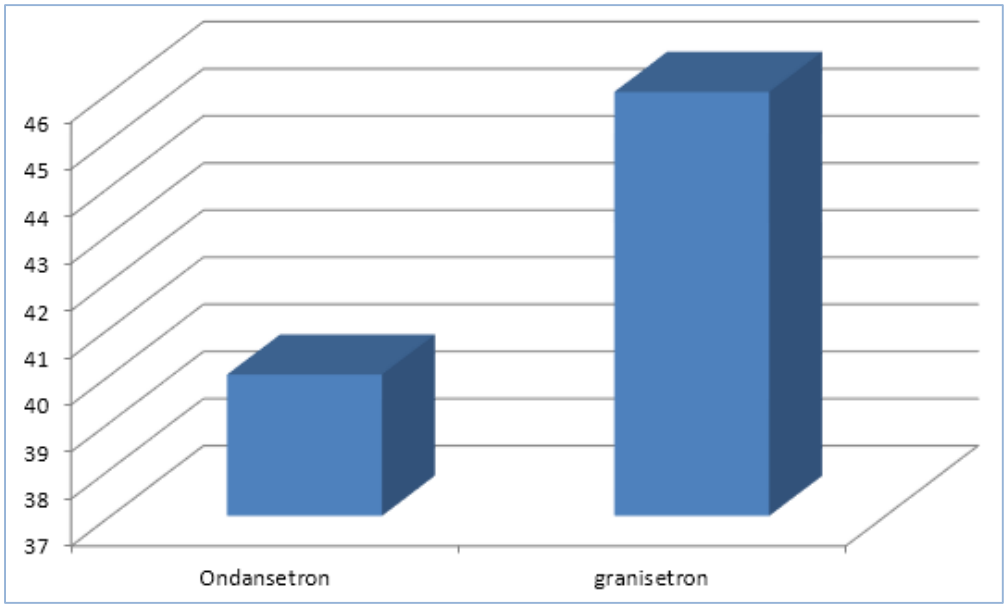

Fig. 7: Complete response from nausea 2-6 hrs. Post-operatively

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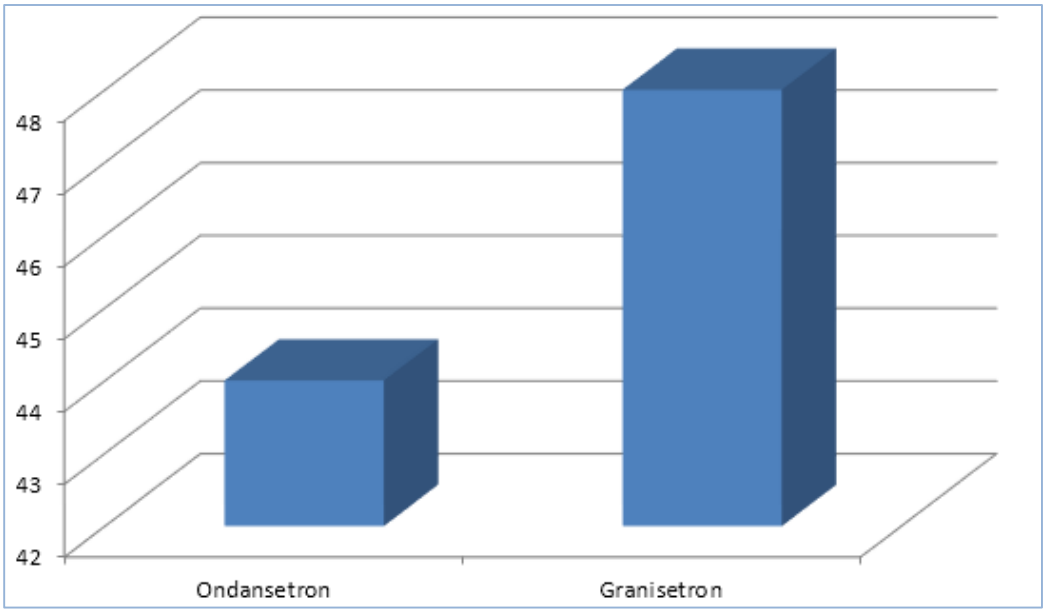

Fig. 8: Complete response from Vomiting 2-6 hrs. Post-operatively

	Ondansetron	Granisetron	$\varkappa^2$	p
Number of rescue anti-emetics	5	0	3.368	0.05

Table 6: Number of rescue anti-emetics given during post-operatively

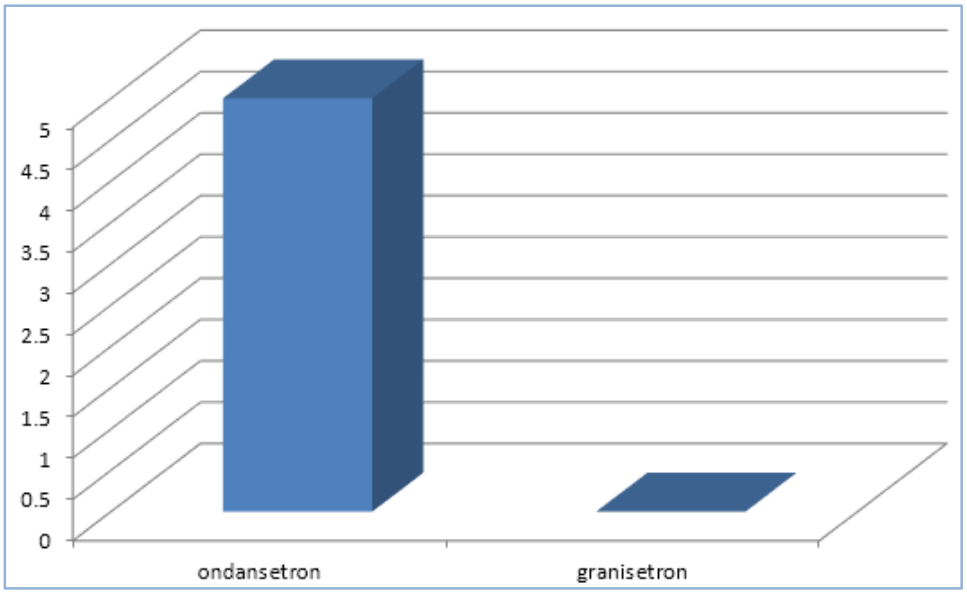

Fig. 9: Number of Rescue anti-emetics

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	Group – I N=50(%) Granisetron	Group – II N=50(%) Ondansetron	p
Head ache	4(8%)	6(12%)	p>0.05
Dizziness	1(2%)	2(4%)	P>0.05
Shivering	0(0%)	1(2%)	p>0.05
Sweating	0(0%)	0(0%)	-
Constipation	0(0%)	2(4%)	p>0.05
hypotension	1(2%)	0(0%)	p>0.05

Table 7: Incidence of side effects

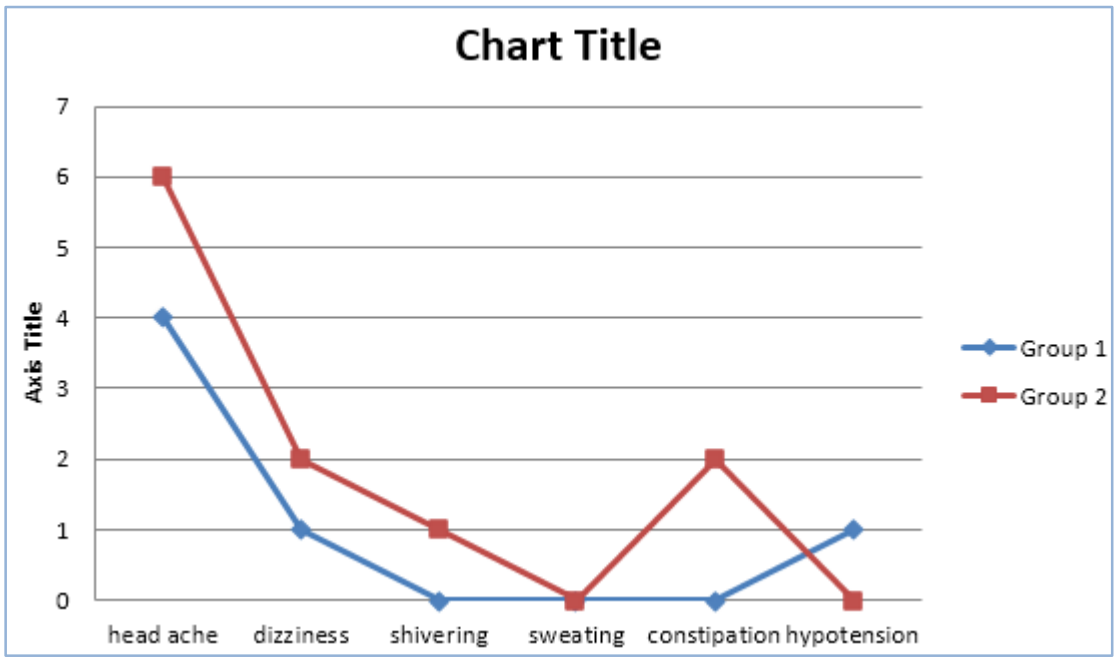

Fig. 10: Graphic representation of incidence of side effects in post-operative period

DISCUSSION: Post-operative nausea and vomiting (PONV) is of multifactorial origin. The incidence of PONV after anesthesia. Despite the advances in antiemetic therapy in the last decades is still found to be relatively high. Gold et al noted that the three most common causes for admission following day care surgery are pain, bleeding and intractable vomiting.[3] Factors affecting PONV include patient related factors (Age, sex, phase of the menstrual cycle), anesthesia related factors (use of volatile anesthetic agents, N2O, opioid) and surgery related factors. Female gender has been associated with higher incidence of PONV compared to male patients. On an average, female patients suffer three times more often from PONV than men. Our study was aimed at comparing the antiemetic efficacy of Ondansetron and Granisetron in preventing nausea and vomiting in laparoscopic surgeries. In our study the factors that would have contributed to nausea and vomiting may be laparoscopic surgery,

surgery for a related gallbladder pathology etc. use of facemask, use of nitrous oxide may or may not have contributed to nausea and vomiting. Ryle's tube aspiration before extubation; avoidance of pethidine towards the end of surgery must have helped in preventing PONV.

In our study, the treatment groups were similar to patient characteristics, surgical procedure, type of anesthesia and analgesics used postoperatively. Therefore the differences in scores can be attributed to the differences in the agents tested.

Laparoscopic cholecystectomy was chosen because of high incidence of PONV associated with it. Naquib et al demonstrated that the incidence of PONV after laparoscopic cholecystectomy in their placebo group was remarkably high. (72%).[4]

In our study, it was observed that 92% of patients who received Ondansetron alone did not have any nausea and vomiting in 0-2hours postoperative period, 80% did not have any episode of nausea and 88% did not have any episode of vomiting in 2-6hrs post operatively, and no one complained of nausea and vomiting during 6-12 hrs. Post-operative period. 5 of patients received rescue antiemetic during the postoperative period. Complete response was achieved in only 68% of this group.

In the study group where Granisetron is used, no one complained of nausea and vomiting during 0-2hrs post operatively, 8% complained of nausea and 4% complained of vomiting during 2-6 hrs. Post operatively. Complete response was achieved in 92% of this group. No one received rescue antiemetic.

In our study, 6 patients in Ondansetron group and 4 patients in Granisetron group complained of mild head ache which is clinically and statistically significant. $5HT_3$ receptors do not affect heart rate, blood pressure, respiratory rate. There is no drug interaction reported with the usual preoperative anesthetic drugs.[5] Minor, asymptomatic, transient ECG changes have been reported in patients receiving $5HT_3$ antagonists.[6] No ECG changes were observed in the patients in both the groups in our study. There was no statistically significant difference in the hemodynamic parameters between the groups. No patient demonstrated a SPO2 below 90.

SUMMERY AND CONCLUSION: The incidence of PONV after laparoscopic cholecystectomy is large. In view of the proven advantage of serotonin antagonists, we decided to study the antiemetic efficacy of Granisetron. After premedication, patients were administered the study drugs intravenously prior to the induction and balanced general anaesthesia was administered. Patients were observed for nausea and vomiting after the procedure at 0-2hrs, 2-6hrs, 6-12hrs post operatively. Granisetron was found to be better in attaining a complete response than Ondansetron. We conclude that Granisetron might be considered clinically relevant in a moderate risk setting.

REFERENCES:

1. Palazzo MGA, Strumin A: Anesthesia and Emesis: Etiology. Can Anaesth Soc J 1984;31:178-187
2. Kapur P A: The big little problem. Anaesth Analog 1991; 73:243-245.
3. Mehernoor F. Watcha, Paul F.White. Post-operative Nausea and Vomiting. Its etiology, treatment, and prevention. Anaesthesiology 77:162-184, 1992.
4. Naquib M, El Bakry AK, Khoshim MHB et al. prophylactic antiemetic therapy with Ondansetron, Tropisetron, Granisetron, and Meatoclopramide in patients undergoing laparoscopic cholecystectomy. Can J Anaesth 1996; 43:226-31.

DOI: 10.14260/jemds/2015/1883

5. Conahan TJ, Young ML, Levy WJ et al. Cardiovascular stability with rapid intravenous infusion of Ondansetron. Anaesth Analg 1992; 24:193-196.
6. Andrews PLR. Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all 5HT3 receptor antagonists same? Eur J cancer 1992; 28:S2-S6.

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